

What are the neural abnormalities underlying a (or any) psychiatric disorder?



Applying various paradigms in neuroimaging research almost invariably reveals brain abnormalities across domains such as attention, working memory, emotion, executive function, reward processing, learning, inhibition, memory, social cognition, and so on.

Too complicated — impossible to make sense of the messy results.



How could that happen — abnormalities in nearly every system?





I give up — let's leave the difficult results to machine learning and AI.



Becoming a dominant engineering trend in psychiatric brain research.



No big deal — let's tackle the complexity through centralized dialectics.



Applying dialectic neuroscience to pinpoint the core neuropathology.



A novel form of dialectics informed by psychiatry and brain science: centralized dialectics

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Abstract

Traditional dialectics based on the “thesis-antithesis-synthesis” model falls short in addressing complex scientific problems devoid of clear opposition/antagonism. A more effective approach is essential for these intricate problems. This paper introduces a novel dialectical method—centralized dialectics—based on “analysis-synthesis” for addressing complex phenomena that lack clear antagonistic features and are governed by parsimonious underlying mechanisms. When applied to neuroscience, this method is referred to as “dialectic neuroscience.” The proposed method mirrors Bayesian model selection, guided by criteria rationality, comprehensive accountability, and parsimony. Analytical components interact through synthesis, analogous to identifying the central missing piece of a jigsaw puzzle (with the peripheral pieces representing analytic facts), hence the term “centralized.” The output is the theory or mechanism derived from this synthesis process through nonlinear or creative thinking. Centralized dialectics principles have been implicitly utilized across various disciplines, particularly in modern physics, yet remain unarticulated. Major depressive disorder (MDD) serves as a demonstration of dialectic neuroscience, wherein the approach successfully identified an abnormal reciprocal suppressive network mechanism associated with MDD, which was later empirically validated. From an engineering perspective, synthetic results correspond to achieving local or global optima. Centralized dialectics provides a rigorous, flexible, and interdisciplinary framework for complex problem-solving. It has the potential to reshape scientific standards, foster creative thinking, and enable cross-validation across diverse fields. This method could help frame non-linear thinking and creativity within a scientific framework. A structured formulation is recommended to ensure synthesis quality and to facilitate mutual verification among different parties. This metascience research employed a systematic and integrative approach, beginning with an extensive literature review to identify limitations in existing dialectical methods and establish the foundation for centralized dialectics. Conceptual modeling and a Bayesian framework were then utilized to formalize the proposed framework, followed by exemplifying its application across diverse disciplines. To illustrate, the author analyzed MDD through the lens of centralized dialectics, proposed a theory, and provided empirical validation. Both the essence of centralized dialectics and its strategic implementation are emphasized. The potential of centralized dialectics to complement current scientific standards by incorporating creative and nonlinear thinking into scientific activities without sacrificing meticulousness is highlighted.

Keywords Bayesian · Dialectics · Major depressive disorder (MDD) · Synthesis · Totality

Prologue

This research, in contrast to conventional empirical analog and categorized as meta-science in *Current Psychology*, presents a novel dialectical approach applicable to a range of issues. Meta-science, which examines science itself, focuses on evaluating scientific methods, practices, outcomes, and impact. Unlike traditional dialectics that adhere to the “thesis-antithesis-synthesis” model, this new method is founded on an “analysis-synthesis” framework, where

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the analytical phases do not necessarily involve opposition. Instead, these components interact through a synthesis process, much like identifying and integrating the central missing piece of a jigsaw puzzle, hence the term “centralized.” This contrasts with conventional dialectics that emphasize antagonistic conflicts. The operational framework is context-dependent; it is particularly effective for addressing complex phenomena with parsimonious underlying mechanisms. A specialized application of this approach, termed “dialectic neuroscience,” seeks to employ centralized dialectics to tackle complex issues in brain science. Major depressive disorder (MDD) serves as a case study, illustrating how a robust theory explaining the disease mechanism is developed through the synthesis process.

Similar to conventional empirical studies, this article is structured into four sections, but with distinctly different content. The **INTRODUCTION** reviews the role of dialectics in philosophy and psychology. The **METHODS** section formulates centralized dialectics, a novel approach whose thoroughness is established through a Bayesian model selection scheme guided by three criteria: rationality, comprehensive accountability, and parsimony. This method aligns with the philosophical concept of totality, offering a potential safeguard against reductionism and parochialism, and aims to meet strict statistical standards through effective synthesis. In the **RESULTS** section, an exploration of how various disciplines—from archaeology to modern physics—tackle complex issues reveals that this method has been widely and implicitly utilized, despite never being formally articulated. The development of a network theory for MDD, along with its empirical validation, is illustrated. The **DISCUSSION** addresses several key aspects. The psychological foundation of this synthetic process involves creative thinking, essential for developing innovative solutions. From an engineering standpoint, successful synthesis resembles achieving local or global optima. Centralized dialectics not only provides a framework for resolving complex problems but also has the potential to influence scientific standards. To ensure synthesis quality and enable verification across various parties, a structured formulation is advised.

In practical application, this approach fosters interdisciplinary collaboration and integration, leveraging insights from various fields to more effectively address complex problems and may propel an ongoing process of development. For example, advancing dialectic neuroscience involves iterative cycles of analysis and synthesis, continually refining models and hypotheses to deepen our understanding of brain function and dysfunction. The flexibility and adaptability of this method make it a valuable tool for both theoretical exploration and empirical research, with the capacity to revolutionize scientific inquiry and problem-solving across multiple domains. In this context, the

approach may complement existing scientific standards and provide a structured framework for incorporating non-linear thinking and creativity into scientific practice.

Introduction: dialectics in philosophy and psychology

Dialectics in philosophy

The word “dialectics” originates from the Greek term “*dialogesthai*,” which translates to conversing or arguing. The process of dialectics involves philosophical inquiry through discussion and argumentation, ultimately leading to the resolution of contradictions and the development of new insights. Philosophy has employed dialectics to investigate diverse subjects, such as the essence of reality and cognition and the framework of society and history (Forster, 1993; Hegel, 1807, 1998; Marx & Engels, 1976; Piaget, 1977; Sartre et al., 2022). The crux of traditional dialectics is to find solutions to conflicting ideas. The primary forms of dialectics are briefly overviewed below.

Hegelian Dialectics: One of the most well-known dialectical forms originated by the German philosopher Georg Wilhelm Friedrich Hegel (Forster, 1993). Hegelian dialectics is a method of understanding and analyzing the development of ideas and history through a process of thesis, antithesis, and synthesis. The presence of opposing forces or ideas creates a constant state of tension, ultimately resulting in conflict or contradiction. However, this conflict is resolved through synthesis, whereby the two opposing views are merged to form a novel and more intricate concept. Hegelian dialectics has been applied to analyze a wide range of topics, from the development of the human spirit, history, sociology, politics, literature criticism, and aesthetics (Hegel, 1807, 1998; Houlgate, 2005; Lukács, 1972, 1974).

Marxist Dialectics: As per the principles of Marxist dialectics developed by Karl Marx and Friedrich Engels (Calinicos, 1983; Marx & Engels, 1976), history is defined by the conflict between different social classes. This conflict arises due to the contradictions between the forces of production and the relations of production. The presence of contradictions often sparks a class struggle, ultimately leading to a revolution and the creation of a new social structure. Marxist dialectics has been employed to analyze various subjects, including the features of capitalism and the state’s role in society (Lefebvre, 2009).

Existential Dialectics: Existential dialectics was first developed by the French philosopher Jean-Paul Sartre, who claimed that human existence is characterized by

a tension between freedom and responsibility (Sartre et al., 2022). This tension arises because humans are free to choose their actions but are also responsible for the consequences. This tension leads to a sense of anxiety and despair, which can only be resolved through a process of authentic choice and commitment. Existential dialectics have been extended to explore a wide range of topics, from the nature of personal identity, and body-world relationships, to the meaning of life (Ginnane, 1964).

Dialectics in psychology

As introduced above, dialectics as an ancient philosophical mode of thinking emphasizes the existence and unity of contradictions. It posits that development and change are driven by the opposition and struggle of these contradictions. In the field of psychology, dialectical thinking has also been widely applied to various theories and practices, contributing to a deeper understanding of the complexity and dynamism of human behavior and psychological activities. Whether in theory construction or clinical practice, dialectical thinking plays a crucial role, briefly summarized below.

Development Theories: In developmental psychology, dialectics has been employed to clarify the process of cognitive development in children. Jean Piaget's theory of cognitive development incorporates elements of dialectical thinking, suggesting that children's cognitive growth emerges through the dynamic interplay and resolution of contradictions between assimilation and accommodation (Piaget, 1977; Riegel, 1973). "Assimilation" refers to the process of integrating new information into pre-existing cognitive schemas, whereas "accommodation" involves altering existing schemas to incorporate new information that doesn't fit. These two processes work together dynamically, allowing cognitive development to occur through adaptation to new experiences. This conflict drives the progression from one cognitive stage to a more advanced one. Likewise, Lev Vygotsky's sociocultural theory emphasizes the dialectical interaction between the individual and their social environment in shaping development. The tension between a child's current abilities and the demand of their cultural context creates the "zone of proximal development"—an area where a child can acquire new skills and knowledge with the help of a more knowledgeable other. Vygotsky viewed development as emerging from this dialectical synthesis of the individual's capacities and the cultural tools and interactions provided by more capable others. Both Piaget and Vygotsky's seminal theories demonstrate how a dialectical metatheory

perceives development as driven by contradictions, whether between cognitive structures and experiences, or individual potentials and sociocultural influences (Bidell, 1988). Addressing these dialectical tensions through adaptive processes leads to reorganization into more advanced developmental stages and enhanced capabilities. In summary, applying dialectical thinking in developmental psychology offers a robust framework for understanding cognitive and sociocultural processes as propelled by contradictions that foster developmental progress when resolved through assimilation, accommodation, or internalization (Riegel, 1975).

Personality Theories: The application of dialectics in personality theories is prominent. Sigmund Freud's psychoanalytical theory incorporates dialectical thinking. Freud posited that human behavior arises from the contradictory dynamics between the unconscious (id) and conscious mind (ego and superego), driving the development of personality and the diverse use of defense mechanisms (Funder, 1997). Karen Horney, a renowned psychologist, incorporated dynamic contradictions in her psychoanalytic social theory, proposing that the interplay between "basic anxiety" and neurotic coping strategies is central to the development of personality and neuroses (Horney, 2013b). Horney theorized that basic anxiety stems from unmet childhood needs for safety, love, and self-esteem, leading to feelings of insecurity and inferiority. To cope with this anxiety, individuals develop neurotic trends—such as compliance, aggression, or detachment—in an unconscious attempt to resolve the inner conflict. Horney's theoretical perspective conceptualized personality and neuroses as arising from the dynamic relationship between basic anxiety and the unconscious strategies developed to cope with it, all shaped by social and cultural forces. This framework exemplifies dialectical thinking in the study of personality formation (Horney, 2013a).

Social Psychology: Dialectics has been employed to explain social dynamics, as seen in Social Identity Theory (SIT), which can be interpreted through a dialectical lens. SIT suggests a tension between personal identity and social identity—the individual self versus the collective self within a group (Hogg, 2016; Tajfel et al., 1979). It is through the interaction and negotiation between these two aspects that one's overall social identity forms and evolves. According to SIT, individuals strive to maintain and enhance their self-esteem and personal identity, while group membership requires conformity to group norms and, at times, the subordination of personal interests to those of the collective. This tension between individual distinctiveness and group conformity drives social competition, in-group/out-group biases, and

discrimination. The dialectical process between self and group aims to achieve a sense of positive distinctiveness for the individual within the collective identity. SIT thereby illustrates how the tension between personal and social identities, as well as between individual and group interests, shapes much of intergroup behavior, including prejudice, discrimination, and social change, as individuals navigate these fundamental dynamics (Hornsey, 2008).

Dialectical Behavior Therapy (DBT): Developed by psychologist Marsha M. Linehan in the late 1980s, Dialectical Behavior Therapy (DBT) is a comprehensive psychological treatment approach that integrates cognitive-behavioral therapy with dialectical thinking from Eastern philosophy. It is particularly effective for patients with borderline personality disorder and other severe psychological conditions (Linehan, 1993).

The core principle of DBT involves achieving a dialectical balance between accepting reality and effecting change. It guides patients to acknowledge their feelings and experiences while enhancing their ability to modify maladaptive behaviors. Throughout the treatment process, patients learn dialectical thinking skills, including concepts such as dialectical abstraction, which involves understanding the complexity of situations, and balancing acceptance with change. These skills aid in better emotion regulation, improving interpersonal relationships, and reducing self-harm and suicidal behaviors (Chapman, 2006).

DBT has demonstrated effectiveness in treating borderline personality and other severe psychological disorders. Its success is largely attributed to the integration of dialectical thinking into the treatment process, helping patients develop a more nuanced and balanced perspective, thereby facilitating behavioral and emotional change (Linehan, 2014).

Other forms of dialectics

Recently, various forms of dialectics have emerged that do not prioritize antagonistic properties in developing their arguments, but instead focus on practical consequences, interpretations, interconnections, and interdependencies. Among these are process dialectics, pragmatic dialectics, hermeneutic dialectics, and ecological dialectics.

Process dialectics emphasizes the dynamic and evolving nature of reality, suggesting that understanding arises through the interplay of different processes rather than static oppositions. A. N. Whitehead, in his work *Modes of Thought* (1938), argues for a philosophy that reflects the fluidity of experience and the importance of relationships in forming knowledge (Whitehead, 1938).

Pragmatic dialectics, as discussed by William James in *Pragmatism: A New Name for Some Old Ways of Thinking* (1901), highlights the practical implications of ideas, asserting that the truth of any concept lies in its applicability and effectiveness in addressing real-world problems (William, 1901).

Hermeneutic dialectics focuses on interpretation and understanding, emphasizing the importance of context and the historical dimensions of meaning. A. C. Thiselton, in *Hermeneutics: An Introduction* (2009), explores how interpretations can evolve through dialogue, bridging diverse perspectives and enriching understanding (Thiselton, 2009).

Ecological dialectics highlights the interdependencies within ecological systems, as articulated by Arne Naess in *Ecology, Community and Lifestyle: Outline of an Ecosophy* (1990). This approach advocates for an understanding of human behavior as fundamentally interconnected with the environment, challenging traditional dualisms between nature and society (Naess, 1990).

In this framework, conversations can unfold across a wide range of contexts and are not limited to debates over opposing viewpoints. The dialectical nature of dialogue emphasizes conflict resolution as one possible outcome, while its broader purpose lies in fostering collaboration and understanding. Instead of merely addressing opposing viewpoints, this foundational understanding of dialectics underscores its primary role as a means of communication and connection, applicable across various scenarios beyond resolving conflicts. However, it is essential that dialectics be framed within a relevant and evolving context, rather than allowing participants to “talk past one another.”

In this article, the author will propose a form of “novel” dialectics, demonstrating its utility in addressing complex issues and its potential to establish a new scientific standard. Additionally, the author will emphasize its advantages in circumventing the pitfalls of parochialism and reductionism. The method has been adopted by many disciplines partially and implicitly, thus the quotation clipping the word novel.

Methods: new disciplines—centralized dialectics and dialectic neuroscience

Because of the author’s background, this article starts with psychiatry and brain science. Nevertheless, no *prior* knowledge is required to understand the following content. It will become clear that the framework provided here can be applied to broad situations.

Take MDD as a canonical example. It is broadly acknowledged that MDD is a complex psychiatric condition, with its lifetime prevalence reaching 7 to 21% (Kessler & Bromet,

2013). The above two statements look ordinary but, in fact, disclose something unusual. They together suggest the existence of a parsimonious mechanism to explain MDD. Why? Let us have a thought experiment here: MDD has a wide array of abnormalities, comprising the domains of attention, cognition, emotion, perception, memory, reward, vegetative function, energy level, behavior, physiology, endocrine, a multitude of psychiatric symptoms, and so on, complicated enough. If the affected domains and manifestations are independent, the probability for them to simultaneously occur to affect an individual is extremely low or nearly impossible. Assume there are N observations, and the chance for each observation to occur is P_i , where $i=1$ to N . The probability P under the assumption of independence is:

$$P = P_1 \times P_2 \times P_3 \times \cdots \times P_N.$$

Even if we cannot rule out the possibility that there is a guy of terrible luck to have all the abnormalities co-occurring by chance but is still not a victim of MDD, this sporadic case will not constitute a disease in medicine with the prevalence as high as 20%. The above inference strongly indicates an underlying simplicity, which can be extrapolated to other similar complicated scenarios. Of a complex phenomenon, as demonstrated above, the contradiction between complicatedness and simplicity can never be resolved by the “thesis and antithesis” argument, and neither is true nor wrong. The two standpoints are equally reasonable and valid, just like two sides of a coin. The contradiction is, in fact, superficial and can be resolved by the new form of dialectics, which aims at dealing with complicated real-world issues. It has also been confirmed in mathematics that systems exhibiting chaos or complexity can generate infinitely diverse trajectories or dynamic behaviors, even when governed by simple underlying equations—a dualism of complexity and simplicity (Kaplan & Glass, 1995).

The new form of dialectics

Notably, all the research results and observations of MDD constitute factual statements or analyses. No one is more authentic than the other if they are derived from procedures that follow scientific or medical standards. Their relationship is neither expected to be concordant nor antagonistic. The dichotomy of thesis and antithesis is not applicable in this context of the real world. Then, how to make the “dialogue” happen between the seemingly different and irrelevant statements? Using the term MDD to bridge separate accounts is redundant and trivial, against the “evolving property” of dialectics. Figure 1 uses a jigsaw puzzle to illustrate the new form of dialectics. The peripheral pieces are the complicated facet (observations, manifestations,

statements, analyses), whereas the central missing piece is the parsimonious counterpart (synthesis). Given that MDD has been acknowledged to be a brain disorder, the ideal brain theory for MDD is a candidate of the central missing piece of the jigsaw puzzle and should perfectly fit the tortuous outline delineated by the available pieces, which represents the characteristics of MDD observed from different angles. It is evident that centralized dialectics can be applied in broad situations. Tailored centralized dialectics to solve complicated issues in brain science is called “dialectic neuroscience”.

With this helpful framework, the author proposed an “extended cortico-limbic dysregulation model” for MDD, a “dysfunctional ventral tegmental area (VTA) model” for bipolar disorder, and an “excitatory–inhibitory equilibrium theory” as a fundamental neural network mechanism to account for a versatile of neural features (Lee, 2016; Lee & Tramontano, 2021b; Lee & Xue, 2017, 2018). The processes of hypothesizing the central missing piece of MDD and the subsequent empirical verification are demonstrated in the Results section: [Deciphering MDD as an Example of Applying Dialectic Neuroscience in Psychiatry](#). It will become conceivable that all the peripheral pieces begin to relate or “talk” to each other (i.e., dialogue) through the “accounting” endeavor. In this regard, “dialectics” is fulfilled.

Criteria for the New Form of Dialectics and its relevance to the Bayesian Scheme

Three criteria are proposed to evaluate the performance of the proposed central piece. First, the theory/model should be able to explain the observed phenomenon as much as possible (comprehensiveness in accountability). Second, the theory/model should be as parsimonious as possible (parsimony). Last, biological plausibility should be fully respected (rationality). The essence of these three standards resembles the Bayesian approach to model selection, where the posterior probability is influenced by the chosen model (for instance, selected network mechanisms for MDD as an example; rationality) and the explained observations (comprehensiveness in accountability), while penalizing for the number of mechanisms selected (parsimony). Use a mathematical formula to describe the concept as follows. Assume M_i is model i in the possible model set M (possible central missing pieces), composed of $\{M_1, M_2, M_3 \dots\}$. O_j is observation j in the observation set O (selected peripheral pieces), composed of $\{O_1, O_2, O_3 \dots\}$. The posterior probability of selecting M_i given the set O can be expressed as:

$$P(M_i|O) = P(O|M_i) \cdot \frac{P(M_i)}{P(O)}$$

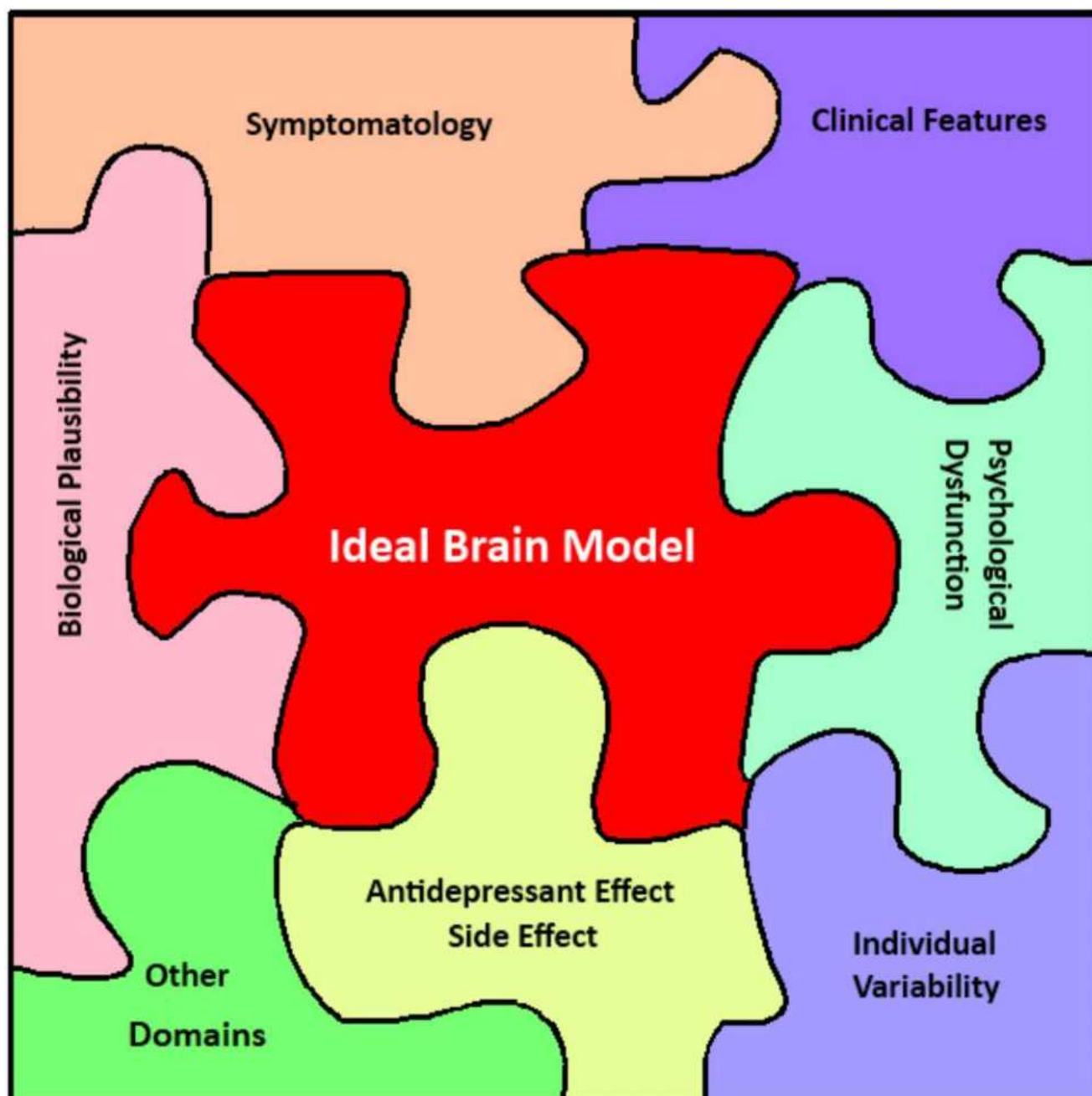


Fig. 1 Using a jigsaw puzzle to illustrate the ideal brain theory that accounts for major psychiatric disorders. The central piece represents the candidate brain model (synthesis) that fits well within the tortuous outline formed by observations from different perspectives (analyses)

where $P(O)$ is a normalization term. It is evident that $P(M_i|O)$ is proportional to the probability of $P(O|M_i)$ and $P(M_i)$, the former is the accountability of M_i , and the latter is the rationality (prior) of M_i . It is notable that these three criteria are not arbitrary but correspond to the key components of the Bayesian framework, aiming to translate mathematical formulas into non-mathematical contexts effectively. The realization will be elaborated on in

the Discussion section: [Analysis–Synthesis Formulation in Non-Mathematical Situations](#).

Centralized dialectics as a continuous process and some technical considerations

As illustrated above, the dialogue between the seemingly irrelevant observations/statements that different research groups or authors declared were bridged by the process of

finding out a proper central missing piece to account for them all together, making the jigsaw puzzle picture holistic. It is important to note that the proposed synthesis may lead to novel prediction(s) that can be verified or rejected by further analytic experiments. In other words, the dialectics may keep on progressing. The previous synthesis may establish the foundation for the analyses for the next round. Figure 2 illustrates the contrast between conventional and novel dialectics and how they progress.

Although dialectic neuroscience holds promise for advancing our understanding of scientific issues, liberal abuse of non-linear thinking may harm academic integrity. To address this concern and ensure rigorous (neuro)scientific standards, a simple heuristic is proposed: the number of explained observations of different (independent) orientations by the synthesis should be no less than 5. In modern research, confidence is often assured by a P -value < 0.05 , meaning the probability of the discovery being due to chance (null hypothesis) is less than 0.05. According to Fisher's combined probability test (a meta-analysis), the likelihood of all 5 observations being contemporaneously valid by chance in a single study is approximately 0.001 ($\chi^2 = 29.96$, $d.f. = 10$) (Fisher, 1925). Robust statistics are necessary for a synthesis because the criteria of parsimony and the synthesis itself imply that the seemingly independent observations can be bridged by the synthetic product; thus, in actuality, the observations are not completely independent. Namely, $P(O1, O2, \dots, O5|M)$ shall be larger than $P(O1|M) \times P(O2|M) \times \dots \times P(O5|M)$. To

evaluate the effectiveness of the synthesis, an arbitrary scale is proposed to assess the performance of a synthetic model: 1–2 explained observations is poor, 3–4 is fair, 5–7 is good, 8–10 is very good, and > 10 is excellent.

The above conceptual frame is general in nature, not limited to the field of neuroscience, and can be extended to cope with other complicated issues. The Results section will provide examples from “soft” and “hard” sciences using the proposed dialectics. In opposition to the trend of de-centralization in the fields of finance, cryptocurrency, supply chain, social media, internet content distribution, and so on, the purpose of finding the central missing piece is to identify the hidden key component or mechanism with the potential to bridge the dazzling complicated phenomenon, thus named “centralized dialectics” when used in philosophy. Like other theories or formulations, the validity of centralized dialectics is context dependent. We cannot exclude the possibility that there is something super-complicated but scarce in this universe, in which centralized dialectics may not be applicable. Its power is most prominent in the situation of complicated phenomena with inferred parsimonious underlying mechanism(s).

Centralized dialectics as a methodology to overcome cognitive reductionism and parochialism

The human tendency to decompose the whole into parts and use partial features to represent the whole stems from our categorical mode of cognition (Smith & Medin, 1981).

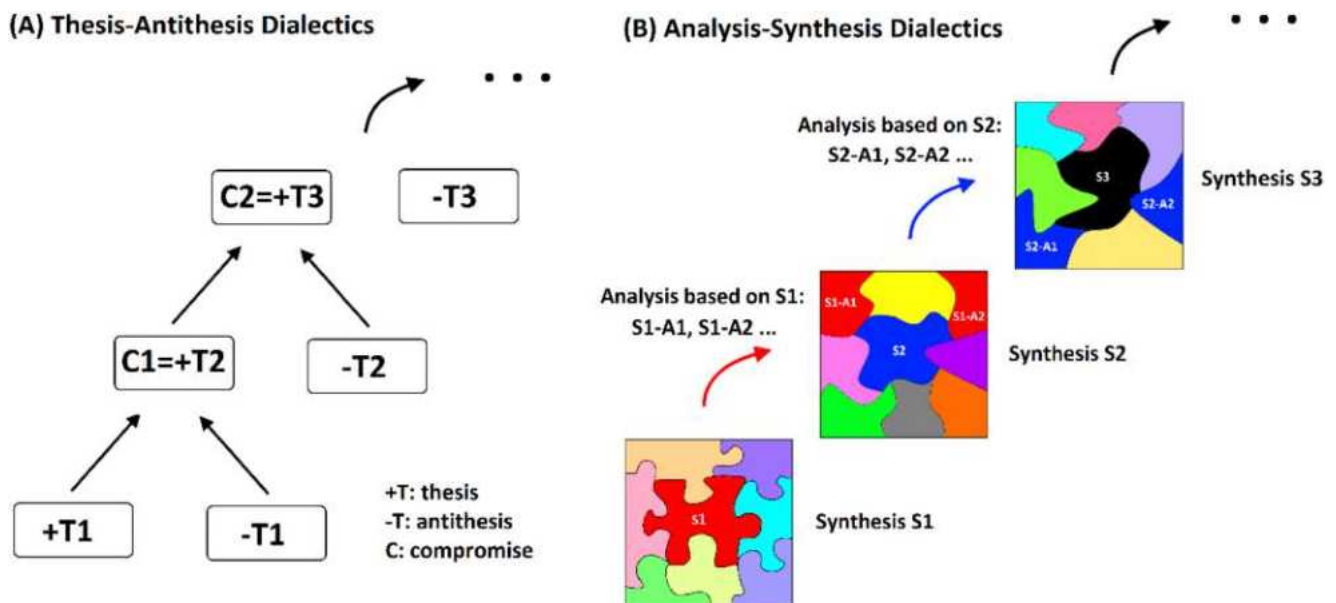


Fig. 2 Contrasting two types of dialectics. The left panel depicts dialectics based on thesis ($T1, T2, T3, \dots$), antithesis ($-T1, -T2, -T3$), and their resultant compromise/synthesis ($C1, C2, \dots$). The right panel shows dialectics grounded in analyses ($A1, A2, \dots$) and synthesis ($S1, S2, S3, \dots$). A jigsaw puzzle represents the ideal theory or mechanism

underlying complex issues. In psychiatry study, the central piece symbolizes the candidate brain model (synthesis), which aligns with the convoluted outline formed by observations (analyses) from multiple perspectives. Abbreviations: T =thesis, $-T$ =antithesis, C =compromise/synthesis of T and $-T$, A =analysis, S =synthesis

For example, Eleanor Rosch's Prototype Theory posits that human cognition is inclined to group objects into distinct classifications, with prototypes serving as the most typical representatives of each group (Rosch, 1978). Prototype Theory elucidates how humans efficiently simplify complex realities into manageable concepts: we identify objects based on their similarity to the prototype, forming dichotomous distinctions such as bright vs. dark, edible vs. toxic, friend vs. foe, sheltered vs. exposed, and predator vs. prey. This strategy aids us in rapidly processing information and making judgments and decisions, which are crucial for survival (Margolis & Laurence, 1999). However, reality is not always reducible or categorizable but often multi-dimensional and exists on a spectrum, with many overlapping and interacting factors. The human tendency to simplify and dichotomize can lead to misinterpretations, oversights, and stereotypical impressions (Allport et al., 1954; Gelman & Rhodes, 2012). Moreover, categorical perception is often influenced by personal experiences, cultural backgrounds, and preconceived notions, leading to systematic biases (Goldstone, 1994). Reductionism inevitably parallels parochialism.

The limitations of human categorical perception manifest themselves in various domains, raising significant concerns. In the realm of social cognition, for instance, stereotyping is a byproduct of this tendency. By reducing individuals to category-based representations, we risk misunderstanding and misjudging others. In decision-making, over-reliance on categorical thinking can result in inappropriate judgments and suboptimal outcomes, especially in complex, multifaceted situations where a more nuanced approach is required. Recognizing these cognitive limitations and taking remedial measures is crucial. Enhancing our metacognitive abilities, acknowledging the strengths and weaknesses of categorical cognition, and adopting strategies such as considering multiple perspectives, maintaining an open mindset, and respecting individual differences can mitigate cognitive biases and

lead to a more comprehensive and objective understanding of reality (Nisbett et al., 2001). By considering the analytics facts, centralized dialectics is one of the many endeavors to supplement efficient but reductive cognitive processes. How does the holistic approach avoid the notorious reductionism and parochialism? Fig. 3 illustrates its merits and power. The left subplot shows that the central missing piece alone is meaningless. The central piece is not informative unless it relates to the peripherals, or they have each other. This way, centralized dialectics is not a reductionism. The middle subplot demonstrates that the central missing piece is not determined or deducted by any peripherals, thus not parochialism. The right subplot presents the holistic picture, reminding us that every peripheral (analysis) contributes to the totality. Different syntheses of the same topic can be compared by the model selection scheme, e.g., Bayesian information criterion (*BIC*) (Schwarz, 1978). *BIC* considers the likelihood $P(O|M)$ (where L represents the likelihood of the observed data given the model), the number of model parameters k , and the sample size n , and is calculated by the equation:

$$BIC = \log(n) \times k - 2 \times \log(L).$$

Again, take psychiatric illness as an example. To confront the enigma of psychiatry, an integrative approach and a holistic attitude are warranted, and the author pertains it to the issue of "totality" in neuroscience. The "totality" here resonates with that of philosopher György Lukács (not the totality of Hegelianism) (Jay, 1977). According to Lukács, a comprehensive understanding of society and its phenomena can only be achieved by grasping totality—the interconnect-edness and interdependence of social, historical, cultural, economic, and material conditions. The holistic approach views society as a dynamic whole, with interrelationships between different aspects. The parts are not isolated entities but dialectically related and mutually constitutive, forming



Fig. 3 Use jigsaw puzzles to illustrate why centralized dialectics may avoid reductionism and parochialism

a complex system that requires a multidimensional appreciation—the whole is not merely the sum of the parts. This spirit is highly concordant with the motivation of centralized dialectics.

Based on the Bayesian framework, the most appropriate models to explain a society's phenomenon can be identified by maximizing the posterior probability $P(M1, M2, \dots, Mq|O)$, where q represents the number of models, such as culture, economics, and social aspects. In contrast to the synthesis that the author employed to investigate MDD with model number only 1, Lukács' insights emphasized a multi-model scenario in which the interaction of selected models must be considered. In such cases, the missing central pieces (plural) are the targets to treat by the applied dialectics. When the models are inter-related, the probability of $P(M1, M2, \dots, Mq)$ is not equal to $P(M1) \times P(M2) \times \dots \times P(Mq)$.

We cannot do much to correct what we are, shaped by evolution for a long time; however, we may try to suspend the attitude/dogma of reductionism and dichotomy and attempt to facilitate dialectic between multiple perspectives and the seemingly irrelevant or even opposite. Following its original definition, "dialectic" is a discourse between two or more different viewpoints (not necessarily contradictory) about a subject, aiming to establish the truth or consensus through reasoned arguments. By way of the dialectic process, the dialogue may occur within different analytic disciplines or between analytic and synthetic facts. Notably, it is the active role of synthetic endeavor that forces the dialogue to happen and the consensus to reach.

Results: centralized dialectics for complex problem-solving

An integrative attitude has already infiltrated different circles. The synthetic approach is generally applied when there is no choice, despite its great power in providing insight. Instead of slanting toward any piece of analytic evidence, it is encouraged to be more synthetic to facilitate the dialectics to occur. Here are a few examples.

(1) Archeology and anthropology: Archeologists and anthropologists always take the synthetic attitude to integrate relics, literature, ecofact, landscape, and architect together to reconstruct history and to build up theory. It is a good example of how analytic and synthetic methods work in synergy. Archeology/anthropology cannot help but be synthetic because its target is all about the past. The discipline is established by the dialectic process between analytic and synthetic endeavors, in the absence of a time machine or time tunnel.

- (2) Ancient history reconstruction: Similar to (1) historians deduce what occurred (synthesis) by examining fragmented literature records and excavated material evidence (analyses) from ancient periods. It's another example of analysis–synthesis process.
- (3) Forensics: The forensic officers collected and analyzed the evidence and micro-evidence. However, only a synthetic attitude may integrate all the pieces of information together to reconstruct what could happen at the crime scene and who the suspect is.
- (4) Cosmology: The origin of the cosmos is a hot topic in physics. Even though it might have happened 13.8 billion years ago, the Big Bang theory was raised based on the observation of redshift that was correlated with distance. The dialectic process has repeated itself several times to sophisticate and perfect the Big Bang theory. The validity lies in its plausibility (based on physics laws) and ample accountability (abundance of light elements, the radial velocity of extra-galactic nebulae, cosmic microwave background, redshift, and so on), similar to the framework suggested in this article. The spirit behind the achievement is synthetic, not purely analytic. Analysis–synthesis has been adopted broadly and implicitly in modern physics. More examples will be given in the next session.
- (5) Empirical neuroscience: In empirical neuroscience, synthetic attitude is still not broadly accepted. Francis Crick, who discovered DNA structure with James Watson, had made interesting attempts to solve complicated issues in neuroscience that adopted a similar attitude to centralized dialectics. In *The Astonishing Hypothesis*, he summarized the prerequisites of conscious experience (analytic) and then tried to synthesize them under a unified framework (synthetic) (Crick, 1984). A core property of our attention system is to suppress distractors and magnify target information simultaneously. In a research paper, he analyzed the features of the search-light hypothesis of attention (analytic) and tried to discover the neural correlates that may simultaneously satisfy the two constraints (synthetic)—excitatory for target and inhibitory for non-target (Crick, 1984). No matter whether the drawn conclusion is correct or not, the taste of combined analytic and synthetic orientation is evident in his presentation, resembling the formula recommended in this article. It is interesting to note that Crick majored in physics in college. That might explain why he naturally applied the implicitly accepted analytic/synthetic hybrid in (modern) physics to empirical neuroscience. Desimone and Duncan's competition resolution attention theory also embodies the taste of synthesis, aimed at reconciling diverse analytical facts (Desimone & Duncan, 1995).

- (6) Computational neuroscience: Computational neuroscientists often examine the validity of their models through synthetic interrogation. For example, a remarkable feature of alpha oscillation is its spontaneous bursts at low- and high-amplitude, called bi-stability. A computation model of EEG that may reproduce the bi-stability at the alpha spectrum is appreciated and is regarded as more convincing than those that cannot (Freyer et al., 2011). The condition(s) pending to be satisfied are based on analytic results (obtained from various sources), and the model that may explain all the requirements well is the result of a synthetic attempt.

Examples of applying the analysis–synthesis Approach in Modern Physics

Among all the scientific disciplines, modern physics (recognized as hard science) has most often applied centralized dialectics, even though physicists themselves may not be aware of it when they propose new theories. It may be because physics is one of the few disciplines that still holds an attitude and ambition to unify and integrate the knowledge of the material world, reflected in the grand unified theory or electroweak unification theory. Here are some classic examples to illustrate how the analysis–synthesis approach was heavily exploited to advance modern physics.

- (1) The theory of general relativity: While Isaac Newton's theory of gravity successfully explained the motion of celestial bodies, it could not account for gravitational lensing, where the gravitational field of a massive object, such as a star, bends the path of nearby light rays. Albert Einstein's theory of general relativity not only refined Newton's theory but also explained gravitational lensing, showing that gravitational effects arise from the curvature of spacetime. In this example, the analytic facts are Newton's theory of gravity and the phenomenon of gravitational lensing, whereas the synthetic result is the theory of general relativity. It demonstrates the process of dialectical synthesis, where the integration of the old theory with new observations creates a novel theory capable of explaining a broader range of phenomena and offering a more comprehensive understanding of the underlying physical laws. The following examples will focus on analytic facts and synthetic efforts, without elaborating on the detailed physics principles.
- (2) Quantum mechanics: In the early 1900s, scientists attempted to understand the fundamental nature of light. They discovered that light exhibited both wave and particle properties, which contradicted the classical physics theories of the time (analyses). To resolve this contradiction, physicists like Max Planck and Niels Bohr proposed revolutionary ideas that unified the wave and particle characteristics of light (synthesis), laying the foundation for quantum mechanics.
- (3) The discovery of the Higgs boson: For a long time, physicists had been working on the Standard Model, which explained the fundamental particles and forces in the universe (analyses). However, a major limitation of the Standard Model was its inability to explain the origin of particle masses. Through the observation of Cooper pairs in the superconducting state, it was discovered that photons could acquire mass, leading to the suppression of their emission and the conservation of energy (analyses). In the 1960s, physicist Peter Higgs proposed a new theory that hypothesized the existence of a particle, now known as the Higgs boson, which was responsible for giving other particles their masses (synthesis). This theory, known as the Higgs mechanism, was eventually confirmed in 2012 with the discovery of the Higgs boson at CERN's Large Hadron Collider.
- (4) The theory of special relativity: In the late 19th century, physicists formulated the theory of electromagnetism, which elucidated the properties of electric and magnetic fields (analyses). However, this theory was inconsistent with the laws of classical mechanics, which were based on Newton's laws of motion and were valid only for objects moving at low velocities, not at speeds approaching light (analyses). In 1905, Albert Einstein proposed the theory of special relativity, which reconciled the apparent inconsistencies between electromagnetism and classical mechanics. Einstein's theory demonstrated that space and time were not absolute, but rather relative to the observer's frame of reference (synthesis). The theory of special relativity successfully synthesized the laws of electromagnetism with the laws of motion, leading to a more comprehensive and unified understanding of the underlying physical laws governing the behavior of objects moving at high velocities.
- (5) Prediction of neutrinos: Early experiments on beta radioactive decay observed that energy and angular momentum did not appear to be conserved (analyses). Physicists at the time were reluctant to postulate the existence of a new particle to explain this phenomenon. To resolve this issue, Wolfgang Pauli hypothesized the existence of neutrinos, suggesting that in the process of beta decay, an electrically neutral and nearly massless particle, called the neutrino, is emitted along with the beta particle (synthesis). According to Pauli's neutrino hypothesis, these neutrinos carry away a portion of the energy and angular momentum, thereby ensuring the conservation in the beta decay process (synthetic explanation).

- (6) Theory of quantum turbulence: In the past, quantum mechanics failed to account for the peculiar behavior of liquid helium when subjected to low temperatures. As per classical statistical mechanics, the liquid was assumed to solidify and lose its ability to flow when the temperature approached absolute zero (analyses). However, experiments showed that liquid helium exhibited an exceptional phenomenon known as superfluidity and could still flow at extremely low temperatures (analysis). Theoretical physicists reconciled the contradiction by introducing the concept of quantum turbulence. As per this theory, superfluidity occurs due to microscopic turbulent motions in liquid helium induced by quantum effects (synthesis). This microscopic turbulence disturbs the ordered lattice structure, facilitating the liquid to flow smoothly without solidifying.

Deciphering MDD as an example of applying Dialectic Neuroscience in Psychiatry

The author tentatively listed 15 cardinal features of MDD and proposed that imbalance between frontoparietal and limbic networks through reciprocal suppression mechanism (RSM) was an ideal brain theory to account for the selected features (Lee, 2016; Lee & Xue, 2018). The theory can also explain other observations that are not specific to MDD. RSM is well-documented (rationality), and the explanatory power was demonstrated (accountability). In addition, since only one neuropathology mechanism was chosen to account for MDD, the parsimony criterion was assured. Compared with traditional analogs, the above dialectics move away from the “thesis–antithesis–synthesis” to “analyses–synthesis”, in which the analyses arm was obtained from various research reports that applied analytic scientific methods. No contradiction exists between them.

Building on the synthesis, the next step is to empirically explore the new theoretical hypothesis through appropriate experimental designs. The development of novel methodologies may be warranted at this stage. Taking MDD as an example again: to substantiate the analysis of the proposed RSM mechanism, the author invented a novel cortical parcellation scheme to enable investigating compartment-level interactions (frontoparietal and limbic compartments) (Lee & Tramontano, 2021a). In addition, the author identified a negative relationship between nodal degree (in graph theory) and nodal power, providing an opportunity to explore how large-scale functional connectivity may suppress regional power (Lee & Tramontano, 2024). Using the two novel methods, the author’s recent research demonstrated that MDD’s functional organization in the limbic system is deviated. Moreover, MDD neuropathology is characterized by more efficient limbic-to-frontoparietal suppression and less

efficient frontoparietal-to-limbic suppression, effectively validating the output theory derived from applying dialectic neuroscience formulation to MDD (Lee, 2024), thus completing a full cycle. Notably, synthesis is not the endpoint of scientific exploration; instead, it leads to empirical verification as illustrated above and perhaps another cycle of adventure (see Fig. 2). Continuing the previous example of MDD, verifying aberrant RSM in MDD may encourage researchers to investigate critical follow-up questions: Based on the compartment-level imbalance, compensatory neural changes and re-organization are anticipated. Could these subsequent neural changes explain the heterogeneity in symptomatology and the subtypes of MDD, or contribute to differential treatment responses? These interesting issues will inspire the next phase of analytic or dialectic neuroscience research and highlight a more constructive approach for neuroscientists to collaborate with experts from computational or engineering backgrounds (see the critique in Discussion). With the above presentation and working example, the author proposes that: following the centralized dialectics and recommended forms inferred from the Bayesian scheme (three criteria), the synthetic procedure and output are assured to be falsifiable and scientific.

Discussion

The underlying cognition in discovering the missing central piece

Human beings share the same fundamental cognitive capabilities. After observing the positive impact of well-executed syntheses from the above examples, it’s natural to consider the mental process that supports these achievements from a meta-cognitive perspective. What is the essence of this capability? Does the cognition endorsing the synthesis endeavor belong exclusively to a minority of people, or to the general population?

The cognition enabling the synthesis endeavor is clearly related to problem-solving through non-linear thinking. In contrast to linear induction or deduction, non-linear thinking emphasizes holistic, interconnected, and multidimensional perspectives in understanding and solving complex problems (De Bono, 2016; De Bono & Zimbalist, 2010). The key characteristics of creative thought process are summarized below:

- (1) Holistic perspective: Approach problems as interconnected wholes rather than isolated parts, aiming to understand the broader context and relationships between various elements (De Bono, 2016; Guilford, 1967).

- (2) Divergent thinking: Non-linear thinking encourages exploring multiple possibilities, making unexpected connections, and generating diverse ideas, instead of following a single path (Sternberg, 1999).
- (3) Flexibility and adaptability: Non-linear thinkers are open to changing their perspectives and approaches based on new information or insights, adapting fluidly to dynamic situations (Treffinger et al., 2023).
- (4) Intuition and creativity: Non-linear thinking relies on intuitive leaps, creative insights, and unconventional associations, going beyond purely logical deductions (Pétervári et al., 2016; Policastro, 1995).

Centralized dialectics align well with all the core features of non-linear/creative thinking. Neuropsychologists have traditionally relied on sophisticatedly designed tests as surrogates to explore different mental constructs. It is notable that these tests are not equivalent to the investigated mental constructs per se but serve as probes. For example, the Wisconsin Card Sorting Test and Stroop Task have been applied to investigate the capabilities of working memory and executive control. However, those two tasks do not fully represent the targeted mental constructs. This limitation is particularly true for creative conceptualization, especially in the endeavor to achieve centralized dialectics. Compared with Duncker's candle problem (e.g., participants are asked to attach a candle to a wall using only a box of thumbtacks and matches), which measures the impact of functional fixedness on problem-solving, it is clear that similar paradigms are inadequate for describing synthesis, as synthesis is not merely a combination of analyses (Weisberg & Suls, 1973). It is imperative to note that synthesis is not simply a mix or amalgam of analyses but frequently requires "qualitative leap", which may be accompanied with enlightening joy at the moment of breakthrough. In a spring morning of 1907, while sitting in his office in Bern, a thought "startled" Einstein that helped work through the mystery of why inertial mass and gravitational mass are equivalent. Einstein called it "the happiest thought of my life" (Peacock, 2017). In contrast to whimsical fantasy, sound and scientific synthesis relies on solid analyses, which require establishing an understanding beforehand. The preparatory step distinguishes itself from abductive reasoning (Walton, 2014), which typically begins with an incomplete set of observations and proceeds to the likeliest possible explanation for the set, although both requires the engagement of non-linear or creative thought process. In addition, the duration for a synthesis to come out may take days, months, or even years, depending on how challenging the faced issue is.

The outcome of centralized dialectics may represent local or global optima

Borrowing the concepts of local and global optima from the engineering field, the author proposes an analogy to describe another feature of the cognition underlying synthesis, or more broadly, non-linear cognition (see Fig. 4). Synthesis is the method to find a solution or model (i.e., model selection in Bayesian) that reaches a local or global optimum for complex issues. Achieving a global optimum may require several rounds of analyses–syntheses (see Fig. 2). Additionally, synthesis or non-linear cognition may require the participation of subconscious or unconscious computation to aid the problem-solving process—another feature not covered by routine neuropsychological evaluations where subjects need to be fully awake and attentive (Kihlstrom, 1987; Shapiro, 1991). Non-linear reasoning for difficult issues may occur when the synthesizer is engaged in other unrelated tasks or may even progress and reach optimum in dreams. Two examples are provided below.

A Russian chemist, Dmitri Mendeleev constructed the constitution of chemistry—the periodic table of chemical elements, which had puzzled researchers in his era for a long time. How did he solve the mystery? He said: "I saw in a dream a table where all elements fell into place as required. Awakening, I immediately wrote it down on a piece of paper, only in one place did a correction later seem necessary." Based on massive analytic facts of different chemical elements, Mendeleev attempted to organize them into one unified framework. The enlightenment in his dream was typical creative thinking, and his attitude was clearly synthetic.

Similarly, Otto Loewi had an inspiring dream in which he designed an elegant and influential physiology experiment, proving that neural transmission to the heart was chemical, not electrical. It was interesting to note that he forgot the dream the second day and could not recognize his scribbles. Fortunately, he had the same dream the second night. Needless to say, his discovery benefited from non-linear thinking. In his Nobel Prize speech, he said: "It was the design of an experiment to determine whether or not the hypothesis of chemical transmission that I had uttered 17 years ago was correct". Synthesis is not an instant response but usually takes time to brew or breed—much like challenging engineering problems, which often require numerous iterations and extended duration to achieve convergent solution.

In earlier examples in archaeology, forensics, and historical reconstruction, centralized dialectics or synthesis has been observed in diverse contexts. Synthesis is also evident in daily life. For instance, in today's era of "entertainment media," detective stories are prevalent. Deciphering such narratives before the resolution is an active synthetic

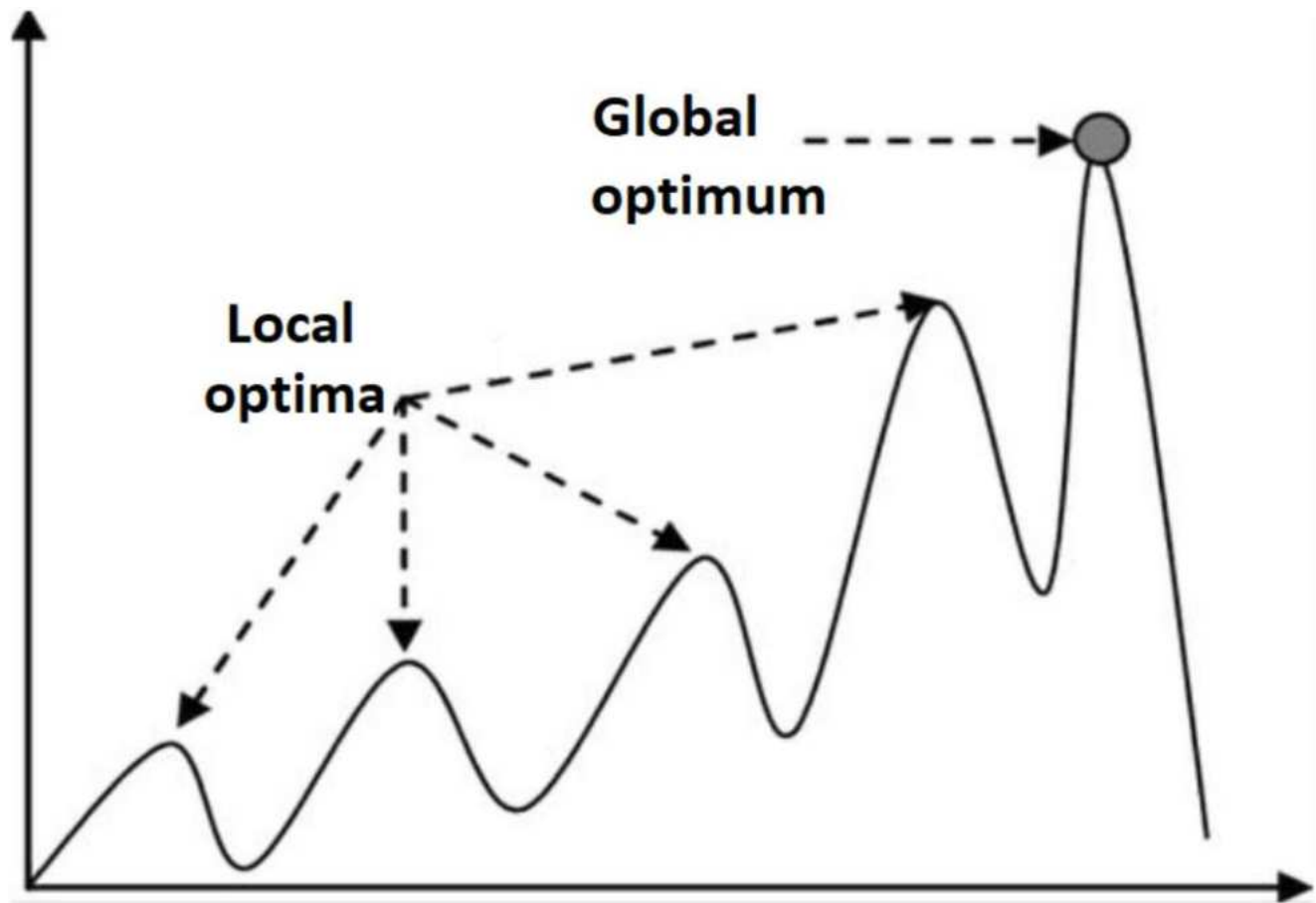


Fig. 4 Use global optimum and local optima to illustrate the cognition behind finding out the central missing piece

process, integrating previously revealed evidence (analyses). Appreciating the story after its ending involves synthesizing the elements into a coherent whole, including the protagonist's role. Therefore, the author posits that centralized dialectics or synthesis, akin to analyses, is a general cognitive capability inherent in everyone. Proficiency in utilizing these skills varies among individuals. When facing complex issues, it is beneficial to step back, thoroughly assess information, prioritize essential features, set aside trivial or unreliable elements, avoid premature conclusions, and maintain an active mindset to develop a parsimonious explanation with high accountability and rationality. Both analytical (linear thinking) and synthetic (creative or non-linear) abilities are fundamental human talents (De Bono & Zimbalist, 2010; Lee, 2016). There appears to be no justification for prohibiting the application of centralized dialectics to neuroscience or other disciplines.

The potential of centralized dialectics to shape scientific standards

Does the synthetic/integrative approach have the potential to be extended to a scientific standard? The answer is yes. Complicated diseases are characterized by complex manifestations, which is valid for nearly every psychiatric disorder. A big problem that arises naturally is how to integrate all the heterogeneous pieces of evidence instead of just leaving them scattered and disjointed. In this article, MDD serves as a workbench to demonstrate the spirit and endeavor. The author concluded that a cortico-limbic compartment imbalance model equipped with RSM, and compensatory network mechanisms can explain a substantial portion of phenomena in MDD. This approach sharply contrasts previous research orientation and fits with three criteria of parsimony, plausibility, and comprehensive accountability. It is not that conventional research never tries to integrate diverse evidence of MDD but that their direction is largely wrong. How did previous researchers fulfill the integrative attempt? They frequently start from parochialism and then are trapped in circular reasoning. For illustrative purposes, the author

tentatively simplifies MDD to the problems of attention, emotion, and cognition. Scholars specializing in attention research may develop their MDD theory based on attention bias and deficit. They reasoned from attention problems to “deduce” the subsequent impact on cognition and emotion and to explain the cognition and emotion defects in MDD. However, scholars in the field of cognition may also develop their MDD theory based on the cognitive style of depression and “deduce” the cognitive impact on attention and emotion to explain the attention and emotion defects in MDD. A similar story happens to the researchers in the emotion field, and so on. We can never claim which one is better. Taken together, they are just circular reasoning. Their integrative endeavor is superficial, innately analytical, and based on a false assumption that one discipline precedes/underlies the other. Superficial integration is a false integration and is constructed by inappropriate serial connections.

When referring to “analytical” and “synthetic” in this article, they do not mean anything relevant to analytic philosophy (e.g., Ludwig Wittgenstein, which focuses on the analysis of language, logic, and the structure of philosophical problems) or synthetic philosophy (e.g., Herbert Spencer, who proposed a comprehensive, evolutionary framework integrating knowledge from various scientific disciplines). Instead, “analytical” refers to the process of breaking down complex phenomena into components, while “synthetic” refers to the integration of these components to form a cohesive whole. The analytic-synthetic distinction does not follow Kant’s philosophy, either (Kant et al., 1999). Instead, the standpoint is positivism and pragmatism, and the methodology is conceptually straightforward and statistical, i.e., scientific, rather than philosophical. Assume that there is a sound synthesis that may account for ten observations of a complicated issue; each is endorsed by independent scientific research with a P value < 0.05 . How confident is the synthesizer about the synthetic result? It could be as high as a P value $< 0.05^{10}$. In other words, even if the deduction is weaved by statements rather than mathematical derivation, strictness is promised.

In contrast to parochialism disapproved and linear deduction questioned above, it would be more suitable to regard the integrative/synthetic approach as mobilizing different sets of cognitive strategies/styles/modes for complicated problem solving, with a flavor of non-linear conceptualization. Analytic strategies tend to separate a whole into its constituents to study the elements and their relations, and linear thinking follows a step-by-step progression. It is not that linear or analytic thinking or logic/syllogism is not essential, but that creativity and enlightenment sometimes could be more critical to cope with complicated issues. In the history of science, it is not uncommon that non-linear intervention brings about true breakthroughs. Fragmented

evidence in life sciences presents a real challenge. The explosive expansion of text (a feature in today’s academia) sometimes adds to ambiguity and confusion. The integration effort has been inadequate, and the main hurdle could be a lack of theoretically sound formulation to apply or follow in addressing complicated issues.

With dialectic neuroscience, a testable hypothesis can be generated and examined, for example, by quantifying the magnitude of network imbalance of MDD and comparing that with controls—the process conforms perfectly to extant scientific research standards. As illustrated in the [Results](#) section, if synthetic endeavor has facilitated tremendous success in modern physics, there is no reason to prohibit it from being applied in other disciplines. Unlike modern physics, however, syntheses for most fields, like psychiatry, cannot be calculated according to well-established formulae or physics rules. It is imperative to note that the risk of abusing centralized dialectics cannot be overlooked. Synthesis is not anything arbitrary or fantastical. Sound synthesis requires a profound understanding of the treated subjects. For the disciplines without concise mathematical underpinnings, following recommended formulation is mandatory to ensure its thoroughness; see next session.

Analysis–synthesis formulation in non-mathematical situations

Even though the synthetic approach has been popular in modern physics, it is yet to be recognized by life science disciplines. Physics has a natural and adorable inclination to integrate knowledge of the material world, which starkly contrasts with other fields that tend to leave the evidence/knowledge from various angles dispersed around. Synthetic attitudes and centralized dialects have been adopted in physics but have yet to be stated explicitly. Furthermore, physics heavily depends on mathematical principles to formulate ideas and comprehend the topics under study. To illustrate, special relativity can be expressed through a mathematical formula, while the concept of asymptotic freedom can be derived from the Yang-Mills gauge field theory. A new proposition can be substantiated by incorporating novel mathematical elements (theoretical physics). The properties of predicted particles can be computed by measurement and derivation (experimental physics). Mathematics assures the strictness of the synthetic approach in physics.

For the field of life science, even though mathematics does not play a similarly critical role, there is no justification to prevent the use of centralized dialectics to further its progress. As inferred earlier, if the criteria of rationality, comprehensiveness in accountability, and parsimony were satisfied, the formulation would be equivalent to the Bayesian framework, and statistics would endorse the synthetic

results. The following formulation is strongly encouraged to follow so that different parties may share similar workflows and standards to evaluate the quality of the synthesis. Take the format of academic publications as an example (an academic paper is generally composed of four sections: Instruction, Methods, Results, and Discussion). There are two recommended parts in the sections of **Methods** and **Results** each:

In the **Methods** section, part I summarizes the main analytic results related to the target illness (or issue), and part II lists the cardinal features that the synthetic endeavor attempts to integrate (the peripheral pieces of the jigsaw puzzle). In the **Results** section, part I proposes the synthetic result (the central piece of the jigsaw puzzle), which is expected to be simple (parsimony) and biologically plausible (rationality), and part II explains how the synthetic product may account for the features described in part II of the **Methods** in a one-to-one correspondence (accountability).

Take the MDD case as an illustrative example, where the aberrance in the RSM between the outer cortex and the limbic system was identified as the central missing piece (the synthetic product) to account for the pathology of MDD (Lee & Xue, 2018):

Methods—Part I: Analytic results. This section aims to summarize “pertinent” analytic results, which provide the material for **Result**—Part II, including: (1) frontoparietal abnormalities in MDD, (2) limbic abnormalities in MDD, and (3) neurophysiological understanding and fact.

Methods—Part II: Cardinal features. This section aims to summarize the key features of the targeted complicated issue, forming the peripheral pieces of the jigsaw puzzle, including 15 paramount and non-overlapping analytic facts (from empirical studies) that were expected to be relatively specific to the treated subject MDD. Based on these facts, the synthesizer needs to employ non-linear/creative thinking to identify the central missing piece.

Results—Part I: Synthetic result(s). This section aims to present the synthetic output, where the synthesizer needs to demonstrate its biological plausibility while keeping the number of synthetic outputs to a minimum. In the MDD example, the RSM is the sole proposed mechanism (central piece), ensuring the criterion of parsimony. RSM itself is supported by abundant research, ranging from emotion regulation to neuromodulation studies, indicating a mutual suppressive mechanism between the frontoparietal network and the limbic system, satisfying the criterion of rationality.

Results—Part II: Exposition of accountability. This section aims to explain how the synthetic product accounts for the features described in Part II of the Methods in

a one-to-one correspondence (accountability; using the material provided in **Methods**—Part I). It is recommended to provide a summary table depicting how each peripheral piece is accounted for by the central piece (see Table 2 in Lee & Xue, 2018). As explained before, since the synthesis is supported by non-linear and creative thinking, the investigators should not be expected to disclose the process of reaching the synthesis. The breakthrough or enlightening moment after prolonged brooding remains a mystery. Detailed induction, inference, reasoning, and supplementary explanations will constitute the main content of the **Discussion**.

In summary, centralized dialectics is within everyone’s cognitive grasp, yet its potential to advance science has never been recognized. Centralized dialectics has been widely employed in modern physics and exemplified in MDD above, verifying its potential to evolve into a novel scientific standard. This evolution can occur through the endorsement of mathematical derivation (modern physics) or by following the forms demonstrated in this study (equivalent to the practical realization of the conceptual Bayesian scheme). Such a framework may channel creative and non-linear thinking into a structure that ensures its meticulousness, and hence scientific. Synthetic endeavors derived from centralized dialectics and regulated by “forms” that meet the three Bayesian criteria are expected to contribute to a wide range of scientific disciplines.

Critique on the Trend of relying on machine learning in modern-day neuroscience

There has been a trend of using machine learning to explore neuroimaging data from psychiatric populations without a proper hypothesis. The implicit assumption is that since psychiatric disorders are too complicated and the multi-dimensional information is beyond human cognition, we cannot help leaving these difficult issues to computers and (applied) mathematics. At first glance, it seems to be a compelled decision. The scientists sit on the couch, throw data into the machine, and wait for the outputs to guide us on what psychiatric disorders are. The prevailing infiltration by the pure engineering approach raises serious concerns: Where does this approach ultimately lead brain science to? Whether this approach is qualified to be scientific?

The author would like to argue that human cognition is sophisticated enough to cope with complicated issues, as evidenced by centralized dialectics in this article, abundant psychological research, and, undeniably, civilization. Referring to Fig. 4, human cognition can attain local or global optimum after adequate incubation if the mental resource is mobilized correctly and adequately. Again, take the MDD

as an example: the outcome of dialectic neuroscience yields network imbalance as the key pathological mechanism, which has never been generated or perhaps will never be achieved by any engineering algorithms. Based on the synthetic results, a novel functional parcellation scheme was developed to investigate the properties of the brain's two major compartments and their interaction. Given this demonstration, wouldn't it be more appropriate that, based on the derived hypothesis from non-linear synthesis, the scientists invite the engineering camp to collaborate and jointly design a novel working platform (mathematical and engineering implantation) to examine or reject the network imbalance hypothesis? Doesn't this collaborative endeavor initiated by dialectic neuroscience better fit the essence and mission of science—finding out the truth? In contrast to, say, surrendering to the blind engineering computation and naively assuming that classifiers or regressors may unveil the nature of psychiatry. Even if we consider the most extreme case where the machine learning approach may reach a local or global optimum that touches psychiatric truth, it is doomed to lack “hermeneutics” of the results (accountability), and it will be like the left subplot of Fig. 3.

Confidence in human cognition is established upon understanding its uniqueness and power. Subjectivity awareness demands that humans take the lead and responsibility to understand ourselves and our world. Passively waiting for the outputs from computational machines and taking them as guidelines is a disgrace. A single person arriving at the global optimum may indicate the potential for the whole human population to reach the same highland after spreading knowledge and technology—enriching civilization. With the enlightening experience that humans are already well equipped with the talents to face complicated reality, we should be open to and love to embrace any possible advancement and challenge, such as the approaching artificial intelligence era.

Future directions and recommendations

Centralized dialectics can be applied across various disciplines and may necessitate collaborative teamwork. To facilitate its progress, borrowing the successful experience of other disciplines is recommended. Take Poincaré Conjecture's prize as an example. The Poincaré Conjecture was posed in 1904 and was selected by the Clay Mathematics Institute in 2000 as one of the seven Millennium Prize Problems. A reward of one million dollars was offered to anyone who could provide valid proof or disproof of the conjecture, which was finally solved by a Russian mathematician Grigori Perelman in 2003.

Take a psychiatric disorder as an example. Advancing dialectic neuroscience may follow similar steps:

- (1) An academic society (or private foundation) convenes a professional meeting and identifies a specific illness's cardinal features.
- (2) Post a reward that invites experts worldwide to submit their synthesis conforming to the formulation suggested in this article (section [Analysis–Synthesis Formulation in Non-Mathematical Situations](#)).
- (3) The academic society reviews the submissions quarterly or bi-annually and then determines whether there is any potential candidate. Syntheses from different candidates can be evaluated qualitatively and quantitatively (e.g., BIC).
- (4) If yes, the society calls on a methodology group to establish or develop a mathematical model, potentially a novel one, to examine the validity of the proposed synthesis using a publicly released dataset.
- (5) If the results are verified, there will be two academic papers, i.e., the synthesis and the verification papers. Other research groups are welcome to replicate the results.
- (6) The verification results may lay the foundation for providing a quantitative network diagnosis of the specific psychiatric disorder. In other words, synthesis, along with its quantification, could offer a new definition of the disorder from a brain science perspective.
- (7) If the synthesis is rejected, the cycle continues from the beginning. Academic society might need to modify its proposed features of the treated subject(s).

The above strategic framework can be extended and adapted to other disciplines to meet their specific objectives. For example, the cognitive psychology society may adopt a similar strategy to advance research on the neural mechanisms of attention and binding phenomenon. To facilitate replication and refinement, individual investigators are strongly encouraged to employ the analysis-synthesis framework and perform verification using publicly available datasets.

Conclusion

Free from the traditional doctrine of thesis and antithesis, centralized dialectics is substantiated by a hybrid analysis–synthesis process. Although already broadly applied in daily life to modern physics, it has not yet been acknowledged as a scientific paradigm. Resorting to the Bayesian scheme and following proper form, with careful formulation and synthesis, the rigor is promised by statistics. In addition, centralized dialectics may avoid parochialism and

reductionism. The psychological capability underlying synthetic endeavor is creative or nonlinear cognition, which requires a profound understanding of the treated subject(s) to be effectively applied in sound synthesis. Notably, analysis–synthesis is a general framework to assess complicated issues not limited to life science. Centralized dialectics can be applied to the past (e.g., deciphering historical events), now (managing real-life or scientific issues), and future (policy-making).

Following the proposed framework, MDD was taken as a benchmark to illustrate an attempt to decipher difficult and complicated issues. It is important to note that centralized dialectics is suitable for complicated phenomena with parsimonious mechanisms, as assured by the thought experiment for MDD ([Methods: new disciplines—centralized dialectics and dialectic neuroscience](#)). Through intense and prolonged brooding and creative thought process, it was concluded that a network imbalance between the frontoparietal network and the limbic system could be a desirable candidate, fitting the three criteria of rationality, accountability, and parsimony. The robustness of the synthesis output is supported by statistics, given that it may account for more than 10 cardinal features of MDD. Based on this novel hypothesis, ensuing empirical examination revealed that the modular structure and network interaction in MDD have both changed significantly, indicating that MDD, unlike regional or inter-regional approaches highlighted in previous research, is a compartment-level disorder—fulfilling a cycle of analysis–synthesis and verification. This novel insight may initiate subsequent scientific questions and empirical explorations, starting the next cycle of “dialectic neuroscience”.

For complicated scientific issues, achieving a sound synthesis is always challenging and may require an extended process. Premature synthesis could be unavoidable in the early phases, making continuous refinement a crucial mindset in the active search for optimal synthesis. The holistic attitude in centralized dialectics is familiar in the field of psychology. For example, “focused dialectics” addresses the investigation and analysis of specific problems or viewpoints through intense debate and dialectical reasoning between opposing sides. It aims to uncover the crux of an issue and potentially reach a consensus or solution through stringent argumentation and the synthesis of contrasting perspectives. “Critical thinking” also involves a holistic approach, as it considers all relevant information and perspectives to make well-informed decisions (Paul & Elder, 2013). The uniqueness of centralized dialectics lies in its focus on supplementation and mutual enrichment, rather than antagonism. Referring to the analogy of a jigsaw puzzle, ideally no peripheral piece will be sacrificed during the process of centralized dialectics. Despite the main difference, a holistic attitude is generally encouraged

since it ensures that no significant factors are overlooked (less biased), underlying connections are recognized, and more comprehensive and balanced conclusions are reached (Facione, 2011).

Since the advent of the postmodern epoch, the academy has been characterized by an explosive growth of text deluge. People of this era engage far more in speaking and writing than in the act of listening. Synthesis emerges as an endeavor to remedy this pitfall and promote an appreciation for diverse contributions, facilitating genuine dialogue. Through synthesis, debates, arguments, findings, viewpoints, analyses, and scientific results become interwoven. Initially, this interaction and dialogue may transpire solely within the synthesizer’s mind; however, upon disseminating the synthetic results, the community or society may acknowledge the novel insights. Subsequently, after careful corroboration, a true consensus can be attained, allowing previous effort to find its rightful place within a new perspective. Sensible dialogue can be fostered when valid synthesis is engaged.

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**EXTENDED CORTICO-LIMBIC
DYSREGULATION MODEL OF MAJOR
DEPRESSIVE DISORDER:
A DEMONSTRATION OF THE APPLICATION
OF AN ANALYSIS-SYNTHESIS FRAMEWORK
TO EXPLORE PSYCHOPATHOLOGY**

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SUMMARY STATEMENT

The application of an analysis-synthesis hybrid to investigate psychopathology is demonstrated. The accountability of the cortico-limbic dysregulation model of MDD is enhanced by incorporating network mechanisms of mutual suppression and limbic-subcortical/raphe feedback.

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ABSTRACT

Major depressive disorder (MDD) is a prevalent and complex disease. Given the associated psychological and physiological dysfunctions are quite broad, research results have been very diverse. Despite the heterogeneous manifestation of MDD, neuroimaging studies have suggested a relatively consistent neural pattern – hypofrontality and limbic hyperactivity, also called the cortico-limbic dysregulation model. Successful treatment is accompanied by normalization of the metabolic aberrancy. The significance of the ventromedial prefrontal cortex (vmPFC) and the subgenual anterior cingulate cortex (sgACC) are also implied. However, the model is descriptive in nature, and its explanatory power regarding MDD complexity has never been systematically examined. This study demonstrates the application of an analysis-synthesis hybrid approach to formulate a candidate brain theory of psychopathology. A good candidate theory is expected to satisfy three criteria: comprehensiveness, rationality and parsimony. Previous research findings (analysis) are integrated by incorporating well-established network mechanisms (synthesis), namely cortico-limbic reciprocal suppression, excitatory-inhibitory feedback between vmPFC / sgACC and raphe nuclei, and fronto-striatal interaction. Equipped with mechanistic interactions, the accountability of the cortico-limbic dysregulation model is enhanced beyond its original content. Various perspectives of MDD are discussed based on the highlighted network mechanisms. The analysis-synthesis approach could provide a simple and useful framework for investigating psychiatric disorders. Ultimately, it is postulated that MDD is a brain organization bug that is the price paid for expanded and integrated mental capabilities. In the future, the analysis-synthesis products could be incorporated into the Research Domain Criteria.

Keywords: analysis, antidepressant, major depressive disorder (mdd); network, neuroimaging, synthesis

INTRODUCTION

Major depressive disorder (MDD) is one of the most prevalent psychiatric disorders and disables a significant proportion of the human population. The clinical profile of MDD and its etiology, course, outcome, and treatment response are heterogeneous. A considerable amount of neuroimaging research designed to elucidate the underlying mechanism has provided great insight to

this difficult illness. Unsurprisingly, some results are controversial, and some debates are still unresolved. Despite the perplexity, there seems to be a gross neurobiological pattern for clinical depression that is repeated across several different neuropsychiatric and medical conditions [1]. Based on the empirical evidence and with special emphasis on the large-scale neural manifestation of MDD, this article aims to apply an analysis-synthesis hybrid approach to explore the underlying pathogenesis of this disorder. Acronyms and abbreviations are provided in Table 1.

Table 1. Selected abbreviations and acronyms

5-HT	serotonin
SERT	serotonin transporter
SSRI	specific serotonin reuptake inhibitor
(S)NRI	(serotonin-)norepinephrine reuptake inhibitor
PFC	prefrontal cortex
ACC	anterior cingulate cortex
MCC	mid-cingulate cortex
PCC	posterior cingulate cortex
OFC	orbitofrontal cortex
dl-	dorsolateral (dlPFC)
vm-	ventromedial (vmPFC)
vl-	ventrolateral (vlPFC)
m-	medial (mPFC, mOFC)
sg-	subgenual (sgACC)
pg-	pregenual (pgACC)
BA	Brodmann area
BG	basal ganglia
NAc	nucleus accumbens
VS	ventral striatum
VTA	ventral tegmental area
RN	raphe nucleus
GM	gray matter
WM	white matter
fMRI	functional magnetic resonance imaging
TMS	transcranial magnetic stimulation
RSM	mechanism of reciprocal suppression

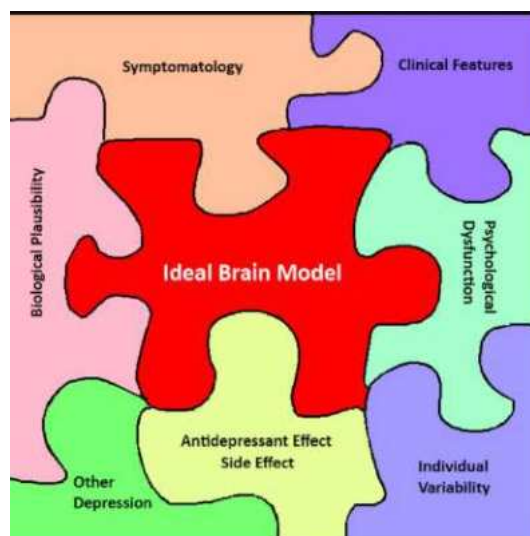


Figure 1. Using a jigsaw puzzle to illustrate the ideal brain theory that accounts for major psychiatric disorders. The central piece represents the candidate brain model (synthesis) that fits well within the tortuous outline formed by observations from different perspectives (analysis).

Many theories have been contrived to explain major psychiatric disorders that are notorious for their heterogeneity and complexity. To tackle the challenges, a novel methodology is obviously needed in order to integrate evidence from different perspectives and to help evaluate the “likelihood” of the proposed theories to explain, in this case, MDD. Herein, a jigsaw puzzle metaphor is used to illustrate the spirit of the methodology of the analysis-synthesis approach (Figure 1). The ideal brain theory for MDD is like the central missing piece (synthesis) that should fit the tortuous outline delineated by the remaining pieces (analysis) which represent the characteristics of MDD observed from different angles. Analysis and synthesis, respectively, rely on linear and non-linear thinking (or lateral thinking) [2, 3]. A typical case of linear thinking is syllogism. If condition A leads to condition B, and condition B leads to condition C, then condition A leads to condition C. Hypothesis testing is another example: if condition A is satisfied, then condition B (the null hypothesis) is rejected. In contrast, non-linear thinking deals with difficult and complicated issues such as, but not limited to, the following: if A, B and C are simultaneously observed, what could be the underpinning of the three conditions? Analysis tends to dissect a whole into parts, whereas synthesis is an attempt to construct or explain the whole from its parts. Notably, the

theories behind observations A, B and C could be incompatible in some way, which generally occurs in situations in which “synthesis” engages to reconcile conflicts and to provide possible solutions. Synthesis requires creativity and is not infrequently divergent from traditional norms. Although non-linear thinking has been attributed to the cognitive capability underlying artistic production, it is also applied in science. Milestone works by Einstein (physics), Mendeleev (chemistry) and Loewi (physiology) are the products of their non-linear thinking and synthetic endeavor [3-5]. The details of analysis and synthesis will be elaborated in the last sub-section of the *Discussion*.

In empirical neuroscience, the synthetic approach is still not broadly accepted and the standards to justify the synthetic endeavor are still lacking. Considering the successful application of synthesis in other scientific fields, three criteria are proposed to appraise the performance of a candidate theory/model (synthetic product) in psychiatry brain research (refer to the *Discussion* for more information) [3]. First, the theory/model should be able to explain the observed phenomenon as much as possible (comprehensiveness or accountability); second, the theory/model should be as parsimonious as possible (parsimony); and third, biological plausibility should be fully respected (rationality). The spirit of these three standards is akin to the Bayesian scheme of model selection, in which the posterior probability is determined by the given models (selected network mechanisms; rationality) and the explained observation (comprehensiveness), and penalty is charged on the number of chosen mechanisms (parsimony). The criteria of comprehensiveness (accountability) and rationality are evident and can be understood through the examples given in the *Discussion*. The criterion “parsimony” is included for both mathematical and theoretical importance. Although MDD is highly complex, the possibility that its pathogenic mechanism could be simple cannot be excluded. If the affected domains of MDD are independent, the joint probability shall be extremely low and will not constitute a disease entity of such high prevalence. Complexity theory suggests that a complicated emergent phenomenon may actually originate from simple rules that govern the interaction of its constituents. For two equally plausible models, better accountability indicates higher posterior probability. If a brain theory fails to explain the findings from various perspectives, the model is either wrong or not adequate, warranting supplementation or modification. The analysis-synthesis hybrid is designed to explore complicated issues and is not limited to MDD [3]. It is important to note that despite the broad citation of the MDD literature, this research by no means should be considered a review article.

Among the proposed network abnormalities in MDD, cortico-limbic dysregulation theory (proposed by Mayberg) and aberrancy in subgenual anterior cingulate cortex (sgACC) are two outstanding frameworks guiding MDD research, and each has gained substantial support [6-8]. The former advocates hypo- and hyper-activity in dorsal cognition-attention and ventral vegetative-somatic domains as the neural features of MDD, whereas the latter addresses the prominent role of sgACC and its clinical relevance [8, 9]. These two viewpoints are not exclusive to each other and were actually integrated as a three compartments model (dorsal, ventral and rostral) by Mayberg [6]. The dorsal compartment comprised the dorsal frontal region (Brodmann area [BA] 9, 44 and 46), mid-cingulate cortex (MCC; BA 24b), inferior parietal region (BA 40) and posterior cingulate cortex (PCC; BA 29, 30 and 31), and the ventral compartment comprised the sgACC (BA 25), inferior frontal region (BA 47), insula, hippocampus, hypothalamus and amygdala. The thalamus, basal ganglia (BG) and pregenual ACC (pgACC) were classified into the rostral compartment. However, there remain many puzzles to be solved. For instance, how does cortico-limbic dysregulation occur and persist? How is the cortico-limbic dysregulation corrected? Why are there so many conditions that lead to clinical depression? Why is sgACC (and its neighboring ventromedial prefrontal cortex [vmPFC]) so particular? What is the role of the BG in MDD? Should the dorsal part of the medial PFC (mPFC) be incorporated into the dorsal compartment? What are the mechanisms of various therapeutic measures? Why is there a remarkable delay for the treatment to take effect? Finally, why is clinical depression so prevalent, spanning early childhood to old age? The advantage of the analysis-synthesis approach lies in the context provided by the synthetic endeavor that could integrate seemingly irrelevant observation and evidence, and make them pertinent to each other.

This article follows the definition of a limbic network proposed by Mega et al. who distinguished two sub-systems: the orbitofrontal cortex (OFC)/amygdala-centered paleocortical division and the hippocampus/cingulate-centered archicortical division [10]. According to Vogt, the cingulate cortex is partitioned into the ACC, MCC, PCC and retrosplenial cortex [11], with the ACC belonging to the OFC/amygdala division and the latter three regions belonging to the hippocampus/cingulate division. The mPFC is divided into ventral (BA 10) and dorsal (BA 8 and 9) sections. For convenience and clarity, the ACC and vmPFC are discussed in the limbic system rather than in the frontal lobe. In this article, the framework of the analysis-synthesis approach is categorized into two phases: (1) collecting neuroscientific evidence and defining features of MDD from various different

disciplines and perspectives (analysis phase; see the *Materials and Methods*) and (2) determining whether the diverse analytic findings can be integrated into a simplified, integrated and mechanistic framework (synthesis endeavor; see the *Results*). This research demonstrates that the synthetic product based on network operations is simple in terms of constituents but may accommodate many aspects of MDD, and conceptually can pass stringent examination using Bayesian statistics. MDD is characterized not only by aberrant emotions but also attention, memory, cognition, social judgment, behavioral inclinations, response inhibitions, vegetative functions and even sensory processing [12, 13]. A detailed psychological interpretation of MDD is temporarily suspended since the affected psychological domains are so broad that single psychological construct is clearly inadequate to explain its multiplex characteristics.

MATERIALS AND METHODS

This section deals with the analytic phase, and is divided into two parts. In the first part, the analytic results from previous research are briefly reviewed. In the second part, the defining (neuro-) features of MDD that the synthesis attempts to integrate are summarized (the peripheral pieces of the jigsaw puzzle).

Part I: Analytic Results

Frontal Abnormality in MDD

- One of the pathognomonic features of MDD is hypofrontality which may include the dorsolateral PFC (dlPFC) and the mPFC [9, 14-17]. Although the dlPFC used to be a major focus of research into MDD pathology, recent research highlights the importance of dorsal mPFC, which has become a new therapeutic target for transcranial magnetic stimulation (TMS) [18]. Elderly depressives with a high risk of suicidality present with reduced volume in the dorsal mPFC [19]. In accordance with the hypofrontality hypothesis, better treatment response is predicted in cases of MDD with higher metabolic activity in the mPFC [20].

- In MDD, reduced fronto-polar activities to both positive and negative social stimuli and to cognitive challenge are observed [21].
- Remission is frequently associated with normalization of the hypo-metabolism in several frontal regions [16, 17, 22], though persistent hypo-metabolism in the medial/superior frontal gyrus (BA 9 and 10) and in the dlPFC have also been reported [15, 17, 23]. Glucose metabolism in the mPFC was shown to increase after treatment [16].
- The re-emergence of depressive symptoms in remitted MDD may follow the short-term discontinuation of specific serotonin reuptake inhibitors (SSRIs), and the accompanied decrease in regional cerebral blood volume in the left mPFC is correlated with the symptom severity [24].
- In either remitted or acute depression, the induction of sadness entails decreased blood flow in the mPFC [25]. Interestingly, the major findings of the above studies in the mPFC largely do not extend to the ACC; this observation is compatible with the delineation between the PFC and the limbic system [10].

Limbic Abnormality in MDD

- Limbic hyperactivity has been observed in the ACC, PCC, OFC, amygdala and parahippocampus during the acute phase of MDD [12, 15-17].
- In MDD, hyper-arousal and amygdalar disinhibition are exhibited in response to cognitive demand and to subliminal facial emotions (both positive and negative) [26, 27].
- Similar to the PFC, less hyperactivity in the limbic system (ACC, insula and parahippocampus) is associated with better treatment outcomes [28], and clinical improvement is accompanied by metabolic normalization [16, 17, 20, 22, 23]. Weakened amygdalar responses to negative facial emotions were noted in treatment responders [29].
- In contrast to other limbic components, higher activity in the vmPFC/sgACC predicts a better treatment response [1, 30].

Neurophysiological Understanding and Fact

- The ACC and adjacent vmPFC interface with the limbic and corticostriatal systems, and are situated at the junction of the two main components of the limbic system, i.e., the hippocampus/cingulate-centered and OFC/amygdala-centered networks [10].
- The vmPFC and sgACC have reciprocal connections with the ventral striatum (VS), brain stem, hypothalamus, and amygdala [31-33]. The pyramidal cells and inhibitory interneurons in vmPFC/sgACC are enriched in serotonergic, dopaminergic and adrenergic receptors. The interaction of vmPFC/sgACC with those modulatory nuclei is bi-directional; for example, the fluctuation of neural activities in the vmPFC/sgACC may influence those in the raphe nucleus (RN) and in turn, cause similar change in the release of serotonin (projection from RN) in the vmPFC [34]. The unique position of vmPFC and sgACC provides the cortex with an avenue to affect the neuro-modulatory nuclei, BG, and other limbic and deep structures [31, 35].
- Network balance, such as excitation from the vmPFC/sgACC to the RN (glutamatergic projection) and inhibition from the RN to the vmPFC/sgACC (serotonergic projection), can be reached at large-scale level (Figure 2B) [34, 36]. Notably, the interactions between the RN (and other diencephalic and brain stem nuclei) and the cortex are asymmetrical. The RN may adjust the neural activities of a widespread area in the cortex but only limited cortical regions may directly access the RN.
- Serotonin and norepinephrine may exert inhibitory and excitatory modulation, respectively, on central nervous system activities [37].
- It was noticed that after 1 week of SSRI treatment, some “normal” brain regions exhibited attenuated glucose metabolism [22]. Moreover, SSRIs may reduce neuronal responses to negative stimuli in both healthy controls and MDD patients [38]. The neural inhibitory effects of acute SSRIs cover a wide range of cortical and subcortical brain areas in depressive patients [23, 28]. Accordingly, lower cortico-electrical power of the serotonin transporter (SERT) genotypes with lower transcription efficiency has been observed in EEG [39]. In the rat forebrain, the long-term administration of SSRIs

results in a tonic activation of inhibitory serotonin 1A (5-HT_{1A}) receptors in the hippocampus [40].

- In non-responders, the acute suppressive influence (1 week) of SSRIs on the brain persisted for up to 6 weeks [22].

Part II: Cardinal (neuro-) Features of MDD

The candidate brain theory of MDD is expected to be able to explain diverse prominent phenomena of MDD, tentatively including the following:

1. The occurrence and reversal of hypofrontality and limbic hyperactivity in MDD [9, 12, 14-17, 20-23, 26, 27];
2. Why MDD lasts (in contrast to transient sadness) [6, 25];
3. Why frontal pathology leads to MDD and why there are diverse causes of clinical depression [1];
4. Why the vmPFC/sgACC predicts treatment response [1, 30];
5. Why both excitatory (norepinephrine reuptake inhibitor [NRI]) and inhibitory (SSRI) anti-depressants provide therapeutic effects [37];
6. Why treatment and recovery take so long (in contrast to transient sadness) [41];
7. In some MDD patients, the temporary worsening of symptoms and even suicidality during the treatment of SSRIs [42];
8. Opposite metabolic profiles observed in the acute and chronic (successful) treatment with SSRIs [16, 17, 22, 23, 28, 38, 39];
9. The therapeutic effects of sleep deprivation [43];
10. The therapeutic effects of PFC TMS [44];
11. The therapeutic effects of vagus nerve stimulation [45, 46];
12. The therapeutic effects of electrical stimulation of the vmPFC [9];
13. Why the effects of SSRIs on the brain metabolism of non-responders (6 weeks of treatment) were similar to those of MDD patients receiving acute SSRIs treatment (1 week) [22];
14. The core symptom is depressed mood or lack of interest [47]; and
15. The associated hypothalamus-pituitary-adrenal axis (HPA) axis abnormality, multitude of psychological dysfunctions, and impairment in vegetative functions [3, 12, 13, 48-50].

RESULTS

This section describes the synthetic phase (the analytic phase is in the *Materials and Methods* section) and is divided into two parts. A candidate brain theory of MDD, cortico-limbic reciprocal suppression mechanism (RSM), is proposed to account for the characteristics of MDD and is the central missing piece of the jigsaw puzzle. The evidence of the existence of cortico-limbic RSM is depicted in the first part of this section (biological rationality), whereas the performance of the synthetic result is scrutinized in the second part (accountability/comprehensiveness).

Part I: Synthetic Product – Evidence of Cortico-limbic RSM

This synthesis addressed a large-scale, automatic network mechanism, i.e., the cortico-limbic RSM, as the main underlying mechanism of MDD; this mechanism was first summarized by Drevets and Raichle and then replicated and elaborated by many other researchers [51]. The cortico-limbic RSM is evidenced by experiments that contrast brain responses to cognitive and emotional demands: cognitive operation generally activates the fronto-parietal network and simultaneously deactivates neural nodes in the limbic system, whereas emotional engagement or anticipation of anxiety elicits the opposite neural response pattern. The nature of the cortico-limbic RSM is best appreciated when both experiential and evaluative components are incorporated into the same experimental design, in which the bidirectional influence of RSM can be deciphered by the commands “feeling” and “judging” [52-54]. For example, a simple “label” of the viewed affect-laden material is enough to decrease amygdala response and skin conductance [53]. Rating the subjective pleasantness/unpleasantness of emotionally salient stimuli may down-regulate the neural activities in the insula and amygdala and may up-regulate those in the dorsal mPFC and dlPFC [53, 54]. The modulation of the emotional response by RSM is automatic, instantaneous, and dependent upon the online intentionality to feel (affective) or to judge (cognitive). Interestingly, under this scenario, the absolute value of the judged emotion intensity correlated positively with neural activities in the dlPFC, mPFC and ACC/MCC, but negatively with those in the amygdala and medial temporal lobe [55], indicating a higher repressive effect when encountering a stronger emotional event. For the designs requiring the participants to rate the emotion

valence/arousal “after” scanning (offline) [56], RSM inclines toward feeling and limbic dominance; by contrast, for the situations demanding online cognitive evaluation [53-55], RSM leans toward judging and PFC. RSM is maintained in a fluidity homeostasis.

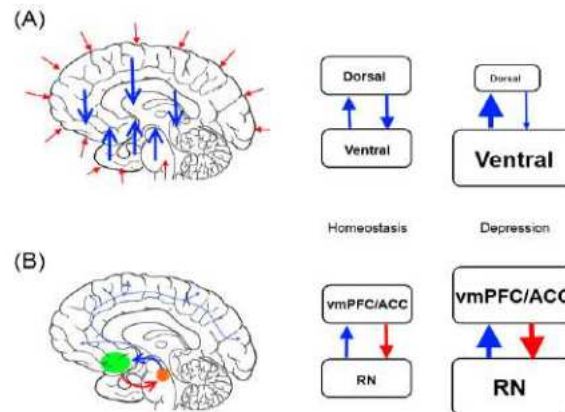


Figure 2. Highlighted interacting patterns of two networks related to MDD: reciprocal suppression between the dorsal and ventral compartments and excitation-inhibition between the RN and the vmPFC/sgACC. Blue, inhibition; red, excitation. (A) Left: short red arrows indicate various excitatory inputs to the dorsal and ventral compartments of the brain. Blue arrows show mutual suppression as an interacting mechanism between the two compartments. Right: under homeostasis, balance is reached and the sizes of the dorsal and ventral compartments (an abstract representative of metabolic or activity level) are approximately equal, with mild perturbation allowed. When the balance is breached to a breaking point, the size of the ventral compartment enlarges and its negative influence on dorsal compartment increases; conversely, the size of the dorsal compartment shrinks and its impact on the ventral limbic system decreases. The overall consequence evolves to a state/attractor of hypofrontality and limbic hyperactivity. (B) Left: the vmPFC/sgACC projects an excitatory influence on the RN, whereas the RN exerts inhibition over widespread cortical and subcortical structures, including the vmPFC/sgACC. Right: the excitation-inhibition interaction generally promises balance since the feedback from the RN to the vmPFC/sgACC is negative.

The cortico-limbic RSM may underlie daily experience in which emotion and cognition could interfere with each other (note: cortico-limbic RSM is one of many possible interactions between emotion and cognition; see the *Discussion*). Via the cortico-limbic RSM, cognitive evaluation itself may attenuate subcortical neural responses to emotional stimulation. Conversely, focusing on a feeling or an experience of emotion may lessen or suspend (cold) cognitive operation. It is clear that the cognition-mediated mitigation of

an emotional response is neither due to distraction, as evaluation implies a deeper assessment of the confronted stimuli rather than avoidance of it, nor to a change in the meaning of the underlying emotional material [57]. The parametric relationship cannot be explained by competition of limited attention resource, either. Correspondently, high frequency TMS over the dlPFC may weaken the response of the amygdala to negative stimuli [58]. Again, the process occurs automatically without voluntary cognitive effort. Although less-appreciated, we believe that the RSM is more primitive and fundamental than other emotion regulation strategies and plays a key role in the pathogenesis and recovery of MDD. Equipped with the RSM (and the network mechanisms of the vmPFC-RN and the fronto-striatal pathway), the accountability of cortico-limbic dysregulation model is greatly boosted, and fits the methodological requirement of the central piece in the jigsaw puzzle (as demonstrated in Part II and explicated in the *Discussion*).

Different network feedback patterns bring about different consequences. Two network mechanisms that are closely pertinent to MDD, i.e., the cortico-limbic RSM and the vmPFC-RN excitatory-inhibitory feedback, are expounded here and in Figure 2. The adaptive benefit of the RSM lies in its efficient switch between different brain modules/functions so that cross-modal interference is reduced and the utilization of limited energy resources is optimized. However, when the balance between the networks is disrupted, RSM aggravates the imbalance (Figure 2A). For small sub-networks that interact via the RSM in the brain, mild imbalance can be corrected spontaneously since each of the sub-networks receives diverse inputs to help maintain equilibrium. However, for large networks, such as the dorsal and ventral compartments, the outcome of losing balance can be catastrophic. When the cortico-limbic imbalance reaches a breaking point, hyperactivity in the limbic system may energize its inhibitory influence on the PFC and consequently, the counteracting effect exerted on limbic system by the PFC is reduced, creating a vicious cycle that ends in the stabilized hyper-limbic/hypo-frontal state of MDD. As discussed in the “analysis” section, the vmPFC/sgACC exerts an excitatory influence on the RN, whereas the nature of RN projection is generally inhibitory. As a member of limbic system, the vmPFC/sgACC functions as a safety valve that may reduce the limbic hyperactivity. Unlike other limbic nodes, vmPFC/sgACC activity may thus predict treatment response [1, 30]. The excitatory-inhibitory feedback in the vmPFC/sgACC-RN differs from the RSM in that the interaction does not fall into a vicious cycle (Figure 2B). Four possible instances are explicated here: (1) increased activity in the RN would reduce the activity in the

vmPFC/sgACC and hence reduce its driving input; (2) decreased activity in the RN would disinhibit the vmPFC/sgACC, resulting in stronger excitatory feedback; (3) increased activity in the vmPFC/sgACC would activate the RN and then would receive stronger inhibitory feedback from the RN; and (4) decreased activity in the vmPFC/sgACC would attenuate activity in the RN and would therefore receive less inhibition. Based on the above, the RN cannot be over-driven under physiological conditions even if necessary. Thus, electrical stimulation to the sgACC and elevation of serotonin via SERT inhibitor aid in the treatment of MDD [32]. Compared with electrical stimulation to the sgACC that may directly augment RN discharge (upstream), SERT inhibitors enhance serotonergic neurotransmission by reducing 5-HT clearance at neuronal clefts (downstream) [9].

Part II: Accountability evaluation of the cortico-limbic RSM and other associated network mechanisms (note: the contents are in one-to-one correspondence with the core features summarized in the *Materials and Methods* section, part II).

1. The occurrence of MDD is caused by large-scale imbalance between cortical and limbic compartments, and recovery involves the restoration of network balance. Both are mediated by the cortico-limbic RSM (Figure 2A).
2. MDD persists because large-scale network imbalance (as opposed to small network imbalance) may lead to super-stable attractors (Figure 2A).
3. When the frontal pathology reaches a breaking point, the cortico-limbic RSM may trigger or aggravate the situation of hypofrontality and limbic hyperactivity, thereby inducing clinical depression. The diverse origins of frontal pathologies across the life span can be accommodated in this framework (Figure 2A).
4. The increased metabolism in the vmPFC/sgACC in MDD is a compensatory mechanism that enhances the discharge of the RN to suppress limbic hyperactivity.
5. Excitatory (NRI) and inhibitory (SSRI) anti-depressants perturb the imbalance of the cortico-limbic network by enhancing and attenuating frontal and limbic activities, respectively. In a biological system, a non-linear, ceiling/floor effect may contribute to the uneven impact of antidepressants on the dorsal and ventral compartments of the brain (see *Mechanisms of antidepressive treatments* in the *Discussion* for more details).

6. Escaping the super-stable imbalanced attractor takes time. However, direct stimulation of the VS may accelerate recovery by energizing the PFC and reward circuitry to reduce the imbalance [59, 60]. Therefore, rapid recovery of clinical depression is possible.
7. For the few patients who experience worsened depression (or even attempt suicide) and declined cognition after initiation of SSRIs, their PFCs could be more sensitive to the inhibitory effect of 5-HT and the cortico-limbic imbalance gap could be temporarily enlarged [19, 61].
8. Opposite metabolic profiles in acute and chronic (successful) treatment are mediated by the reversal of cortico-limbic imbalance and the operation of the RSM (Figure 2A).
9. Sleep deprivation functions similarly to reuptake inhibitors by enhancing monoaminergic neurotransmission, thereby exerting therapeutic effects [62].
10. TMS to the PFC increases frontal activities to reduce cortico-limbic imbalance, thereby exerting therapeutic effects [44].
11. Vagus nerve stimulation decreases limbic hyperactivity to reduce cortico-limbic imbalance [45, 46].
12. Electrical stimulation to the vmPFC may drive RN discharge beyond its original range to perturb the cortico-limbic imbalance, thereby exerting therapeutic effects [9].
13. The inhibitory effects of SSRIs persist because the reversal of network imbalance does not occur in non-responders [22].
14. The severity of lack of interest depends on the degree to which the RN influences the ventral tegmental area (VTA) and VS. Hypofrontality and stress-mediated reaction may also influence the reward circuit and decrease motivational behaviors in MDD (see *Network mechanisms of MDD: The cortico-striatal pathway* in the *Discussion*).
15. The limbic system has intense interactions with the hypothalamus and hence the HPA, also known as the limbic-HPA system, that controls reactions to stress and regulates vegetative functions through the neuroendocrine and autonomic nervous systems. Since MDD is a “compartment level” disorder, the affected (neuro-) psychological domains are broad [3, 12, 13, 48-50].

The accountability of the synthesis is briefly summarized in Table 2, and a detailed explanation is elucidated in the *Discussion*.

Table 2. Summary of the phenomenon of MDD explained by proposed network mechanisms

Queries/Phenomenon	Explanations
The occurrence of MDD?	Large-scale imbalance of cortico-limbic interaction mediated by RSM
Why MDD last?	Cortico-limbic imbalance by RSM leading to a stable attractor
Why frontal pathology leading to MDD?	Cortico-limbic imbalance aggravated by RSM
Why vmPFC/ACC predicts treatment response?	Compensatory reaction may cool down limbic hyperactivity
Why treatment and recovery take so long?	Restoration of normal cortico-limbic RSM is not immediate
Kindling phenomenon?	Higher chance for RSM to progress to loss of balance
Therapeutic effect of PFC TMS?	Enhancement of frontal activities to reduce cortico-limbic imbalance
Therapeutic effect of vagus nerve stimulation?	Decreasing limbic hyperactivity to reduce cortico-limbic imbalance
Therapeutic effect of electrical stimulation at vmPFC?	Driving the inhibitory action of RN out of physiological range
Therapeutic effect of electrical convulsive therapy?	Exciting whole brain to reduce cortico-limbic imbalance
Therapeutic effect of sleep deprivation?	Like antidepressants, reducing cortico-limbic imbalance
High prevalence of MDD?	Large-scale RSM propagating to a vicious cycle, a bug in brain organization
Depressed mood or lack of interest?	Dependent on the degree of RN influence onto VTA-VS
Accommodate a diversity of causes of MDD?	Yes, when cortico-limbic imbalance reaching breaking point
Explain multitude of psychological dysfunctions?	Large-scale imbalance of cortico-limbic network and its consequence
Accommodate HPA axis abnormality?	Yes
Explain impairment in vegetative function?	Yes
Explain negative bias?	Limbic hyperactivity*
Explain reduced positive bias?	Limbic-BG and fronto-VS-VTA interaction*
Individual variability in symptom manifestation?	Adjustment of sub-networks to cortical and limbic changes
Opposite vegetative and behavioral manifestation?	Mixed hypo-frontal and hyper-limbic inputs to deep nuclei

Queries/Phenomenon	Explanations
<i>Pharmacological Antidepressants</i>	
Therapeutic effect of SSRI?	Decreasing limbic hyperactivity to reduce cortico-limbic imbalance
Side effects of SSRI?	Lacking in regional specificity of inhibitory neural modulation
Why inhibitory antidepressant may activate frontal region?	Restoration of balanced cortico-limbic RSM
Why excitatory and inhibitory anti-depressants both work?	NRI reduces cortico-limbic imbalance by correcting hypofrontality
Opposite metabolic profiles in acute and chronic treatment?	Reinstatement of balanced cortico-limbic RSM
Brain metabolism of non-responder similar to acute treatment?	RSM still not restored (not in homeostasis)

* The issues of affective bias in MDD is complicated and not treated in the main text [3].

DISCUSSION

The cortico-limbic theory proposes that dysregulation of the dorsal and ventral brain plays a key role in MDD [6]. Hypoactivity in the frontal region and hyperactivity in the limbic system have been consistently reported in both the baseline and activation states, with altered functional relationships between neural nodes within each compartment [14-17]. Similar abnormalities have also been observed in clinical depression associated with various medical conditions [1, 63]. Previous research has highlighted the significance of cortico-limbic model from the perspective of psychopathology (MDD), though other equally important facets include the following: how does the model operate when the brain is functioning normally? How does fronto-limbic dysregulation occur? Finally, what is the relevance of this model to MDD recovery? The literature on emotion regulation is obviously pertinent [64]. However, achieving cortico-limbic homeostasis seems to be an automatic/effortless process, and healthy people generally do not have to resort to cognitive reappraisal of their situation or oppression of their feelings to avoid sinking into a depressed mood [65]. The synthesis disclosed that the cortico-limbic RSM (together with several other well-documented network mechanisms) may substantially account for the remarkable features of MDD. The details are elaborated below.

Frontal and Limbic Abnormalities of MDD

Hypofrontality, primarily in the mPFC and dlPFC, is believed to be crucial in the pathogenesis of MDD [9, 14-17]. Functional aberrancy occurs together with morphometric abnormalities, such as decreased glial/neuronal density using microscopic examination, in the mPFC, OFC and dlPFC [48, 66, 67]. A prominent reduction in pyramidal neuron density was observed in the OFC of elderly depressives [68]. There seems to be a trend that glial pathology precedes neuronal changes as MDD progresses [48]. MDD pathology is not restricted to gray matter (GM), and white matter (WM) pathology in the frontal brain has also been identified [19, 69, 70]. Consequently, these GM/WM changes may affect regional and inter-regional neural computation. The role of the PFC in MDD is complicated: abnormalities in the PFC may cause MDD, MDD may affect the PFC through stress-related pathways (discussed below), and pathological changes in the PFC may constitute factors of vulnerability for subsequent episodes [48]. In

addition, PFC dysfunction may impair the regulation of emotion and interpersonal stress, which may increase the risk of MDD recurrence [64, 71]. Concordant with the remarkable pathology in PFC, cognitive deterioration, notably in the domains of executive function and attention, may persist even in the remitted phase [72]. The “dysexecutive syndrome” predicts a poor functional outcome regardless of clinical improvement in depressive symptoms.

The abnormal limbic activities of MDD that disturb homeostasis in HPA and cortisol may impose detrimental effects on the brain [48]. The consequent neuronal/glial cell loss may constitute undesirable susceptibility in the disease course of MDD. In a rat model, glucocorticoid receptors expressed in ACC has been shown to play a major role in the negative feedback of glucocorticoid secretion in response to stress, and increased local corticosterone level may attenuate the HPA-mediated stress reaction [73]. Conversely, lesions of the prelimbic and infralimbic portions of the ACC enhance the corticosterone responses to restraint-induced stress. In summary, increased metabolism in the ACC/vmPFC may provide inhibitory modulation on brain dynamics (via the RN) and cortisol response (via projection to the hypothalamus). In addition to the effects of stress hormones, long-term hyper-activation may also result in brain cell loss, which is likely to be mediated by calcium overload toxicity [74]. Immunological abnormalities (e.g., through the kynurenine pathway) and decreased level of brain-derived neurotrophic factor may also contribute to the morphological changes in the limbic structure [35, 75]. The volumes of several limbic and subcortical structures, such as the sgACC, caudate, thalamus (anterior nucleus), amygdala and hippocampus, are reduced in MDD [76-78]. The causes of volume reduction in the PFC and limbic region could be partly overlapping (e.g., via the HPA) and partly different (e.g., over-excitation toxicity). Morphometry tracing studies of the hippocampus and amygdala have revealed that the volumetric reduction is correlated with the total duration of depressive illness [77, 78]. Nevertheless, the cell number in the hypothalamus and dorsal raphe nucleus might be increased [48]. The implication of these quantitative morphometric studies is twofold. First, these studies raise a debate as to whether volume reduction is the consequence, correlate or causal factor of MDD. The ambiguity is difficult to disentangle because these three possibilities might co-exist and may vary among different brain regions. Since major psychiatric disorders generally have an insidious onset, full-blown MDD is frequently preceded by a stressful life event and mal-adaptive coping style for a period of time [79],

which may have already had a negative impact on brain structures [80]. Second, the reduction in volume may mask any increase in brain activity especially when neuroimaging tools with low resolution, such as positron emission tomography or single photon emission computed tomography, are used, and may thus explain the inconsistent findings about metabolic level in the sgACC [81]. The volumetric change is not limited to adulthood MDD. Children and adolescents with depressive symptoms show reduced volume in the rostral ACC [80], whereas geriatric depressive patients display reduced volumes or neuron densities in several limbic structures, such as the OFC, insula, parahippocampus and subcallosal cingulate region [19, 68]. This convergence alludes to a shared neural mechanism of MDD across the life span.

Network Mechanisms of MDD: The Cortico-Limbic Pathway (Synthetic Results 1-4)

Distant inhibition is a common network interaction of the brain. For the PFC, different sub-regions may substantiate different inhibitory controls that are not restricted to the cortico-limbic RSM. Among them, the anterior-ventral division of the dlPFC is responsible for attentional shift and action inhibition, whereas the OFC is critical for the reversal of stimulus-reward associations [82, 83]. Injury to the mPFC may result in personality changes, disinhibition and impulsivity, whereas damage to the temporal lobe may lead to hyperphagia and hypersexuality [84-86]. The phenomenon of reciprocal suppression can be found in additional regions other than the PFC and temporal lobe. For instance, the ACC and MCC generally do not activate together, and their enhanced activities denote emotional and cognitive endeavors, respectively [87]. Likewise, the lateral and medial dorsal striatum compete with each other in selecting habitual or goal-directed behaviors [88]. RSM also occurs in binocular rivalry, taste (bitterness and saltiness), and in the coordination of respiratory and laryngeal muscles. A recent functional magnetic resonance imaging (fMRI) study revealed an RSM within cognition functions in which physical and social cognitions are mutually suppressive [89]. Compulsive drug-seeking behavior may also result from an RSM (network imbalance), i.e., the over-excited reflexive compartment over-rides the control of the reflective counterpart [3]. Generally, the organization of an RSM in motor networks, such as the Delong-Wichmann loop, is much more conspicuous than that of other RSMs in non-motor networks [90]. The

existence of an RSM in the brain can be inferred from activation-deactivation patterns in neuroimaging research and from psychological “antagonism” in mental activities [51]. The antagonism here indicates mutual exclusion. For example, increased emotionality is often associated with less cognitive flexibility, engagement in goal-directed behavior usually implies inhibition of a habitual response, and a switch into the resting mode entails the suspension of the working mode [91, 92], and vice versa. The underlying neural operations that fulfill an RSM may be multiplex and executed synergistically. A few possible operations include: organized excitation/inhibition between the cortex and subcortical nuclei (e.g., the Delong-Wichmann loop), the innervation of inhibitory interneurons on antagonistic regions, neuro-modulation (e.g., serotonergic inhibition and noradrenergic excitation), competition for a limited resource budget, attention-mediated inhibition or gating of unselected mental modules, and so on. The RSM is one of the fundamental brain principles that contributes to balance or imbalance of a large-scale neural network.

With the cortico-limbic RSM and the excitatory-inhibitory interaction between the vmPFC/sgACC and the RN, various pathways leading to MDD can be elucidated as follows. Frontal lobe injury such as cerebrovascular events may induce hypofrontality and disturb cortico-limbic homeostasis. WMs lesions in the frontal region may interfere with the cortico-limbic RSM, as seen in both late-onset and young depressives [69, 70]. From the limbic side, stress and trauma in early life may enhance limbic activation as an enduring trait [93]. When reaching a breaking point, RSM may trigger or aggravate hypofrontality and limbic hyperactivity, thereby leading to clinical depression. A recent study suggested that glutamatergic dysfunction in ventral ACC could be one of the molecular underpinnings that mediate the abnormal RSM in MDD [94]. Moreover, an MDD-associated HPA-mediated stress reaction may negatively affect the PFC. Structural changes of GM and/or WM in the PFC may become a biological “scar” that postpones the recovery of the RSM and predicts a lower rate of remission [69]. The scar may render the cortico-limbic network vulnerable to further disturbances. With the accumulated pathology in the course of MDD, a higher risk of relapse actually reflects the propensity (the inverse of robustness) of the brain to become trapped in cortico-limbic imbalance; this effect is known as the kindling phenomenon. Hypofrontality is also a hallmark of schizophrenia, and unsurprisingly, the prevalence of comorbid depression can be as high as 50% [95]. Dysthymia might indicate an intermediate attractor in which moderate hyper-limbic and hypo-frontal states coexist; and this imbalance may

sometimes evolve to the MDD extreme, thereby constituting “double depression” [96].

It is notable that the jargon of “dorsal-ventral” or “cortico-limbic” dysregulation is used for convenience. Situated at the border between the dlPFC and OFC, both increased and decreased baseline activities in the ventrolateral PFC (vlPFC) have been reported [1, 64]. The controversy may stem from decreased and increased inputs from the dlPFC and OFC. In addition, the PCC and MCC may not conform to the simple dorsal-ventral or cortico-limbic distinction. The directionality of the metabolic profile in the MCC and PCC is more complicated because they not only belong to the limbic system but also receive strong input from cortical regions. Nevertheless, sporadic evidence has indicated that in acute MDD, hypoactivity may occur in the MCC (or the posterior part of the pgACC), a result that is compatible with the dorsal-ventral distinction [9]. The metabolic directionality is also consistent with the intense intra-cingulate connection between the ACC, PCC and perisplenial cortex, with little involvement of the MCC [11]. Although not directly engaged in emotional memory and emotion processing, the MCC, as a member of the limbic system, supports pertinent motoric functions, such as approach/avoidance and body orientation through response selection. Both decreased and increased regional glucose metabolism in the PCC have been reported in MDD patients who respond to treatment with antidepressants. The former and the latter could, respectively, originate from reduced and enhanced inputs from limbic and fronto-parietal networks following successful treatment [17, 97].

Network Mechanisms of MDD: The Cortico-Striatal Pathway (Synthetic Results 14)

Clinical depression is a frequent comorbidity of neurodegenerative conditions involving the BG, such as Parkinson’s disease and Huntington’s disease, and may occur even at the very early phase in the disease course [98, 99]. Among the BG structures, the VS and caudate are of particular interest in MDD. The corticostriatal-thalamocortical circuit is the fundamental structure for the functionally segregated parallel networks centered on the BG, with the cortical ends including the motor, PFC, oculomotor and limbic regions [100]. In the limbic-striatal network, the VS has been proposed to bridge the motor/cognition system and the limbic system [33]. The nucleus accumbens (NAc) is one of the main elements of VS, with inputs from the limbic

structures (mPFC/ACC, amygdala, hippocampus and parahippocampus), thalamus (midline and intra-laminar) and mesencephalon (VTA, RN), and outputs to the BG (ventral pallidum, substantia nigra), hypothalamus and mesencephalon. NAc comprises a core and shell which can be distinguished by calbindin D28K and by their differential afferent/efferent distributions. The nerve bundle arrangement at the VS, especially the shell of the NAc, does not conform to the regularity observed in other BG pathways. In addition to the classical striatal-thalamocortical organization (by way of the ventral pallidum to the thalamus), VS has connections with deep nuclei, and like the vmPFC, VS may impose a direct influence on the hypothalamus [33]. The core and the shell receive input from dorsal and ventral mPFC/ACC, respectively, and the shell region has stronger mutual projections with the midbrain/brainstem and is modulated by monoaminergic neurotransmissions. Limbic-VS may gate information flow from the prefrontal region by providing contextual constraint (e.g., the hippocampus), motivational saliency (e.g., the VTA), physiological state (e.g., arousal, as indicated by the midline thalamus) and affective significance (e.g., the amygdala) to generate adaptive, goal-directed behaviors [101]. In MDD, limbic hyperactivity may bias behavior selection (connections from the PFC to the NAc) by negative affect (amygdala) and context (hippocampus).

Although the VTA does not belong to the BG, the proper functioning of the NAc requires the participation of the VTA which together with other reward-related nuclei is implicated in some core symptoms of MDD, including anhedonia, abnormal stress reactions and altered reward signaling. Dopaminergic neurons in the VTA innervate broad cortical and subcortical areas relevant to MDD, including the mPFC, limbic system (ACC, hippocampus, amygdala), BG (VS, pallidum), hypothalamus, lateral habenula, and bed nucleus of the stria terminalis [102, 103]. A unique feature of the VTA is that almost all areas receiving afferents from the VTA feedback to this region. Previous VTA research has shown a trend in which dopaminergic neurotransmission to the mPFC is modified by aversive stimuli whereas such transmission to the NAc is modified by reward (or both aversion and reward) [104]. Susceptibility to depression was reported to be associated with an opposite trend in phasic firing by mPFC-projecting and NAc-projecting VTA neurons [105]. This finding is largely compatible with the distinction of cortical and limbic compartments in the cortico-limbic dysregulation model. As the VTA receives strong glutamatergic input from the mPFC, VTA bursting is directly affected by hypofrontality. Stress-related neuroendocrine molecules, such as cortisol,

cortisol-releasing factor and dynorphin, also substantially impact the neurodynamics of the VTA [106]. Notably, reward/appetitive behaviors are mediated by a distributed network (i.e., not restricted to the meso-corticolimbic dopamine pathway), and are highly resistant to local insults [107]. Self-stimulation and self-administration studies have unraveled interacting neural nodes beyond the VS-VTA; these nodes encompass the supramammillary nucleus, RN, habenula, septal area and mPFC. In opposite to the reward-reinforcing neural nodes, such as the VTA, VS and supramammillary nucleus, the RN carries out reward-suppressing effect (as well as the lateral habenula and rostromedial tegmental nucleus), similar to its cortical inhibitory influence [108]. Taken together, hypofrontality, stress-mediated reaction and compensatory activities in RN may all influence the reward circuit and decrease motivational behaviors in MDD. Conversely, NAc stimulation may improve depressive symptoms [59].

Another striato-cortical pathway relevant to MDD relays through the caudate nucleus which is connected to the PFC and the pre-supplementary motor area [88, 109]. The caudate nucleus contributes to instrumental goal-directed behaviors, including the responses relevant to reward, flexibility in response selection, executive function and spatial processing [88]. Excitation over the dlPFC may increase neural activity and induce dopamine release in the caudate nucleus [110]. Volume reduction and decreased metabolism in the caudate nucleus was noticed in refractory MDD and may underlie cognitive inflexibility in a depressive state [9, 76, 111]. Depression in neurological disorders involving the BG frequently presents with hypofrontality [112-114] and hence, frontal dysfunction is shared by both primary and secondary depression even though the etiology can vary [115]. In clinical depression, decreased activity in caudate could be either the consequence (e.g., due to attenuated corticostriatal drive in MDD) or the cause (e.g., decreased striato-thalamocortical feedback) of abnormal PFC activity. In summary, the functions of the BG and VTA may be impaired in MDD by both hypofrontality and excitation of the RN. Conversely, BG and VTA pathology may directly result in hypofrontality; subsequently, clinical depression occurs when the balance of the cortico-limbic network is breached. The course of MDD in neurodegenerative conditions is certainly more complicated than the scenario described above, and is contingent upon the affected network, disease progression, and the degree of injury and compensation.

Mechanisms of Antidepressive Treatments (Synthetic Results 5-13)

In psychiatric research, a discrepancy has been frequently noticed between pathogenesis and therapeutic mechanisms. For example, in schizophrenia, the dopamine system is the main target of anti-psychotics, but it is the treatment response rather than the occurrence of disease that is associated with genetic polymorphisms of molecules involved in dopaminergic neurotransmission [116]. According to the history of psychopharmacology, the dopamine theory of schizophrenia was developed from the discovery of chlorpromazine not vice versa (i.e., the creation of a dopamine blocker was not based on dopamine theory). Similar story also applies to serotonin theory and MDD. The abnormal manifestation in the serotonin system, if any, may be consequential, compensatory or concurring with MDD rather than causal. Psychotropic medications resort to these neuro-modulatory systems to adjust the balance of a dysfunctional neural network and, thereby, obtain therapeutic effect. The good thing for these modulatory systems is that they distribute widely, which enables them to exert a large-scale influence. However, one drawback is that these systems lack regional specificity. These pros and cons explain the efficacy, side effects and inadequate response rate to treatment of MDD.

The neural inhibition of acute SSRI administration covers a wide range of cortical and subcortical brain areas [23, 28, 38]. Nevertheless, clinical improvement is usually associated with the normalization of limbic over-activity and PFC hypoactivity [1, 15]. How then does an inhibitory neural modulator finally enhance neural activities in the PFC or dorsal compartment? Analogous to the opposing effects of acetylcholine and epinephrine in the peripheral nervous system, Brodie and Shore proposed that serotonin and norepinephrine may exert inhibitory and excitatory modulation, respectively, on central nervous system activities [37]. Like SSRIs, NRIs have been acknowledged as effective antidepressants. A confusing question arises naturally: why do both inhibitory and excitatory agents treat the same disease, namely, MDD? It is herein proposed that a restoration of the physiological range of the RSM is critical for recovery from MDD. When the imbalance between the dorsal and ventral compartments is out of homeostasis, the hyperactive brain regions impose much greater inhibitory influences on the hypoactive brain regions to which they project. Then, the inter-regional inhibition is no longer balanced, as shown by Figure 2. To induce the therapeutic effect, the imbalanced cortico-limbic network must first be perturbed. The initial suppressive (or excitatory) effects of antidepressants

would reduce the imbalance between the dorsal and ventral compartments: Hyper-active (or hypo-active) brain regions respond more to suppressors (or stimulants) than do their hypo-active (or hyper-active) counterparts; this phenomenon is likely mediated by a non-linear response curve such as that of the ceiling/floor effect. When the reduction of the dorsal-ventral gap reaches a physiological level, the homeostatic operation of the RSM between the frontal region and the limbic system resumes, and the brain regains the control of the dorsal/cognitive system over the ventral/limbic system.

Equipped with the RSM, the explanatory power of the cortico-limbic dysregulation model of MDD is enhanced. As summarized earlier, once the large-scale excitation-inhibition balance is disrupted, limbic hyperactivity and hypofrontality may evolve to a super-stable attractor through the RSM, thereby giving rise to MDD. The network mechanisms further explain why, in responders, inhibitory neuro-modulators (e.g., SSRIs) may ultimately enhance frontal activity and why excitatory analogs (e.g., NRIs) may attenuate limbic hyperactivity. In non-responders, the acute suppressive influence (1 week) of SSRIs on the brain persists (up to 6 weeks) [22]. The incorporation of the cortico-limbic RSM thus helps to interpret these inconsistent findings, as the directions of brain metabolic changes before and after restoration of the RSM are expected to be opposite [117]. Although previous research has focuses on intra-cellular cascades to explain the delayed therapeutic effects of SSRIs, this research suggests that it is the timing at which the mechanism of the dorsal-ventral RSM is restored to its physiological regime that brings about full and lasting recovery. In addition to antidepressants, many other different treatment modalities can be integrated into the framework of the cortico-limbic RSM. TMS over the PFC improves hypofrontality [44], and vagus nerve stimulation (an FDA-approved device to treat resistant depression) ameliorates hyperactivities in the limbic system [6, 45, 46]. The common consequence of these two very different non-pharmacological interventions lies in their lessening of the imbalance between the dorsal and ventral compartments. For several monoamine systems (serotonin, norepinephrine and histamine), REM sleep is accompanied by a reduction in discharging and, hence, suppression in the release of neurotransmitter. Accordingly the therapeutic effects of sleep deprivation mimic those of the monoamine reuptake inhibitors [62]. Under physiological conditions, the RN is not over-driven because of the negative feedback to the sgACC/vmPFC; however, electrical stimulation to the sgACC/vmPFC may push the RN discharge beyond its original range, thereby perturbing the cortico-limbic imbalance [9]. Electroconvulsive therapy excites cortical, subcortical and limbic structures simultaneously to reset the cortico-

limbic balance. After antidepressant treatment for 6 weeks, the functional connectivity strengths between the pgACC and several limbic structures (thalamus, amygdala and striatum) increased in MDD patients but decreased in healthy subjects [38]. The opposite trends in functional connectivity suggest the engagement of a novel mechanism as a common third party to synchronize the limbic system in MDD, which could be the restoration of cortico-limbic reciprocity. In the controls, the attenuation of neural activity itself (by SSRIs) may reduce the signal-to-noise ratio of fMRI measurements, and, hence, the correlation levels. Stimulation of the NAc, which is surprisingly rapid in ameliorating depression symptoms and is also associated with increased metabolism in the dlPFC and decreased metabolism in the vlPFC, insula and thalamus, may improve depression in refractory cases [59, 60]. These research results indicate the possibility of a speedy recovery of MDD through the simultaneous stimulation of PFC and reward circuitry. Again, remission of MDD depends on the restoration of dorsal-ventral homeostasis and is not simply determined by duration. To summarize, regaining cortical control over the limbic system is a key component for MDD recovery and relies on the physiological balance of the RSM between the dorsal and ventral networks.

Evidence has suggested that neurodegenerative disorders of BG may result in depressive symptoms. However, the general inhibitory effects of SSRIs may reduce the metabolism or blood flow in the BG, which could be further aggravated by decreased fronto-striatal input [24, 118, 119]. The negative impact of SSRIs on the PFC-BG accounts for the unsatisfactory treatment response of the associated clinical depression and the occasional side effects of extrapyramidal syndrome [99, 120, 121]. Like antidepressants, simultaneously beneficial and deleterious effects over different brain regions have also been noticed for other neuro-modulatory agents. For instance, in Parkinson's disease, levodopa may impair as well as improve certain cognitive functions [122]. In refractory MDD, reduction in the size of the caudate nucleus as well as decreased metabolism in the caudate nucleus, anterior thalamus and NAc have been observed [9, 76], and SSRIs themselves may also decrease glucose metabolism in the PFC, BG and thalamus [23]. This article speculates that MDD patients with innately lower metabolic activity in the BG may be less responsive to SSRIs and may benefit from dopamine and norepinephrine enhancers. Nevertheless, for a substantial portion of patients with MDD, the unfavorable influence of SSRIs on the BG is clinically insignificant. In addition to their modulatory effects, antidepressants and mood stabilizers are also neurotrophic (or neuro-protective). The recovery of volume

loss in the sgACC may facilitate remission, lessen kindling propensity, and improve the prognosis [12]. The clinical efficacies of SNRIs and SSRIs are comparable (or still in controversy) since monoamine reuptake inhibitors do not possess strong regional specificity [123]. Newly developed antidepressants that target 5-HT_{2A} and 5-HT_{2C} receptors show differential affinity toward corticostriatal and limbic networks (higher regional specificity) and have demonstrated better treatment outcomes in resistant cases [124]. It is interesting to compare the influence of psychotherapy and antidepressants on the brain. Similarly to the acute or sub-acute effects of SSRIs, psychotherapy suppresses metabolic activities in the cortical, striatal and limbic structures [117, 125]. These change in activities and connectivity patterns in the limbic system may directly contribute to symptom reduction and to lower scores on depression rating scales; however, psychotherapy might require more time to reinstate the cortico-limbic reciprocity.

Recovery from MDD is a large-scale neural phenomenon that does not promise a complete repair of fine-scale glial/neuronal abnormalities in the dlPFC, mPFC, and vmPFC/sgACC. At the tissue level, pathology constitutes vulnerability, and its accumulation over recurring episodes may make the dorsal-ventral balance easier to break, thereby shortening the symptom-free intervals. In psychiatry, the underlying mechanism of the “kindling” phenomenon differs from that of epilepsy; the former (in this case, MDD) involves the tendency of large-scale networks to become imbalanced, whereas the latter involves the epileptogenic foci. In terms of MDD patients who receive sufficient antidepressant treatment but do not reach full remission, so-called partial responders, much remains to be explored. Evidence suggests that disinhibition in the limbic system may play an important role in incomplete remission [26]. In detail, during cognitive endeavors, healthy controls normally exhibit depressed limbic activity (as introduced in the cortico-limbic RSM), but for partial responders with MDD, the amygdala shows an increased response to cognitive demand. Furthermore, the beta value of the amygdala is positively correlated with the severity of depression and anxiety. The disinhibition in the limbic network indicates that the cortico-limbic interactions are ineffective. Reduction in symptom severity without the restoration of cortico-limbic reciprocity may lead to partial remission, relapse and recurrence. Although less aberrancy (less hypofrontality and less limbic hyperactivity) tends to predict a better treatment response, the actual story is much more complicated since the recovery of MDD involves network restoration and is not simply determined by the amount of hypo- or hyper-metabolism [20, 28].

Symptomatology and Others (Synthetic Results 15)

The diagnostic criteria for an MDD episode requires the persistence of either a depressed mood or the loss of interest and pleasure in association with at least four of the following symptoms: inattention, self-depreciating or suicidal thoughts, fatigue, and disturbances in psychomotor activity, circadian rhythm, appetite and weight (DSM-IV) [47]. The symptoms are required to last over a two-week period and to occur most of the day, nearly every day. MDD is obviously not equal to transient sadness; however, the induction of sadness is also accompanied by limbic hyperactivity and frontal hypoactivity [6]. The state of sadness and depressive disorders share similar features in metabolic/perfusion characteristics, suggesting a link between symptoms, the brain and psychopathology. Referring to the cortico-limbic framework, their notable differences lie in whether the network imbalance is in fluidity homeostasis and can be reversed easily, or whether this neural phenomenon becomes static. The duration criterion actually implies a super-stable attractor of the imbalanced network, which requires substantial time or demands external intervention to disengage. The "number criterion" of at least four symptoms indicates that the involved network in MDD should be large enough.

The distinction between dorsal and ventral compartments does not imply within-compartment homogeneity. Instead, the constituent sub-networks respond to environmental hypo- and hyper-metabolism via plasticity, feedback and compensation which may mask neural patterns of MDD to a certain degree [126]. To alleviate over-excitation, a sub-network within the hyperactive ventral compartment may ward off input from other brain regions, and after successful treatment, the distant couplings of limbic structures are expected to increase. This strategy could be reversed to allow the dorsal hypoactive compartment to overcome inertia. These inferences have gained preliminary support from connectivity analysis centering on the amygdala and frontal regions [127-130]. Moreover, variations in the sub-network features may explain individual symptom heterogeneity, neurophysiological subtypes and differential treatment responses [131, 132]. For the ventral compartment, unusual amygdalar hyperactivity and abnormal connectivity patterns may indicate comorbid anxiety [26, 133], whereas enhanced interactions between the sgACC and PCC may determine the expression of ruminative symptom [134]. Hippocampus atrophy is related to recent memory impairment [135]. For the dorsal compartment, remarkable hypofrontality, fronto-striatal hypoactivity (especially of the caudate nucleus) and fronto-striatal

disconnection are associated with dysexecutive syndrome [88, 136]. The impairment in input/output gating of the affected fronto-striatal network may contribute to the symptom of indecisiveness [137]. Although the mPFC participates in a wide range of cognitive functions, the dorsal part is particularly important in decision making and social interaction [138, 139], whereas the ventral portion is implicated in associative learning and adaptive response [135]. Dysfunction in the dorsal mPFC may contribute to impaired social interaction and judgment in MDD [26, 135, 140], and may enhance the risk of suicide [19]. Since both frontal and limbic systems may (directly and indirectly) affect the VS-VTA and deep nuclei, the neural manifestation of subcortical and deep structures could be inconsistent and patients may even present with opposite symptoms, such as hyperphagia versus poor appetite, or hyper-somnolence versus insomnia. The resultant imbalance in sympathetic and parasympathetic tone may elevate the risk of cardiac arrhythmia and sudden death [141]. To diagnose MDD, either the symptom of a depressed mood or the symptom of a lack of interest should be present. The alternate core symptom could be related to individual differences in the degree of compensatory feedback from the vmPFC/sgACC to the RN (and other inhibitory deep nuclei). In patients with stronger RN activation in response to limbic hyperactivity, both limbic hyper-metabolism and depressed mood are somewhat mitigated; however, the strong inhibitory modulation from the RN may contemporaneously impact the VS-VTA to such a degree that the patients cannot feel pleasure. This conjecture was endorsed by the observation that the degree of anhedonia was positively correlated with the activities in the vmPFC, which is not regarded as a pure reward center; not surprisingly, a negative correlation was also reported between the anhedonia score and neural activities in the VS [142]. Cortical midline structures, including the mPFC and limbic components, constitute the building blocks of self-referential processing, which is known to be abnormal in MDD and may be characterized by self-focus and self-critical tendencies [143, 144]. Despite the widely accepted symptomatology approach, it is noteworthy that the symptom-brain relationship is quite complicated: some symptoms may co-occur; opposite symptoms may not indicate reversed metabolic profiles; and some symptoms can be deciphered to different phases [3]. In psychiatry, clinical rating scales are frequently adopted to quantify symptom severity and to define treatment response and remission. The indicators derived from brain dynamics, such as the magnitude of cortico-limbic imbalance, the degree of involvement of the BG, and the restoration of the cortico-limbic RSM, might provide useful information for clinical judgment.

Given that the pathology of MDD covers such a wide range of cortical, subcortical and deep structures, neural computations over many neuropsychological domains are affected. This article does not cover this important topic, and interested readers may refer to materials published elsewhere for reviews of neuropsychological impairment and affective bias in MDD [3, 49, 50]. It is notable that similarly to symptomatology, individual differences in neuropsychological impairment may also result from the distinct re-organization of sub-networks to counteract large-scale network imbalance that occurs in MDD; this possibility demands further research and network models to investigate. It has long been regarded that male and female brains can be distinguished by the degrees of cerebral lateralization, which is endorsed by a recent connectome analysis [145]. Assuming a condition in which cortico-limbic imbalance occurs in one half of the brain, less inter-hemispheric cross-talk may render the other hemisphere a safety valve or reservoir such that the whole system does not easily descend into a vicious cycle of dorsal-ventral imbalance via the RSM. Thus, the cortico-limbic RSM together with gender differences in lateralization might also account for the much higher prevalence of MDD in the female population.

MDD and other forms of clinical depression are prevalent, similar in neural manifestation, and may occur at any age (from early childhood to old age). With the dysfunctional RSM in mind, it is herein postulated that MDD actually reflects a bug of brain organization. The RSM is evolutionarily adaptive since it allows for a swift switch between brain modules with minimal interference and with frugal energy consumption. The RSM is a necessity for a powerful and efficient machine that carries out a multitude of distinct, sometimes incompatible functions. For small networks, the RSM does not cause any problems since the equilibrium is guaranteed by the diverse origins of inputs. For large networks that fulfill complicated, integrated and expanded mental functions, however, a vicious cycle is a potential trajectory when the imbalance reaches a certain breaking point (Figure 2A). Moreover, in the case of MDD, the discharge of the RN (one of the physiological compensatory mechanisms) may only moderately reduce limbic hyperactivity because the activity of RN is constrained by the interaction with the vmPFC/sgACC (Figure 2B). Individual resilience can be defined by resistance to becoming trapped into the maladaptive attractor and by the capability to maintain equilibrium. Recently, the Research Domain Criteria (RDoC) project was initiated by the National Institute of Mental Health with the hope to improve the diagnosis and treatment of psychiatric disorders [146]. Despite the similarity in incorporating biological discoveries to improve psychiatric

knowledge, this work is not directly related to RDoC, which currently aims to provide nosology and classification. Instead, this work focuses on the fundamental “mechanism” of MDD, and from a mechanistic understanding, a neurological definition of MDD may be achieved. Certainly, the products and by-products of the iterative analysis-synthesis process may have the potential to be integrated into the RDoC.

Analysis-Synthesis Approach

What is the difference between analysis and synthesis, and why do we need an analysis-synthesis approach? Modern science is dominated by analysis and linear thinking, which have been hugely successful. However, under some circumstances, synthesis and non-linear thinking may result in a breakthrough. Though synthesis has already been applied to other scientific fields, it is still very uncommon and unacknowledged in neuroscience. It is noteworthy that analysis and synthesis are not exclusive of each other; instead, they are complementary and may enrich each other [3]. Several examples are illustrated below:

- 1) *Archeology and anthropology*: Archeologists and anthropologists always take synthetic approach to integrate relics, literature, ecofact, landscapes and architecture to reconstruct the history of an empire or civilization. This approach is a good example how analytic and synthetic methods work synergistically. Archeology/anthropology cannot help but being synthetic because its targets are all about the past. In the absence of time machine or time tunnel, the discipline of archeology/anthropology must involve a “dialectic” process between analytic and synthetic endeavors.
- 2) *Forensics*: Forensic officers collect and analyze physical evidence and micro-evidence. However, only a synthetic attitude may integrate all of the pieces of information to reconstruct what happened at a crime scene. Clearly, the persuasiveness of the synthetic stories of (1) and (2) relies on the accountability of the pieces of evidence (analytic products).
- 3) *Physics*: The formation of the universe is a hot topic in physics. Even though this event might have occurred 13.8 billion years ago, the Big Bang theory was raised based on a variety of observations. Its validity lies in its plausibility (physical laws) and accountability (abundance of

light elements, radial velocity of extra-galactic nebulae, cosmic microwave background, redshift, and so on) [147]. The spirit behind this achievement (or, more modestly, this theory) is not only analytic but also synthetic. It is important to note that the proposed theory may lead to novel predictions that can be verified or rejected by further analytic experiments (e.g., large particle accelerators). Astrophysics generally applies synthesis to construct theories about celestial objects light years away. The grand unified theory is another example of synthesis in physics which attempts to integrate electromagnetic, weak and strong forces into a single force [148]. The theory can be examined by its prediction of novel particles (analysis).

- 4) *Chemistry*: Rigorous linear thinking always occurs when we are awake. However, non-linear thinking may even occur during dreaming. The Russian chemist Dmitri Mendeleev constructed the “constitution” of chemistry, the periodic table of chemical elements, which had long puzzled researchers in his era. How did he solve the mystery? He said, “I saw in a dream a table where all elements fell into place as required. Awakening, I immediately wrote it down on a piece of paper, only in one place did a correction later seem necessary.” Based on the massive analytic facts of different chemical elements, Mendeleev attempted to organize these elements into one unified framework. The enlightenment in his dream was typical of non-linear thinking, and his attitude was clearly synthetic [149].
- 5) *Biology*: In another inspiring dream, Otto Loewi “designed” an elegant and influential experiment that was very important to physiology since it proved that the neural transmission in heart was chemical, not electrical. It is interesting to note that he forgot the dream the second day and could not recognize his scribbles. Fortunately, he had the same dream the second night. Needless to say, his discovery benefited from non-linear thinking [150].
- 6) *Empirical neuroscience*: In empirical neuroscience, a synthetic attitude is still not broadly accepted. Francis Crick, who discovered the structure of DNA with James Watson, had made interesting attempts to solve complicated issues in neuroscience by adopting the spirit of synthesis. A core property of our attention system is to simultaneously suppress distractors and magnify target information. In a research paper, Crick analyzed the features of searchlight hypothesis of attention (analytic) and tried to discover the neural correlates that may satisfy the two contradictory constraints

(synthetic), namely, excitation for the target and inhibition for the non-target [151]. In his book “The Astonishing Hypothesis,” Crick summarized the prerequisites of a conscious experience (analytic) and then tried to synthesize them under a unified framework (synthetic) [152]. Although his propositions are still debated, the combination of analytic and synthetic perspectives is obvious in his methodology. Interestingly, Crick majored in physics in his college education, which may explain why he applied the accepted analytic/synthetic attitude in physics to empirical neuroscience so naturally.

- 7) *Computational neuroscience*: The only way for computational neuroscience to examine the validity of its model is through synthetic investigation. For example, a remarkable feature of alpha oscillation is its spontaneous bursting at low- and high-amplitude, called bi-stability. A computational model of EEG that may reproduce the bi-stability at alpha spectrum (and thereby satisfying the two constraints concurrently) is appreciated and is regarded as more convincing [153]. The conditions that must be satisfied are analytic results (from various sources), and the model that can clearly explain all the conditions is the result of synthesis.
- 8) *Psychiatry*: As a discipline, psychiatry emphasizes the holistic assessment of a person. Its diagnostic instruments do not rely on a single complaint but on a constellation made up by clusters of symptoms/signs (i.e., synthesis). As an analogy, though a single star in the night sky does not mean much, a set of stars that constitute a constellation becomes recognizable and informative [47, 154].

The nature of human cognition is a mystery and is still under debate. For simplicity and clarity, this study contrasts linear and non-linear thinking that are assumed to be the respective capabilities underlying (but not limited to) analysis and synthesis, and both are our given talents [2, 3]. A distinguishing feature of linear and non-linear thinking lies in the “visibility” of the reasoning processes. For the former, the step-by-step logic is clear to the thinkers and the readers/listeners (e.g., the elaboration in most academic papers), whereas for the latter, even the inventors of a theory/concept/methodology generally have no idea how they reached their insight. The process of non-linear thinking usually requires prolonged breeding. In Loewi's Nobel Prize speech, he said, “It was the design of an experiment to determine whether or not the hypothesis of chemical transmission that I had uttered 17 years ago was correct.” Synthesis is opposite to mathematical derivation in some way. Mathematical

derivation usually follows a forward, step-by-step process; however, synthesis and non-linear thinking may resort to backward verification. For example, Albert Einstein tried to fix the velocity of light to all observers using non-linear thinking (it is unknown how he postulated that); the consequence was deduced theoretically in the special theory of relativity and examined experimentally [155]. From the above examples, it is evident that synthesis and non-linear thinking have been applied in other scientific fields. There seems to be no reason to prohibit the application of synthesis in neuroscience and neuroscientific research of psychiatric disorders. Non-linear or lateral thinking has been regarded as the creative aspect of mental capabilities and could also be the cognitive foundation of artistic works (or fantasy, imagination and Mozart's music) [2]. Accordingly, it is mandatory to contrive a standard to regulate the activity of synthesis/non-linear thinking in (neuro-) science which has not been clearly articulated yet.

Based on abundant examples in the history of science, the three criteria of rationality (in this article, biological plausibility), comprehensiveness (accountability) and parsimony are proposed to evaluate the synthetic endeavors and non-linear thinking in science. The first two criteria are obvious: the theory itself must be plausible and may account for the observations, as many as possible, from different perspectives. In terms of Bayesian posterior probability, the probability of the network mechanisms/models given the observation is $P(M|O)$, which is proportional to $P(O|M) \cdot P(M)$, where P , M and O denote probability, observations and the selected mechanisms/models, respectively. In this article, $P(M)$ can be expressed as $P(M1, M2, M3)$ since there are 3 network mechanisms (cortico-limbic reciprocal suppression, excitatory-inhibitory feedback between the vmPFC/sgACC and raphe nuclei, and fronto-striatal interaction), while $P(O)$ can be expanded to $P(O1, O2, \dots O15)$ given there are 15 different observations (see the *Materials and Methods* and *Results*). The $P(M)$ and $P(O|M)$ offer indices of plausibility and comprehensiveness in accountability, respectively. The performance of different sets of network mechanisms/models can be evaluated by Bayes factor (i.e., model comparison) such as $P(M1, M2, M3|O)/P(M4, M5, M6, M7|O)$. The last criterion of parsimony is reminiscent of Occam's Razor and is assumed to be a general constraint in many contexts [156]. In physics, the grand unified theory is a typical case of parsimony, in which one is used to explain many. In psychopathology, it is inferred in the *Introduction* that a parsimonious, vantage perspective is feasible from the viewpoints of probability and complexity theory. Furthermore, it is a common practice in engineering (e.g., machine

learning) to impose penalties on the complicatedness of a model (including disease models) to avoid over-fitting of the data (observation) [157]. The Bayesian information criterion (BIC) claims that $BIC = \log(n) \cdot k - 2\log(L)$, where n is the number of data, k is the number of free parameters to be estimated, and L is the likelihood function, or $L = P(O|M)$ [158]. In this research, n is fixed and is the observation number ($n = 15$), and k is the model number ($k = 3$). The goal is to find the set of models that altogether have the lowest BIC, and a smaller number of mechanisms/models is preferred (note: $\log(P(M|O))$ is closely relevant to BIC, which can be derived mathematically. In other words, a penalty may be implicitly charged in the Bayesian posterior probability and Bayes factor). To sum up, the proposed three criteria to justify synthesis and non-linear thinking in science are distilled from other scientific disciplines, expounded by reasoning and philosophy, and endorsed by mathematics. In an ideal situation, analysis and synthesis interact and enrich each other. A synthetic product may facilitate the development of novel theories and hypotheses, which may subsequently generate new predictions and guide new experiments that can be examined by analytic procedures. In other words, the analysis-synthesis hybrid is dialectic in nature and undergoes iterative modification and advancement. A recent example of the iterative/dialectic process is the Big Bang theory, which is still under refinement [147].

This study demonstrates the application of the analysis-synthesis hybrid to psychopathology. As analytic facts are the materials referenced, this information is in Part I of the *Materials and Methods* section, whereas the observations (O1 to O15) to be accounted for are listed in Part II. The synthetic products are the main results, and the biological plausibility and accountability of O1 to O15 are explicated, respectively, in Parts I and II of the *Results*. The above framework is what the authors recommend for the future application of the analysis-synthesis hybrid to neuroscientific issues. On the one hand, the synthetic approach should be encouraged to advance neuroscience, whereas on the other hand, the liberal abuse of non-linear thinking may harm academic integrity. To reconcile this conflict and to assure rigorous neuroscientific standards, a simple heuristic is proposed: the number of explained observations of different (independent) orientations by the synthesis should be no less than 5. In the modern era, the confidence of analytic research is usually promised by $P < 0.05$, which means that the probability of the discovery by chance (null hypothesis) is lower than 0.05. According to Fisher's combined probability test (a meta-analysis), the likelihood for all 5 observations to be contemporaneously valid by chance in a

single study is approximately 0.001 (chi-square = 29.96, d.f. = 10) [159]. In this article, O1 to O15 easily exceed the cutoff. Robust statistics are necessary for a synthesis because the criteria of parsimony and the synthesis itself imply that the seemingly independent observations can be bridged by the synthetic product; thus, in actuality, the observations are not completely independent. Namely, $P(O1, O2 \dots O5|M)$ shall be larger than $P(O1|M)*P(O2|M)*\dots P(O5|M)$. An arbitrary scale is proposed to evaluate the performance of a synthetic model: the explained observation number 1–2 is poor, 3–4 is fair, 5–7 is good, 8–10 is very good, and > 10 is excellent. Obviously, this synthetic endeavor should not be mistaken as an extensive review article. It is noteworthy that there are different forms of synthesis. This article resorts to an “underlying mechanism” to fulfill the synthesis, whereas Mendeleev’s periodic table is another example in which the integration was implemented. Since synthesis is the product of non-linear thinking, there is no reason to limit its format in neuroscience.

CONCLUSION

It is believed that neuro-psychiatric disorders must have their signatures at a large-scale network level. The holistic influence of all the neurobiological correlates of MDD, such as neurochemical and neuroendocrine factors, genomic expression, glial and neuronal pathology, abnormal synaptic neurotransmission, apoptotic and degenerative change, and derangement in the intra-cortical plexus, will manifest themselves together in brain dynamics. The original concept of cortico-limbic dysregulation model of MDD that was proposed 2 decades ago is still valid in general. However, the model is descriptive in nature and current insights are much more differentiated. Equipped with the RSM, limbic-striatal network and interaction of vmPFC/sgACC-RN, the explanatory power of the cortico-limbic dysregulation model is enhanced beyond its original content. With simple network mechanisms based on biological plausibility, many phenomena and controversies are explained, satisfying the three criteria of rationality, parsimony and comprehensiveness. In fact, this research attempts to demonstrate and formulate a useful framework, analysis-synthesis hybrid, to discover the underlying mechanism of complicated emergent phenomena and to investigate fundamental neuroscientific issues [3]. Although not resorting to statistical examination, this methodology is in accordance with model selection and posterior probability, and the ability of the synthetic product to

reasonably explain various observations is crucial. The synthesis is obviously not the end point, and may provide new predictions to guide further research in more theoretically sound directions.

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Conflict of Interest

No conflicts of interest to declare.

Author Contributions

TW Lee and SW Xue provided intellectual input to this work. TW Lee wrote the first draft.

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Framing major depressive disorder as a condition of network imbalance at the compartment level: a proof-of-concept study

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Major depressive disorder (MDD) is associated with hypoactivity in the frontoparietal (FP) system and hyperactivity in the limbic (LM) system. The widely accepted limbic-cortical dysregulation model has recently been extended by the concept of imbalanced reciprocal suppression between these 2 systems. This study investigates the refined theoretical framework. Neuroimaging datasets from 60 MDD and 60 healthy controls were obtained from the Canadian Biomarker Integration Network in Depression database, including structural magnetic resonance imaging (MRI) and resting-state functional MRI (rsfMRI). The cerebral cortex was parcellated using the modular analysis and similarity measurements (MOSI) technique. For each node, the average amplitude of low-frequency fluctuation (avgALFF) and nodal strength were calculated. Correlation analyses were conducted to establish an adjacency matrix and assess the relationship between nodal power and strength. The results indicated that the LM system in MDD displayed higher partition numbers and avgALFF ($P < 0.005$). A significant negative correlation between nodal strength and power was replicated ($P < 1E-10$), suggesting that greater functional input enhances regional neural suppression. Notably, MDD participants exhibited a higher negative correlation between FP nodal power and LM-FP connectivity (stronger suppression) but a lower negative correlation between LM nodal power and FP-LM connectivity (weaker suppression). These findings support the theory of abnormal cortical signal organization and reciprocal suppression in MDD.

Keywords: amplitude of low-frequency fluctuation; frontoparietal network; functional connectivity; limbic system; major depressive disorder.

Introduction

Major depressive disorder (MDD) is a prevalent and disabling condition that imposes a significant burden on patients, their families, and society (Ferrari et al. 2013; Vos et al. 2015). In the United States, the 12-mo prevalence of MDD is estimated to be 7%, with females experiencing rates 1.5 to 3 times higher than males, beginning in early adolescence (American Psychiatric Association 2013). While the core symptoms include depressed mood and loss of interest, along with social and occupational impairment, MDD manifests a broad array of additional symptoms. These include cognitive decline ("pseudodementia"), fatigue, feelings of guilt or worthlessness, psychomotor agitation or retardation, sleep disturbances (insomnia or hypersomnia), appetite changes, significant weight fluctuation, suicidal ideation, and even psychotic symptoms. Furthermore, MDD is often comorbid with other psychiatric disorders, such as anxiety disorders, obsessive-compulsive disorder, post-traumatic stress disorder, and substance dependence (Oquendo et al. 2005; Kessler et al. 2008; Brière et al. 2014), suggesting an underlying pathology that increases susceptibility to various conditions.

Consistent with its clinical presentation, brain abnormalities in MDD are widespread, affecting both cortical regions and sub-cortical nuclei (Drevets 1999; Wu et al. 1999; Mayberg et al. 2000; Kennedy et al. 2001; Sheline et al. 2001; Drevets et al. 2002; Mayberg 2003; Holthoff et al. 2004; Mayberg et al. 2005; Aihara et al. 2007; Siegle et al. 2007; Hwang et al. 2010; Smith et al.

2011b; Elliott et al. 2012; Ruhe et al. 2012; Lee et al. 2013; Phillips et al. 2015; Pilmeyer et al. 2022). This distributed pattern of neural dysfunction suggests that MDD is unlikely to be caused by a single abnormal brain region or circuitry, but rather by the malfunctioning of large-scale networks. In line with this, a consistent neural pattern in MDD has been identified—hypoactivity in the frontal (or frontoparietal; FP) network and hyperactivity in the limbic (LM) system (Drevets 1999; Mayberg 2003; Pilmeyer et al. 2022). This observation supports the limbic-cortical dysregulation model proposed by Mayberg (Mayberg 1997), which has since been refined and expanded, forming the central focus of this study (Lee 2016; Lee and Xue 2018b).

Rationale for conceptualizing MDD as an imbalance between LM and FP compartments

Strong evidence supports LM hyperactivity and hypofrontality in MDD. LM hyperactivity—observed in regions such as the anterior cingulate cortex, posterior cingulate cortex, orbitofrontal cortex, amygdala, and parahippocampal gyrus during acute MDD—normalizes with clinical improvement (Kennedy et al. 2001; Sheline et al. 2001; Drevets et al. 2002). Of particular relevance, amygdalar disinhibition is evident in response to cognitive demands and emotional stimuli (Sheline et al. 2001; Lee et al. 2013). Note that this proposal uses the term "limbic system" to represent a broader concept that hosts the midline, outer, and deep cortical portions of the default-mode network (DMN) (Lee and Xue 2018c).

Hypofrontality—another pathognomonic feature of MDD—was noticed in the dorsolateral prefrontal cortex (PFC) and the medial PFC (Kennedy et al. 2001; Drevets et al. 2002; Mayberg et al. 2005; Aihara et al. 2007; Siegle et al. 2007). In addition, during the depressive state in MDD, reduced frontopolar activities to both positive and negative social stimuli and cognitive challenges were observed (Elliott et al. 2012). Remission is associated with normalizing hypo-metabolism in several frontal regions (Mayberg et al. 2000; Kennedy et al. 2001; Drevets et al. 2002). Transcranial magnetic stimulation over the dorsolateral PFC and medial PFC may enhance frontal function and improve depression (Speer et al. 2000; Downar et al. 2014). Although the superior and inferior parietal cortices have attracted less attention in MDD research, their decreased activities are often in tandem with those in the PFC (Disner et al. 2011; Pimontel et al. 2016). Cerebrovascular lesions in white matter may unfavorably impact the operation in the FP compartment and lead to secondary depression (Culang-Reinlieb et al. 2010; Santos et al. 2010). A recent review substantiated the above-summarized patterns consistently observed for 2 decades (Pilmeyer et al. 2022).

Notably, the findings from independent brain research of MDD are distributed broadly in the PFC, parietal cortex, and LM region. The involved circuitries comprise—but are not limited to—emotion regulation, emotion processing, reward, saliency, executive control (Brand et al. 2015; Phillips et al. 2015; Pimontel et al. 2016), etc. The abnormality of single or few circuitries cannot accommodate the multifaceted symptomatology of MDD (Chen et al. 2005; Heinzel et al. 2009; Hwang et al. 2010; Lee et al. 2011; Busatto 2013; Bagherzadeh-Azbari et al. 2019). They altogether decline the conjecture that the pathological foci of MDD are localized/confined or attributable to limited circuitries but indicate an imbalance between the LM system and the FP portion of the cortical mantle. The insight is paramount since it suggests compartment-level dysfunction to account for MDD, which signifies a possible fundamental difference between psychiatric and neurological conditions. MDD pathology—as a canonical example of psychiatric disorders—may engage 2 (or more) large networks (Lee 2016; Lee and Xue 2018b). “Compartment” is henceforth used to represent the neural substrates that embraced much broader brain regions (large network), in contrast to circumscribed circuitry/network (eg saliency circuitry and DMN) used in extant literature. Even though the insightful limbic-cortical dysregulation theory was proposed 2 decades ago, the exploration that takes the whole FP and LM systems as processing units is still pending.

Analytic framework to examine compartment-level pathology

Although assessing large brain networks (compartments) appears straightforward, it faces inherent challenges due to the vast number of voxels generated by magnetic resonance imaging (MRI)—often tens to hundreds of thousands—recorded at millimeter-level spatial resolution. While finer resolution is advantageous, it leads to high-dimensional data that impose heavy computational demands. Fortunately, the temporal dependencies between neighboring voxels provide a rationale for dimension reduction strategies. Cortical partitioning is commonly based on anatomy, but its validity has been frequently questioned (Amunts et al. 1999; Smith et al. 2011a; Wig et al. 2011; Stanley et al. 2013; Lee et al. 2014; Xue et al. 2014). Functional cortical parcellation (FCP)—which segments the brain based on functional MRI (fMRI) signals rather than structural atlases—offers a physiologically plausible alternative (Shi and Malik 2000; Damoiseaux et al. 2006; Smith et al. 2009; Shen et al. 2013). To address this challenge,

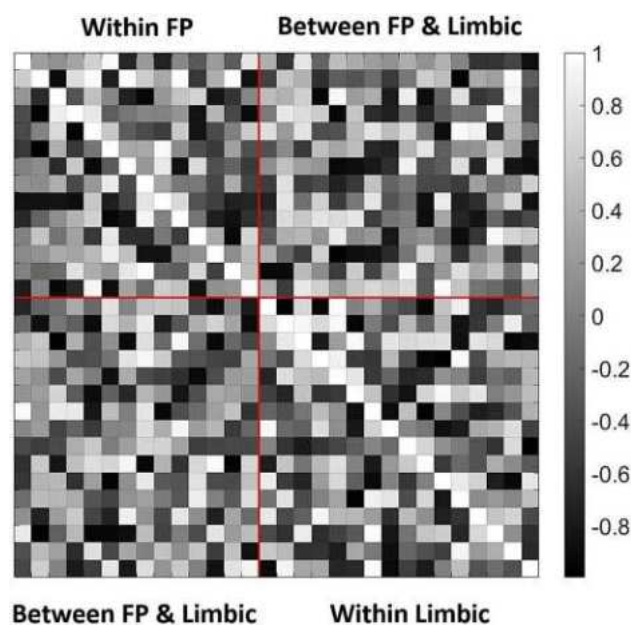


Fig. 1. An illustration of the 3 categories of analyses using a tentative correlation matrix: within the FP compartment (left upper), within the LM compartment (right lower), and between the FP and LM compartments.

the author developed Modular Analysis and Similarity Measurements (MOSI), a data-driven algorithm introduced in *Materials and methods* section. MOSI enables individualized, multi-resolution parcellations of resting-state fMRI (rsfMRI) data into functionally homogeneous clusters, which form neural nodes. Communication between these nodes defines the brain network, forming the analytic basis for this study.

Following MOSI, the mean power—represented by the amplitude of low-frequency fluctuations (ALFF)—was calculated for each node. The interaction between nodes was quantified using the degree of correlation between their mean temporal series, also known as functional connectivity (FC). Given this, the negative relationship between regional and inter-regional profiles was examined based on the author’s recent work (Lee and Xue 2017b; Lee and Tramontano 2024). It is expected that the interaction between FP and LM compartments will deviate in MDD. Comparisons between MDD and normal groups can be categorized into 3 domains: within the FP compartment, within the LM compartment, and notably between the FP and LM compartments, see Fig. 1.

The Desikan–Killiany Atlas delineates anatomical regions belonging to the FP and LM systems (Desikan et al. 2006). For the LM system, Mega et al.’s definition—distinguishing the orbitofrontal cortex/amygdala-centered paleocortical division and the hippocampus/cingulate-centered archicortical division—was followed (Mega et al. 1997). Each MOSI’s partitions can then be categorized into FP, LM, or other brain lobes. Based on the understanding that the DMN carries LM information flow (Lee and Xue 2018c), the middle temporal cortex and angular gyrus were also categorized as part of the LM system in terms of functional (not anatomical) attributes. By fulfilling FCP, MOSI offers flexibility regarding the spatial extent of functional units (modules) while adhering to established observations in brain dynamics.

Materials and methods

Subjects, MRI data, and preprocessing

Baseline MRI data were collected from a total of 140 subjects, including 70 patients with MDD and 70 healthy controls (HC),

all sourced from the Canadian Biomarker Integration Network in Depression (CAN-BIND) (Lam et al. 2016), in which written consent was obtained from each participant. Private Pearl IRB (www.pearlirb.com) approved this study and issued a certificate of “Exempt Research Determination” (IRB ID: 2023-0133) at the request of CAN-BIND. Functional and structural MRI images of the whole brain were acquired using 3.0 Tesla MRI scanners (GE, TR=2 s, voxel size=4 × 4 × 4 mm³, 300 volumes). For detailed information about the scanning procedures and study protocol, please refer to Lam et al. (2016).

The echo planar imaging (EPI) data were processed using the Analysis of Functional NeuroImages software package (Cox 1996). Preprocessing steps for rsfMRI included despiking, slice-time correction, realignment (motion correction), registration of T1 anatomy, spatial smoothing, and bandpass filtering at 0.01–0.15 Hz (Tong et al. 2019). The first 4 scans were discarded to ensure magnetization equilibrium. A smoothness kernel of 8 mm was applied to the EPI data. The FreeSurfer software was used to segment gray and white matter from T1-weighted structural MRI data and to parcellate the cortical mantle into 68 regions of interest based on the Desikan–Killiany Atlas (Dale et al. 1999; Fischl et al. 1999; Desikan et al. 2006), providing the initial partition for subsequent MOSI analysis. Following the analytic pipeline developed by Jo et al. (Jo et al. 2010; Lee et al. 2014; Xue et al. 2014), 12 movement parameters, along with white matter and ventricular signals, were modeled in the regression (Jo et al. 2010). Additionally, third-order polynomials were used to fit baseline drift. ALFF was calculated as the square root of the band-passed power of BOLD dynamics. Pearson correlation coefficient (CC) was computed between the temporal traces of any paired voxels or the mean temporal traces of paired clusters to indicate FC.

MOSI analysis and adjacency matrix construction

The connectivity map based on CCs is the foundation for modular analysis. Modules or communities are groups of nodes within a network that are more densely connected to one another than to other nodes, as defined by the CCs. MOSI incorporates modular analysis and similarity measurements, splitting a module into sub-modules and uniting similar sub-modules into a bigger module. MOSI fulfills the parcellation of the cortex, abiding by only 2 criteria: neighborhood and similarity, with adjacent voxels sharing similar neural activities grouped together, precisely the rationale behind the FCP of cortical signals. The splitting-unifying processes were repeated until convergence. The current version of MOSI uses the Louvain community detection algorithm. The number of modules and, hence, the partition resolution can be titrated by gamma values, with a higher value yielding more modules (Lee and Tramontano 2021). The author explored gamma values ranging from 0.45 to 0.90 (10 different resolutions). At gamma 0.45, the partition numbers are on the order of tens, aligning with the partition numbers of commonly used atlases. At gamma 0.85/0.90 and beyond, the partition numbers reach a plateau, showing no significant increase (Lee and Tramontano 2021), as illustrated in Fig. 2. The unique features of MOSI are as follows: (i) it is an individualized analysis feasible for the heterogeneity in MDD, (ii) it lays out a plausible foundation for subsequent network analysis, and (iii) it enables a multi-resolution approach to investigate brain informatics at different scales (Lee and Tramontano 2021).

With MOSI-defined partitions and corresponding neural nodes, an adjacency matrix can be constructed by first calculating the correlations between the mean time series of each node pair, and

these CCs are then converted to z-scores using Fisher’s transformation. Given that the module sizes derived by MOSI vary, it is crucial to apply an appropriate weighting strategy to the resulting adjacency matrix. Assume there are N nodes, and nodes i and j have sizes N_i and N_j , respectively. The connection strength between nodes i and j can be weighted by $\sqrt{N_i \cdot N_j}$ and then normalized by average weight across all possible connections excluding the diagonal components (weighting strategy I).

Statistical comparisons MOSI result analysis

For each gamma value and the associated partition, two-tailed, independent, two-sample t-tests were performed between MDD and HC groups regarding the partition number, mean voxel number per module, and average ALFF (avgALFF) per voxel, with a null hypothesis that there were no between-group differences. Since spatial extents of the MOSI results were not fixed and varied with different gamma values, the total voxel number and ALFF were also compared. QQ-plots were employed to explore differences in module size distributions between the MDD and HC groups. If differences are confirmed, *post hoc* analyses will be conducted to clarify the effects of size on neural metrics described above. Multiple comparisons were addressed for each set of tests as follows: 5 metrics derived directly from MOSI (P -value=0.05/5, Table 1), 2 comparisons of inter-compartment power-connectivity (P -value=0.05/2, Table 3), and 4 comparisons of neural metrics for the 15% largest vs. the 85% remaining modules (P -value=0.05/4, Tables 4 and 5). Since the outputs from different gamma values are not entirely independent, applying further Bonferroni correction would be overly harsh, potentially leading to false negatives. Therefore, statistical thresholds were set at P -values < 0.01 and < 0.005 to reflect varying levels of stringency. Several indices that are not central to the main focus of this study are summarized in the Supplementary Material (Part IV), including the mean CCs of the FP system, LM system, between the FP and LM systems, and overall mean CCs (combining the FP and LM compartments) and their associated integrative graph indices (Rubinov and Sporns 2010).

Exploring the relationship between power and connectivity

The investigation of regional and inter-regional relationships is driven by the observation that the global connectivity of a node (ie nodal strength in weighted graphs or nodal degree in unweighted graphs, both defined as the sum of connection metrics centered on a node) may influence the power of that specific node (Lee and Xue 2017b; Lee and Tramontano 2024). It has been noted that the nodal strength at the lower end of the spectrum of neural signals (fMRI and delta/theta spectrum in electroencephalography [EEG]) may reflect more inhibitory information, with a higher nodal strength robustly correlating with reduced nodal power (ALFF) (Lee and Tramontano 2024). In terms of methodology, this report was improved by considering different module sizes. Since smaller modules may exhibit a higher nodal strength due to a greater proportion of external connections from the remaining units, this report instead employed the averaged nodal strength (ie mean FC) as a normalization procedure. Similarly, because smaller modules tend to have lower summed ALFF values, the avgALFF was adopted. Unless otherwise stated, all nodal strength and ALFF values reported in this study refer to their mean values. Importantly, while correlation analysis is typically bidirectional, in this context, the relationship assumes a certain degree of directionality: It is the nodal strength that may influence nodal

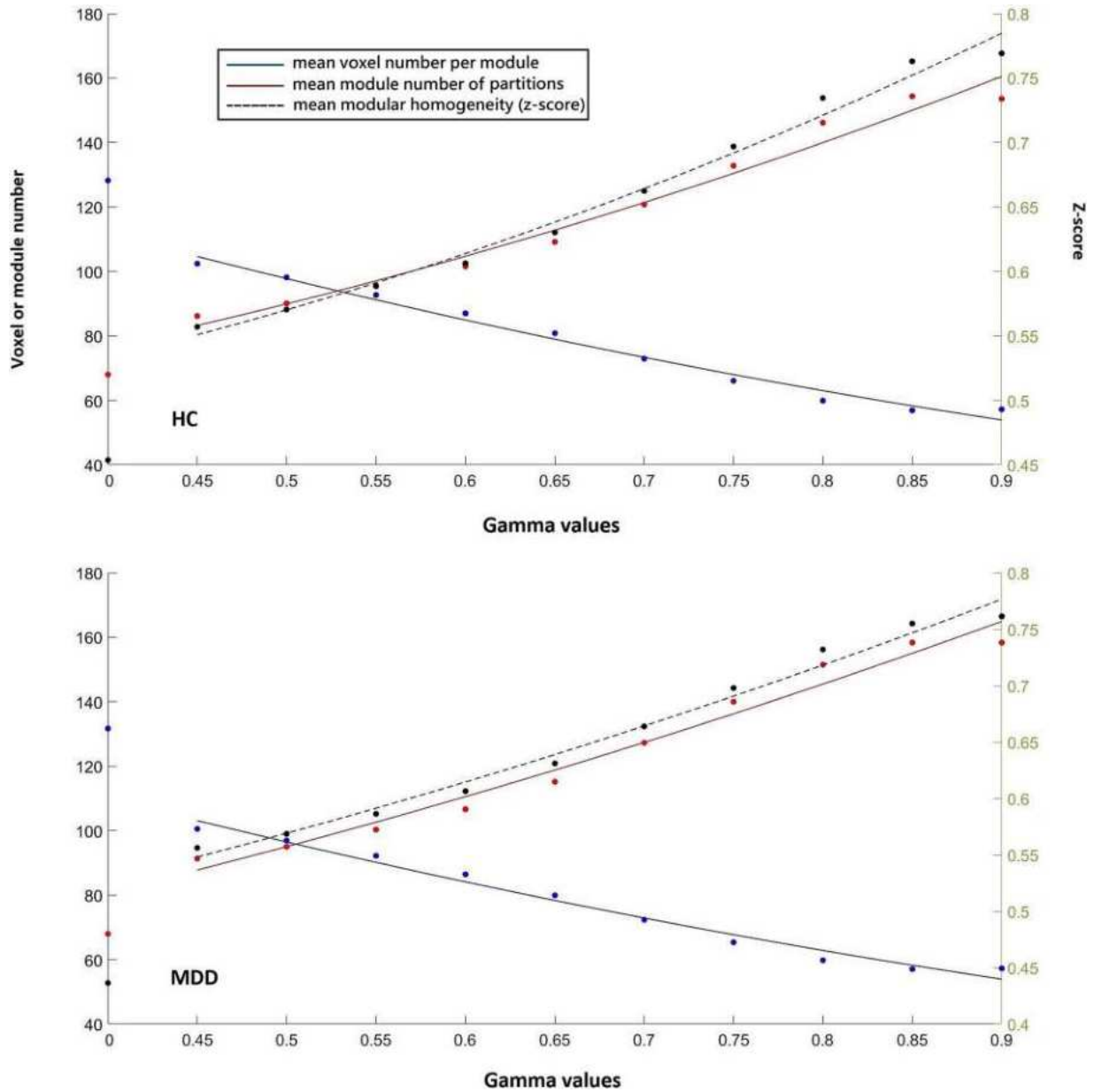


Fig. 2. Scatter plots of three indices derived from the CAN-BIND dataset, with the X-axis showing 10 gamma values (resulting in 10 data points per index) and second-order polynomial regression fits. The top panel shows the HC group, and the bottom panel shows the MDD group. The origin ($x = 0$) indicates the initial partition based on the Desikan–Killiany Atlas. Among the three trends shown, the dashed line and its corresponding dots represent the mean module z-score (homogeneity within a module; black), referring to the right Y-axis. Of the two solid lines referring to the left Y-axis, the upward-trending line and dots represent the mean module number (red), while the downward-trending line and dots represent the mean voxel number per module (blue).

power (from an all-to-one perspective), less likely vice versa (one-to-all counterpart). This assumption is supported by 2 arguments: (i) similar to FC, a negative relationship between nodal degree derived from structural connectivity (SC) and ALFF has also been observed (Lee and Xue 2017b). Since the underlying hardwiring dictates the emergent property—indicating that SC influences local power, not the reverse—the fact of a substantial correspondence between FC and SC suggests that the causal inference can similarly be extended to the FC scenario (Skudlarski et al. 2008; Honey et al. 2009; Lee and Xue 2018d). (ii) Consider a system that has nodes ranked by ALFF magnitude, with power driving connectivity in a negative direction. Given the negative relationship, the node with the lowest ALFF is expected to have the weakest connections (nodal strength) from the remaining

nodes with higher ALFF values. However, this creates a contradiction, as the negative relationship suggests that a lower nodal strength should result in higher ALFF. This reinforces that nodal strength (or degree in an unweighted graph) influences nodal power, rather than the opposite. It is expected that the slope relating regional power to inter-regional FC is altered in MDD. Referring to Fig. 1, 3 classes of power–connectivity relationships are to be explored. (i) FP-LM: the FP nodal ALFF influenced by the connections between FP and LM systems, (ii) LM-FP: the LM nodal ALFF influenced by the connections between FP and LM systems, and (iii) the overall relationship between nodal power and connection combining FP and LM systems. Class (iii) is used to examine whether the negative relationship between nodal power and nodal strength can be replicated in these data samples, while

Table 1. Statistics of the MOSI results (MDD–HC).

	Gamma	Frontoparietal				Limbic			
		MDD	HC	t-scores	P-values	MDD	HC	t-scores	P-values
Partition No.	0.70	38.7(10.0)	37.4 (7.3)	0.83	0.406	49.1 (9.2)	45.1 (7.9)	2.57	0.011
	0.75	43.1(10.4)	41.7 (8.0)	0.82	0.412	53.6 (8.7)	49.6 (7.5)	2.71	0.008*
	0.80	47.8 (10.0)	47.7 (7.6)	0.04	0.967	58.6 (8.6)	54.5 (7.0)	2.89	0.005**
	0.85	51.8 (9.3)	51.4 (7.2)	0.31	0.760	62.6 (8.2)	58.8 (6.9)	2.74	0.007*
	0.90	52.8 (9.0)	53.0 (6.8)	−0.13	0.900	66.0 (7.7)	61.3 (7.0)	3.54	5.74E-4**
Mean voxel No. per partition	0.70	98.5 (25.8)	96.6 (24.8)	0.43	0.671	74.3 (13.4)	78.0 (13.5)	−1.50	0.137
	0.75	84.9 (23.0)	82.7 (19.3)	0.55	0.585	71.1 (13.7)	75.5 (13.3)	−1.80	0.074
	0.80	72.5 (20.0)	69.0 (14.0)	1.11	0.271	68.8 (13.2)	71.6 (11.8)	−1.22	0.226
	0.85	63.4 (12.5)	61.2 (10.7)	1.02	0.308	68.1 (14.5)	69.8 (10.6)	−0.75	0.455
	0.90	60.3 (10.4)	57.5 (10.5)	1.48	0.141	67.2 (15.2)	69.3 (10.5)	−0.87	0.384
Total voxel No	0.70	3630 (658)	3448 (618)	1.21	0.228	3627 (929)	3496 (782)	0.84	0.404
	0.75	3496 (650)	3358 (630)	1.18	0.241	3811 (1005)	3724 (761)	0.53	0.594
	0.80	3352 (680)	3232 (568)	1.05	0.295	4036 (1029)	3887 (772)	0.89	0.373
	0.85	3218 (544)	3107 (533)	1.13	0.260	4254 (1040)	4089 (669)	1.03	0.305
	0.90	3137 (535)	3037 (648)	0.92	0.360	4407 (1027)	4224 (665)	1.16	0.250
Total ALFF	0.70	865.4 (288.6)	769.9 (215.4)	2.05	0.042	1235.6 (628.0)	1023.0 (340.0)	2.31	0.023
	0.75	836.8 (296.0)	740.3 (217.1)	2.04	0.044	1283.6 (647.9)	1077.7 (340.6)	2.18	0.031
	0.80	813.6 (333.4)	708.7 (196.8)	2.10	0.038	1341.5 (612.5)	1127.2 (344.4)	2.36	0.020
	0.85	768.9 (269.2)	684.8 (212.1)	1.90	0.060	1408.3 (645.1)	1176.5 (308.5)	2.51	0.013
	0.90	750.9 (285.7)	669.2 (223.5)	1.75	0.084	1450.2 (632.5)	1211.4 (307.2)	2.63	0.010*
Mean ALFF per voxel	0.70	0.24 (0.06)	0.22 (0.05)	1.64	0.103	0.33 (0.08)	0.29 (0.06)	3.13	0.002**
	0.75	0.24 (0.06)	0.22 (0.05)	1.66	0.099	0.33 (0.08)	0.29 (0.05)	3.22	0.002**
	0.80	0.24 (0.07)	0.22 (0.05)	1.85	0.066	0.32 (0.07)	0.29 (0.05)	3.10	0.002**
	0.85	0.24 (0.06)	0.22 (0.05)	1.73	0.087	0.32 (0.08)	0.29 (0.05)	3.06	0.003**
	0.90	0.24 (0.07)	0.22 (0.05)	1.70	0.092	0.32 (0.07)	0.29 (0.05)	3.09	0.003**

The columns “MDD” and “HC” are presented as mean (SD). No.: number. * and ** indicate P-values of less than 0.01 and 0.005, respectively.

Table 2. Correlation differences of overall power–connectivity relationship (MDD–HC).

Power: ALL nodes, Connectivity: Overall				
Gamma	MDD	HC	z-scores	P-values
0.45	−0.38	−0.41	1.43	0.151
0.50	−0.38	−0.41	1.73	0.085
0.55	−0.38	−0.40	1.33	0.183
0.60	−0.38	−0.39	0.73	0.463
0.65	−0.37	−0.38	1.10	0.270
0.70	−0.35	−0.37	1.26	0.208
0.75	−0.34	−0.36	1.19	0.234
0.80	−0.34	−0.35	0.74	0.462
0.85	−0.32	−0.33	0.19	0.849
0.90	−0.31	−0.32	0.53	0.596

The P-values of the negative correlations in each group are all less than 1E-10.

classes (i) and (ii) are the primary foci for uncovering insights into FP and LM interactions. Two types of between-group comparisons were conducted: grand trend analysis, capturing the aggregate trend, and correlation strength analysis, which emphasizes the association at the individual level, as described below.

For the grand trend analysis, nodal power (avgALFF) and mean nodal strength for all nodes in each individual were concatenated to facilitate group-level analysis of the power–connectivity relationship. Before concatenation, the individual data were standardized by subtracting the mean and dividing by the standard deviation to allow valid comparisons, with the sample number equal to the product of module count and subject count for each Gamma value. The statistical examination of the difference between power–connectivity CCs for MDD and HC groups was computed as follows: Assume the CCs for MDD and HC groups are

r_1 and r_2 , with data numbers N_1 and N_2 . The statistical z-score—denoted as z_{Diff} —can be calculated using the formula $(\text{atanh}(r_1) - \text{atanh}(r_2))/\sqrt{1/(N_1-3) + 1/(N_2-3)}$ (see Cohen et al. 2002, p. 53), where atanh and $\sqrt{}$ indicate hyperbolic arctangent function and square root function, respectively. The p-value is then computed as $2 \times (1 - \text{normcdf}(\text{abs}(z_{\text{Diff}})))$, where normcdf is a MATLAB function (R2023a; The MathWorks, Inc., Natick, Massachusetts, United States) that calculates the cumulative distribution function of the normal distribution, providing the probability that a normally distributed random variable is less than or equal to a specified value. For the second analysis, the CCs between nodal powers and nodal strengths were transformed using Fisher’s r -to- z transformation for each participant, and independent two-sample t -tests were performed to compare the z -score differences between MDD and HC.

Special consideration is required for the weighting strategy in this power–connectivity scenario. The homogeneity in brain signals within a module could be mediated and maintained by intra-modular interactions (Freeman et al. 1997; Chialvo 2010), so it appears more reasonable to weight the connectivity based solely on the “inputs” from node j to node i by $\sqrt{N_j}$, where $j \sim i$, then again normalized by average weight (weighting strategy II), before exploring the relationship between the average nodal power and nodal strength. Both weighting strategies I and II were adopted, with the results based on weighting strategy II reported in the main text and the other in the Supplementary Material (part II).

Results

Among the MDD groups, subjects with insufficient clinical evaluations (2 cases lacking baseline ratings on the Montgomery–Åsberg Depression Rating Scale; MADRS) or suboptimal EPI

Table 3. Correlation differences of inter-compartment power-connectivity relationship (MDD–HC): grand trend analysis.

Gamma	Power: FP nodes, Connectivity: LM-to-FP				Power: Limbic nodes, Connectivity: FP-to-LM			
	MDD	HC	z-scores	P-values	MDD	HC	z-scores	P-values
0.45	−0.20	−0.08	−3.58	3.45E-4**	−0.42	−0.49	2.89	0.004**
0.50	−0.19	−0.09	−3.23	0.001**	−0.42	−0.50	3.05	0.002**
0.55	−0.18	−0.08	−3.00	0.003**	−0.43	−0.50	2.84	0.004**
0.60	−0.18	−0.06	−3.97	7.26E-5**	−0.43	−0.49	2.69	0.007*
0.65	−0.15	−0.04	−3.52	4.36E-4**	−0.42	−0.47	2.61	0.009*
0.70	−0.14	−0.04	−3.27	0.001**	−0.40	−0.46	2.98	0.003**
0.75	−0.14	−0.02	−4.06	4.98E-5**	−0.39	−0.45	2.83	0.005**
0.80	−0.11	−0.03	−3.15	0.002**	−0.39	−0.44	2.50	0.012
0.85	−0.09	−0.03	−2.36	0.018	−0.38	−0.42	2.15	0.031
0.90	−0.04	−0.00	−1.70	0.088	−0.38	−0.41	1.61	0.107

* and ** indicate P-values of less than 0.01 and 0.005, respectively. LM-to-FP and FP-to-LM do not imply causal connections; refer to the main text for further clarification.

Table 4. Correlation differences of inter-compartment power-connectivity relationship (MDD–HC): two-sample t-tests.

Gamma	Power: FP nodes, Connectivity: LM-to-FP				Power: Limbic nodes, Connectivity: FP-to-LM			
	MDD	Normal	t-scores	P-values	MDD	Normal	t-scores	P-values
0.45	−0.27 (0.43)	−0.10 (0.31)	−2.48	0.014	−0.52 (0.34)	−0.60 (0.31)	1.51	0.167
0.5	−0.27 (0.43)	−0.10 (0.32)	−2.36	0.020	−0.52 (0.35)	−0.61 (0.29)	1.12	0.134
0.55	−0.25 (0.42)	−0.10 (0.30)	−2.22	0.028	−0.53 (0.35)	−0.60 (0.27)	1.15	0.264
0.6	−0.24 (0.39)	−0.07 (0.30)	−2.63	0.010	−0.52 (0.35)	−0.58 (0.26)	0.94	0.254
0.65	−0.21 (0.37)	−0.06 (0.28)	−2.48	0.015	−0.51 (0.35)	−0.56 (0.28)	0.98	0.348
0.7	−0.19 (0.32)	−0.06 (0.27)	−2.33	0.021	−0.48 (0.34)	−0.54 (0.26)	0.80	0.330
0.75	−0.17 (0.30)	−0.04 (0.27)	−2.42	0.017	−0.47 (0.33)	−0.51 (0.26)	0.60	0.426
0.8	−0.13 (0.28)	−0.04 (0.26)	−1.74	0.084	−0.47 (0.32)	−0.50 (0.25)	0.34	0.552
0.85	−0.11 (0.27)	−0.04 (0.24)	−1.57	0.119	−0.45 (0.31)	−0.47 (0.23)	0.46	0.731
0.9	−0.06 (0.25)	−0.01 (0.26)	−0.98	0.329	−0.44 (0.30)	−0.46 (0.25)	1.61	0.647

Table 5. Comparisons of mean power (avgALFF) and connectivity strength between the 15% largest and the remaining 85% of modules (HC).

Gamma	Power: FP nodes				Power: Limbic nodes			
	15%	85%	t-scores	P-values	15%	85%	t-scores	P-values
0.45	0.22 (0.06)	0.22 (0.04)	−0.05	0.961	0.25 (0.06)	0.33 (0.08)	−5.70	8.97E-8**
0.50	0.22 (0.04)	0.22 (0.05)	−1.00	0.320	0.26 (0.07)	0.32 (0.07)	−4.41	2.32E-5**
0.55	0.22 (0.05)	0.22 (0.04)	−0.59	0.558	0.27 (0.07)	0.32 (0.07)	−4.39	2.48E-5**
0.60	0.22 (0.06)	0.22 (0.04)	−0.62	0.536	0.27 (0.08)	0.32 (0.07)	−3.97	1.25E-4**
0.65	0.22 (0.05)	0.22 (0.05)	−0.66	0.512	0.26 (0.07)	0.32 (0.07)	−4.87	3.54E-6**
0.70	0.22 (0.06)	0.22 (0.04)	−0.40	0.690	0.25 (0.07)	0.32 (0.07)	−5.29	5.70E-7**
0.75	0.22 (0.06)	0.22 (0.05)	−0.43	0.670	0.26 (0.07)	0.31 (0.07)	−4.48	1.73E-5**
0.80	0.22 (0.05)	0.22 (0.05)	−0.21	0.831	0.26 (0.06)	0.31 (0.07)	−4.03	1.01E-4**
0.85	0.22 (0.07)	0.22 (0.04)	−0.10	0.920	0.27 (0.08)	0.31 (0.07)	−2.83	0.006*
0.90	0.22 (0.06)	0.22 (0.04)	−0.56	0.579	0.27 (0.07)	0.30 (0.07)	−2.54	0.012
Gamma	Connectivity: LM-to-FP				Connectivity: FP-to-LM			
	15%	85%	t-scores	P-values	15%	85%	t-scores	P-values
0.45	0.29 (0.12)	0.22 (0.11)	3.07	0.003**	0.32 (0.16)	0.21 (0.10)	4.54	1.35E-5**
0.50	0.28 (0.12)	0.21 (0.11)	3.37	0.001**	0.31 (0.15)	0.20 (0.10)	4.58	1.16E-5**
0.55	0.28 (0.12)	0.21 (0.10)	3.37	0.001**	0.30 (0.15)	0.20 (0.09)	4.42	2.17E-5**
0.60	0.27 (0.12)	0.20 (0.10)	3.46	0.001**	0.29 (0.15)	0.19 (0.09)	4.36	2.80E-5**
0.65	0.26 (0.12)	0.19 (0.10)	3.59	4.82E-4**	0.28 (0.15)	0.18 (0.09)	4.41	2.27E-5**
0.70	0.25 (0.12)	0.18 (0.09)	3.49	0.001**	0.26 (0.14)	0.17 (0.08)	4.23	4.70E-5**
0.75	0.24 (0.12)	0.17 (0.08)	3.58	0.001**	0.25 (0.13)	0.16 (0.08)	4.24	4.51E-5**
0.80	0.22 (0.11)	0.16 (0.07)	3.12	0.002**	0.23 (0.12)	0.16 (0.07)	3.88	1.74E-4**
0.85	0.21 (0.10)	0.16 (0.07)	3.06	0.003**	0.22 (0.11)	0.16 (0.07)	3.66	3.74E-4**
0.90	0.20 (0.09)	0.16 (0.07)	2.78	0.006*	0.21 (0.10)	0.16 (0.07)	3.55	5.49E-4**

* and ** indicate P-values of less than 0.01 and 0.005, respectively. LM-to-FP and FP-to-LM do not imply causal connections; refer to the main text for further clarification.

imaging quality (3 cases with excessive movement, 3 with significant signal loss, and 2 with suboptimal segmentation results) were excluded, leaving 60 MDD participants for the study. To ensure balanced sample sizes, 60 HC participants were randomly selected from the original HC pool. This process resulted in a final sample of 120 subjects (60 MDD, 60 HC) for analysis. The sample size (statistical power) is adequate based on prior neuroimaging literature (Szucs and Ioannidis 2020). The MDD group had a mean age of 34.1 yr (SD=12.9), while the HC group had a mean age of 32.7 yr (SD=11.6), with no significant difference ($P=0.552$). The mean MADRS score for the MDD group was 29.7 (SD=5.2), which was significantly higher than the HC group's mean score of 0.7 (SD=1.6), with an extremely significant P -value ($<1E-10$). Gender distribution did not differ significantly between the 2 groups, with 22 males and 38 females in the MDD group compared to 21 males and 39 females in the HC group ($\chi^2=0.302$, $P=0.583$). For all two-sample t -tests, the degrees of freedom were 118.

MOSI outputs and the ensuing neural metrics analyses

Concordant with the nature of MOSI, the cluster number increased, and the number of voxels in each cluster decreased with the gamma values. For the HC group, the segmented module numbers of the cortex were 85.8 and 152.6 at gamma 0.45 and 0.90, respectively, with the module z -scores increasing from 0.54 (CC 0.50) to 0.75 (CC 0.64); see the top subplot in Fig. 2. The module number of the initial partition based on the Desikan–Killiany Atlas was 68, with an average voxel number of 129.5 (64 mm³/voxel) and a module z -score of 0.40 (CC 0.38). For the MDD group, the segmented module numbers of the cortex were 90.8 and 159.0 at gamma 0.45 and 0.90, respectively, with the module z -scores increasing from 0.56 (CC 0.50) to 0.76 (CC 0.64), see the bottom subplot in Fig. 2. The module number of the initial partition based on the Desikan–Killiany Atlas was 68, with an average voxel number of 131.1 (64 mm³/voxel) and a module z -score of 0.43 (CC 0.41). The MOSI-derived module z -scores outperformed their atlas-based counterparts and increased monotonously with higher gamma values, indicating that BOLD signals within a module became more homogeneous at finer resolutions, thereby confirming the validity of the MOSI scheme.

For the between-group comparisons, independent t -tests revealed that the MDD group had a higher partition number and avgALFF per voxel in the LM compartment but not in the FP compartment. Other indices—such as the mean voxel number per partition and total voxel number in each compartment—did not disclose significant statistical differences. Total ALFF showed a trend where the MDD group was higher than the HC group in the LM compartment, as summarized in Table 1. Previous reports indicated that MOSI's results were comparable to those of existing network approaches at gamma values around 0.80–0.85 (Lee and Tramontano 2021). The results at lower Gamma values (0.45–0.65) showing a similar pattern are therefore included in the Supplementary Material (Part I).

Inter-compartment power–connectivity relationship analyses

Consistent with previous reports, the negative CCs between nodal powers and nodal strengths were highly significant (P values $<1E-10$) when combining the FP and LM systems (class (iii) of the *Materials and methods* section: the relationship between power and connectivity). These coefficients ranged from -0.31 to -0.41 across all gamma values in both the MDD and HC groups, with

no significant differences between the two groups, see Table 2. Nevertheless, the main focus remains on the inter-compartment power–connectivity relationship, ie, class (i) FP-LM and class (ii) LM-FP, detailed below.

Class (i) FP-LM examined the relationship between mean FP power and the mean FC (mean nodal degree) between the FP and LM compartments, with the latter referred to as LM-to-FP FC for clarity, while acknowledging the bidirectional nature of FC. Similarly, class (ii) LM-FP focused on the mean LM power and mean inter-compartment FC, designated as FP-to-LM FC. Notably, under weighting strategy II, the mean FCs of LM-to-FP and FP-to-LM differ, requiring distinct naming for clarity. Moreover, the influence of connectivity between the FP and LM systems on FP power must operate in an LM-to-FP direction. The same logic applies to LM power and FP-to-LM FC. Therefore, the deliberate abuse of notation is justified for the sake of clarity in this context. Significant differences in the inter-compartment power–connectivity relationship were observed between the MDD and HC groups at gamma values 0.45 to 0.80 (P -values less than 0.01 or 0.005). Interestingly, opposite patterns are observed: for the FP nodal power and LM-to-FP connectivity, the MDD group showed a more negative correlation at all gamma values, whereas, in the case of LM nodal power and FP-to-LM connectivity, the MDD group exhibited less negative correlation. These results together highlight that individuals with MDD display deviant FP-LM and LM-FP inter-compartmental interactions, as illustrated in Fig. 3 and summarized in Table 3.

The z -scores of CCs between nodal power and nodal strength for each participant in HC and MDD were analyzed using two-sample independent t -tests across different gamma values, as summarized in Table 4. The results showed a high variance in the power–strength relationship, reducing the robustness of the statistical findings. However, consistent yet opposing trends were replicated, as indicated by the signs of the t -scores: MDD exhibited higher and lower values than HC in the LM-to-FP and FP-to-LM relationships, respectively. The overall probability of this pattern occurring by chance is 0.5^{10} , approximately 0.001, complementing the global trend analysis that these opposing trends persist across different gamma values.

QQ plot and ensuing analyses

A QQ plot was employed to assess the module size distribution in the MDD and HC groups. It was observed that as the size increased beyond the top 15%, group-level differences emerged; see Fig. 4. Opposite patterns were noticed again: MDD's module sizes tended to be larger in the FP compartment (below the equal line in Fig. 4) and lower in the LM compartment (above the equal line in Fig. 4), compared with the HC group. Given the observation, further exploratory analyses were conducted to compare the avgALFF values and mean inter-compartment connectivity strengths between the largest 15% and the remaining 85% modules.

For the HC group, Table 5 demonstrates that larger modules were associated with lower avgALFF, with significant results in the LM compartment (P -values <0.005 for gamma 0.45 to 0.85) and a trend in the FP compartment (all t -scores are negative, with a non-parametric P -value <0.001 based on binomial distribution). Regarding connectivity, both LM-to-FP and FP-to-LM FCs showed that the largest 15% of modules had significantly greater connectivity strength compared to the remaining 85% across all gamma values (P -values <0.005). The results suggest that larger modules play a more prominent role in inter-compartment interactions while also supporting the notion that stronger global or inter-compartment FCs carry more inhibitory information (Lee and Tramontano 2024).

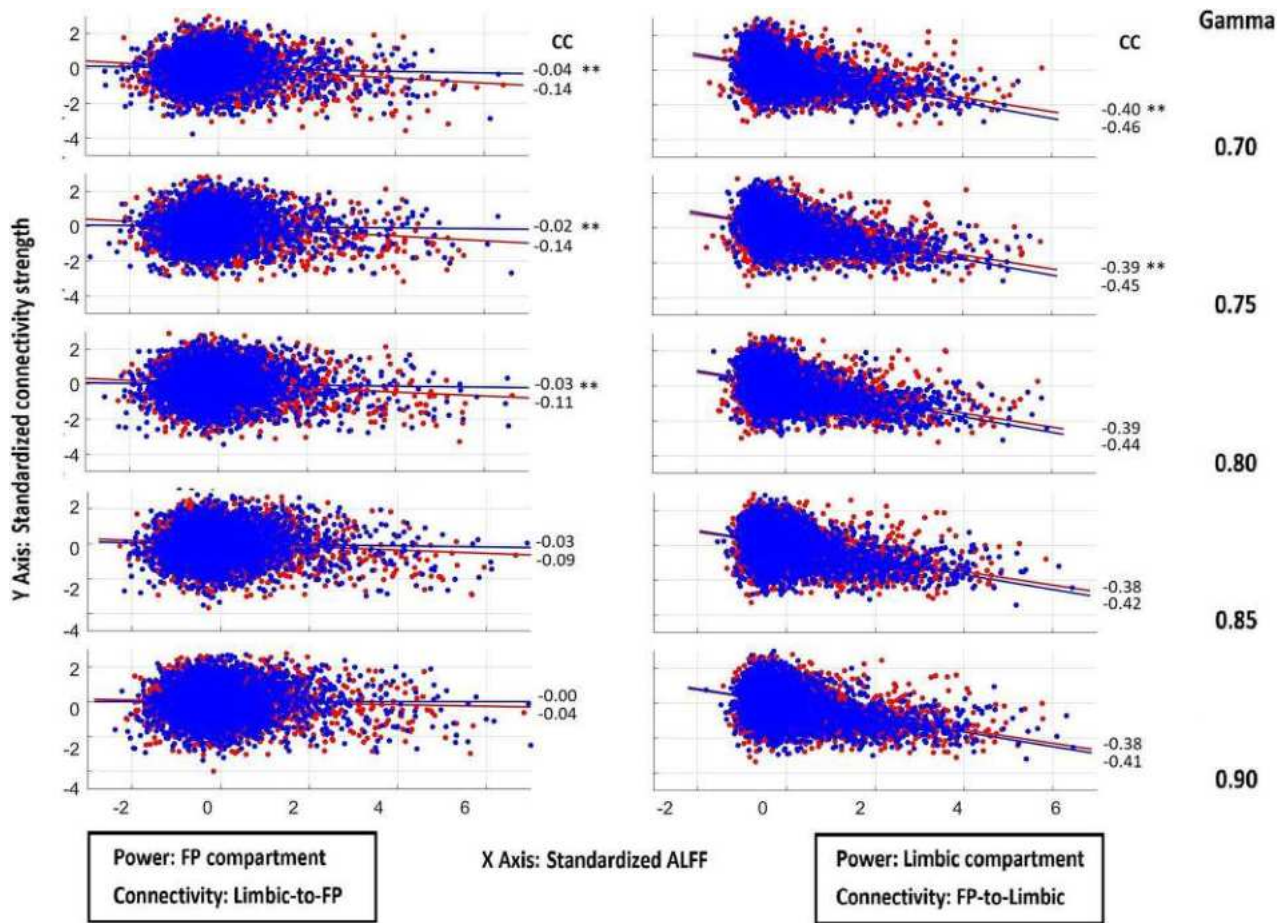


Fig. 3. Scatter plots with regression lines illustrating the relationships between power and connectivity. The left column shows relationships between FP powers and LM-to-FP connectivity strengths, and the right column shows LM powers and FP-to-LM connectivity strengths. The five rows correspond to gamma values ranging from 0.70 to 0.90. In the left column, the regression line corresponding to the healthy control (HC) group lies above that of the major depressive disorder (MDD) group; in the right column, the MDD line is above the HC line. (HC: blue; MDD: red.) CC: correlation coefficients. **: statistical significance of CC difference with P -value < 0.005 .

For the MDD group, Table 6 summarizes the patterns in power and FC, noting that while the latter resembles those in Table 5, the former differs. As observed in the HC group, the larger modules in both the FP and LM compartments in the MDD group were associated with stronger inter-compartment interactions. However, this differential size effect was less pronounced in terms of power. It is noteworthy that since weighting strategy II was adopted, the FC is not influenced by the number of voxels in the node, but rather reflects the (input) connectivity strengths with the other compartment. The interaction of 2-way ANOVA was not significant (15% vs. 85% and MDD vs. HC), and thus no further analyses were conducted.

Although this study centers on the relationship between mean nodal strength and mean ALFF to account for variations in partition size, extra analyses examining overall nodal strength vs. mean ALFF yielded similar findings (data not shown). This is expected, as the number of cortical voxels far exceeds that of any partitioned module, making mean nodal strength essentially a scaled version of nodal strength with a roughly constant denominator, exerting minimal impact on the correlation analyses.

Discussion

Identifying the neural mechanisms underlying MDD have been a challenging issue in brain science. Extensive research has been integrated into the limbic-cortical dysregulation model (Mayberg

1997), which provides an insightful descriptive framework. However, findings from independent studies of MDD are widely distributed across the PFC, parietal cortex, and LM regions. The compromised circuits involve broad cognitive and affective domains (Brand et al. 2015; Phillips et al. 2015; Pimontel et al. 2016). Moreover, abnormalities in just one or a few circuits cannot explain the full spectrum of symptoms observed in MDD. Thus, an effort has been made to expand the limbic-cortical dysregulation model to encompass the FP and LM compartments, particularly emphasizing their imbalanced reciprocal suppression (briefly summarized in the section: *Potential mechanism mediating the frontoparietal and limbic imbalance*) (Lee 2016; Lee and Xue 2018b). Notably, both the compartments are well-acknowledged neural entities (Mega et al. 1997; Lee et al. 2014; Lee and Xue 2018b), and the compartment-level model provides broader explanatory power than models focused on specific circuits, as it may better account for the subtypes of MDD and heterogeneity in symptomatology through compensatory changes and neural reorganization/plasticity (Lee et al. 2011; Boessen et al. 2012; Lee 2016; Drysdale et al. 2017; Lee and Xue 2018b). In accord, systemic analyses have failed to demonstrate a consistent relationship between lesion location and the occurrence of post-stroke depression, further supporting the notion of a compartment-level disorder, not confined to a specific circuitry or region (Carson et al. 2000; Ríos et al. 2025). Additionally, compartment-level neuropathology may offer an initial explanation for

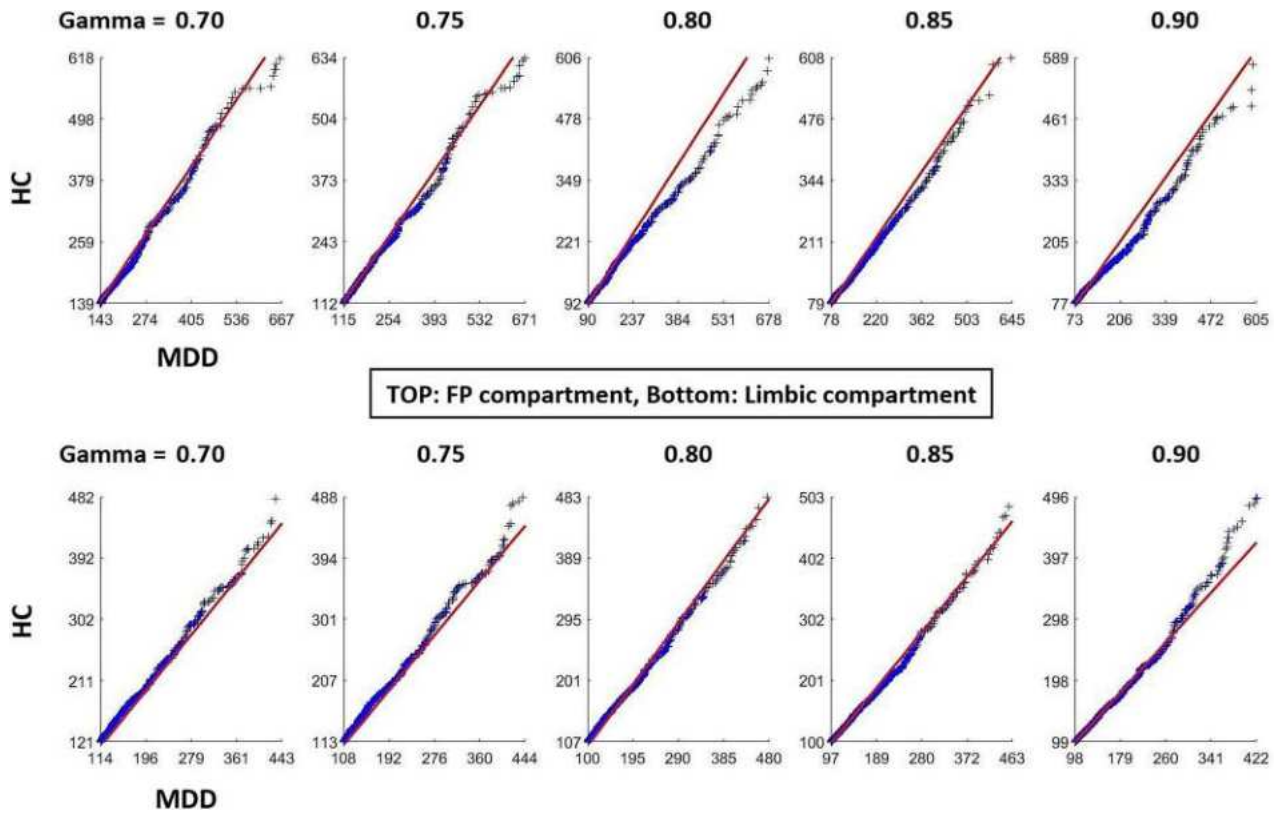


Fig. 4. Q–Q plot of module size distributions for the largest 20% of modules in the MDD and HC groups. Each cross marker (blue) represents a pairwise comparison of module sizes between the two groups. The solid diagonal line (red) indicates equal sizes along both axes.

Table 6. Comparisons of mean power (avgALFF) and connectivity strength between the 15% largest and the remaining 85% of modules (MDD).

Gamma	Power: FP nodes				Power: Limbic nodes			
	15%	85%	t-scores	p-values	15%	85%	t-scores	P-values
0.45	0.24 (0.08)	0.24 (0.06)	0.55	0.585	0.30 (0.11)	0.36 (0.10)	−3.03	0.003**
0.50	0.24 (0.08)	0.24 (0.06)	0.15	0.883	0.30 (0.12)	0.36 (0.11)	−2.65	0.009*
0.55	0.24 (0.08)	0.24 (0.06)	0.09	0.930	0.31 (0.12)	0.35 (0.09)	−2.01	0.047
0.60	0.24 (0.08)	0.24 (0.06)	0.03	0.973	0.31 (0.12)	0.35 (0.09)	−2.40	0.018
0.65	0.24 (0.08)	0.24 (0.07)	−0.31	0.757	0.30 (0.12)	0.35 (0.09)	−2.43	0.017
0.70	0.24 (0.08)	0.24 (0.05)	0.00	0.998	0.31 (0.12)	0.34 (0.09)	−1.74	0.085
0.75	0.24 (0.08)	0.24 (0.05)	−0.02	0.986	0.31 (0.12)	0.34 (0.08)	−1.87	0.064
0.80	0.24 (0.09)	0.24 (0.06)	0.45	0.651	0.31 (0.11)	0.34 (0.08)	−1.38	0.169
0.85	0.24 (0.08)	0.23 (0.06)	0.08	0.937	0.32 (0.12)	0.33 (0.07)	−0.21	0.835
0.90	0.24 (0.09)	0.23 (0.05)	0.30	0.763	0.33 (0.10)	0.32 (0.08)	0.32	0.748
Connectivity: LM-FP					Connectivity: FP-LM			
0.45	0.28 (0.16)	0.21 (0.13)	2.68	0.008*	0.31 (0.18)	0.20 (0.12)	4.02	1.01E-4**
0.50	0.28 (0.16)	0.20 (0.12)	2.94	0.004**	0.31 (0.18)	0.19 (0.12)	4.17	5.92E-5**
0.55	0.27 (0.15)	0.20 (0.13)	2.90	0.004**	0.29 (0.17)	0.19 (0.12)	3.89	1.67E-4**
0.60	0.26 (0.14)	0.19 (0.12)	2.88	0.005**	0.28 (0.16)	0.18 (0.11)	4.10	7.60E-5**
0.65	0.25 (0.14)	0.18 (0.11)	2.76	0.007*	0.27 (0.17)	0.17 (0.10)	4.09	7.79E-5**
0.70	0.24 (0.14)	0.17 (0.11)	2.93	0.004**	0.25 (0.16)	0.17 (0.10)	3.70	3.30E-4**
0.75	0.23 (0.13)	0.16 (0.10)	2.89	0.005**	0.24 (0.15)	0.16 (0.09)	3.70	3.23E-4**
0.80	0.21 (0.13)	0.16 (0.09)	2.71	0.008*	0.22 (0.14)	0.15 (0.09)	3.02	0.003**
0.85	0.20 (0.12)	0.15 (0.08)	2.58	0.011	0.20 (0.12)	0.15 (0.08)	2.88	0.005**
0.90	0.20 (0.11)	0.16 (0.09)	2.40	0.018	0.20 (0.12)	0.15 (0.08)	2.79	0.006*

* and ** indicate P-values of less than 0.01 and 0.005, respectively. LM-to-FP and FP-to-LM do not imply causal connections; refer to the main text for further clarification.

the high comorbidity and increased susceptibility to other neuropsychiatric conditions associated with MDD (Oquendo et al. 2005; Kessler et al. 2008; Brière et al. 2014). Despite its

simplicity and biological plausibility, 2 major obstacles had hindered the empirical verification of this extended model. First, an individualized and physiologically constrained FCP of cortical

signals is required to enable whole-brain and compartment-level analyses. Second, due to the lower sampling rate inherent in fMRI compared to EEG, mathematical models such as Granger causality or isolated effective coherence (Barnett and Seth 2014; Pascual et al. 2014) are not feasible for investigating inter-compartmental causal interactions, which are expected to occur within tens to hundreds of milliseconds (Lee et al. 2023). These 2 issues have been addressed by MOSI (Lee and Tramontano 2021), which realizes FCP, and by the recent discovery of a robust negative relationship between nodal strength and nodal power (Lee and Tramontano 2024), enabling the study of inhibitory interaction using rsfMRI—especially, nodal strength may causally influence nodal power.

The neuropathology of MDD unveiled through MOSI-facilitated compartment analyses

Statistical analyses revealed that MDD is associated with a higher partition number and greater avgALFF per voxel in the LM compartment. These findings not only align with the observed LM hyperactivity (elevated avgALFF) but also indicate that LM neural activities become more heterogeneous and differentiated (increased module number). It is imperative to note that the insight provided by this study is at the compartmental level, in contrast to the sporadic brain regions reported by conventional fMRI analyses, which lack consistency and are sometimes hard to explain. For example, both increased and decreased ALFF values have been reported in the LM system, even within a single study (Jiao et al. 2011; Hou et al. 2022).

Reproducibility has been a persistent challenge in neuroimaging research, particularly in neuropsychiatric studies (Holiga et al. 2018). This research may offer novel insights into this critical issue. Compartment-level exploration occurs at a broader or coarser scale, with the abnormalities triggering compensatory and plasticity changes at finer scales to counteract dysfunction. Evidence suggests that neural plasticity and reorganization are highly individualized processes (Poldrack 2000; Kanai and Rees 2011; Kolb and Gibb 2014). Consequently, neural metrics across different scales may exhibit varying degrees of replicability, with the appropriate resolution expected to yield the highest consistency (in this study, compartment). An outstanding feature of MOSI is its multi-resolution investigation. By adjusting the resolutions through different gamma values, the optimal resolution that reveals the key abnormality in MDD can be identified, which will be discussed later. Another advantage of MOSI is its full consideration of individuality. As shown in Table 1, the variance in module number, module size, and compartment size underscores MOSI's suitability for imaging studies characterized by heterogeneity, such as in the case of MDD. This stands in sharp contrast to fixed partitions informed by anatomical atlases (Lee et al. 2014; Lee and Xue 2017a). The variability in partition size is effectively managed through a weighting strategy, laying the groundwork for subsequent network analyses.

In the FP compartment, however, reduced ALFF as an indicator of hypoactivity was expected but not present. MDD even demonstrated a mild trend of increased avgALFF across all resolutions (Table 1 and Part I in Supplementary Material). It is noteworthy that previous research has also failed to demonstrate decreased ALFF in the PFC of individuals with MDD (Hou et al. 2022). Some studies even indicated that MDD was associated with enhanced regional power (ALFF) in the PFC (Jiao et al. 2011). It is reasonable to assume the engagement of compensatory mechanisms to alleviate FP hypoactivity. This conjecture is

particularly applicable to the FP compartment, given its diverse cortical and subcortical inputs (Alexander et al. 1986; Shipp 2004; Arnsten 2013), which extend well beyond the LM system. In this context, a trend of increased ALFF as compensation in the FP conversely suggests its hypoactivity. Accordingly, it is inappropriate to oversimplify the concepts of hyperactivity and hypoactivity as merely increased or decreased regional power. Instead, they may be better understood as relative concepts, for example, reflected in the altered interactions between the FP and LM compartments, as discussed in the next section.

A QQ plot assessed module size distribution in the MDD and HC groups, prompting a comparison of avgALFF values and inter-compartment connectivity strengths between the largest 15% and the remaining 85% of modules. Larger modules were associated with lower avgALFF and greater connectivity strength, suggesting a more prominent role in inter-compartment interactions. These findings reinforce the argument that nodal strength in rsfMRI carries more information about inhibitory coupling. However, the two-way ANOVA interaction analyses of avgALFF and connectivity strengths were both negative and for the MDD group, the results mirrored those in Table 1 and Part I of the Supplementary Material. Nevertheless, there appears to be an interesting trend in avgALFF for the larger LM modules in MDD: compared to their 85% counterparts, the 15% largest modules exhibited lower avgALFF in MDD as expected, but the decrease was less pronounced than in the HC group. This finding implies relative LM hyperactivity in the larger modules and suggests their possible role in maintaining the depressive state; please see Part III of the Supplementary Material for details.

The insight derived from inter-compartmental power-connectivity analyses

The power-FC relationship within a large-scale network may serve as a surrogate for studying causal and inhibitory coupling in rsfMRI. The former indicates that nodal strength influences nodal power, not vice versa, while the latter is inferred from a negative correlation. This discovery was inspired by the author's previous report (nodal degree derived from SC vs nodal power ALFF) and an anecdotal observation that in-house software frequently revealed abnormally increased regional power in patients characterized by diffuse hypo-connections (Lee and Xue 2017b; Lee and Tramontano 2024).

For both the MDD and HC groups, combining the FP and LM compartments as a whole revealed a robust negative correlation between nodal strength and nodal power, replicating a previous report (Table 2) (Lee and Tramontano 2024). However, when focusing on the FCs between the FP and LM compartments and investigating their influence on nodal power, interesting patterns unfolded. First, the negative relationship is asymmetric, with regulation from the FP compartment to the LM compartment being much stronger than from the LM to the FP compartment. This asymmetry aligns with literature on emotion regulation, cognitive therapy, and the effects of transcranial magnetic stimulation over the PFC in alleviating depression severity (Speer et al. 2000; Taylor and Liberzon 2007; McRae et al. 2012; Lee and Xue 2018a). Throughout evolution, the PFC has expanded significantly, particularly in humans and higher primates, enhancing its role in regulating behaviors and emotions. This development has led to the greater top-down control over the LM system, especially in modulating emotional responses from regions such as the amygdala (Miller and Cohen 2001; Fuster 2002; Phillips et al. 2008). As a result, the influence of the PFC on the LM system has gradually surpassed the LM system's capacity to affect PFC

conversely (Liberzon et al. 2003; Phan et al. 2004), reflected in the asymmetry of the nodal power and strength relationships.

Second, the 2 inter-compartmental relationships in the MDD group deviated in opposite directions compared to the HC group. Specifically, the MDD group's slopes of FP nodal power and nodal strength (ie FP power vs LM-to-FP connectivity) became steeper, while those of LM nodal power and nodal strength (ie LM power vs FP-to-LM connectivity) became flatter. This can be observed in the regression lines representing the relationship between power and connectivity strength in the scatter plots shown in Fig. 3, as well as in the significant statistical comparisons summarized in Table 3. The same trend—though with less robust statistical support—was observed in between-group comparisons (see Table 4). The results altogether suggest that the MDD group is characterized by more efficient suppression from the LM to frontal compartments and less efficient suppression in the reverse direction.

This intriguing pattern prompts a reappraisal of the implications of FP hypoactivity and LM hyperactivity in MDD. As discussed in the previous section, the absolute magnitude of power is not an ideal measure for representing the concepts of hypoactivity and hyperactivity; rather, these should be assessed in a relative manner. The relativism revealed by the nodal power vs nodal strength analyses indicates an imbalanced interaction between the FP and LM compartments in MDD. The hypoactive FP compartment may arise from and/or be maintained by abnormally stronger suppression from the LM counterpart, while the hyperactive LM compartment may originate from and/or be maintained by abnormally weaker suppression from the FP counterpart. This MDD theory of inter-compartmental network imbalance is thus empirically verified, expanding the insightful limbic-cortical dysregulation model proposed by Mayberg (and elaborated by many others) and shedding light on a paramount issue of MDD: its genesis and maintenance (see the section on *Potential mechanism mediating the frontoparietal and limbic imbalance*). The consequences of imbalanced reciprocal suppression can be readily applied to activation design experiments, which are beyond the scope of this article. The neural metrics from activation designs in MDD exhibit an alignment with the characterization of hypoactive FP and hyperactive LM systems, as noted in the summary of previous research (Lee and Xue 2018b).

One merit of the multi-resolution approach lies in its potential to provide the appropriate scale(s) for unveiling the neuropathology of various neuropsychiatric conditions (or other neuroscientific issues). The analyses above revealed that the most informative gamma values for partition size, avgALFF, and power-connectivity correlation are 0.55 to 0.90, 0.45 to 0.90, and 0.45 to 0.75, respectively. Taken together, gamma values ranging from 0.55 to 0.75 seem to offer suitable resolutions for exploring the neuropathology of MDD, which is lower than the recommended range for reproducing canonical networks (ie gamma values of 0.80 to 0.85 (Lee and Tramontano 2021)). Such resolution-dependent findings are conceptually linked to the various scales inherent in the hierarchical organization of brain tissues (Meunier et al. 2009) and warrant further research to investigate.

Future studies could expand this work by explicitly modeling the interaction effects of gender and age with diagnostic status (MDD vs. HC or active vs. remission). While the current dataset reflects the natural epidemiology of depression, with a female-to-male ratio of approximately 2:1, testing these interaction effects requires a larger and more balanced sample size. Incorporating gender and age as covariates in the analysis is essential for clarifying how these demographic factors modulate the observed network imbalance in MDD. This direction would offer a more

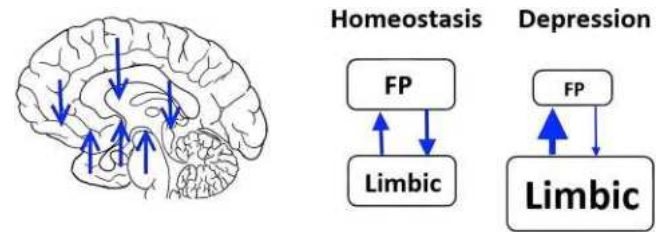


Fig. 5. Highlighted interacting patterns of 2 networks related to MDD: reciprocal suppression between the FP and LM compartments. Left: arrows (blue) represent mutual suppression as an interaction mechanism between the 2 compartments. Right: under homeostasis, balance is achieved, with the sizes of the dorsal and ventral compartments (abstractly representing metabolic or activity levels) approximately equal and allowing for mild perturbations. When this balance is disrupted to a breaking point, the LM compartment enlarges (conceptually), increasing its negative influence on the dorsal compartment; conversely, the dorsal compartment shrinks, reducing its impact on the ventral LM system. The overall consequence evolves into a state/attractor of FP hypoactivity and LM hyperactivity, characteristic of MDD.

nuanced understanding of the disorder's neural underpinnings and its variability across different demographic groups, providing a foundation for personalized interventions.

Potential mechanism mediating the FP and LM imbalance

Humans universally experience switching between exteroception and interoception in daily life, a process supported by 2 major networks: the FP mantle and the LM system (Lee et al. 2014), each receiving abundant and diverse inputs from other cortical and subcortical regions (Alexander et al. 1986; Shipp 2004; Arnsten 2013). The author proposes that a reciprocal suppressive mechanism (RSM) exists to facilitate fluid switching between these 2 states/compartments. Further, the RSM must be maintained in a dynamic equilibrium. If this balance is disrupted, a vicious cycle may occur and the consequences are catastrophic, potentially leading to MDD, as illustrated in Fig. 5. Various medical conditions may disrupt the inter-compartment balance. For instance, prolonged stress can simultaneously enhance LM activity and attenuate FP activity (Diorio et al. 1993; Arnsten 2009). Vascular insufficiency in the white matter may impair FP functioning (O'Sullivan et al. 2001). When the cortico-LM imbalance reaches a critical threshold, LM hyperactivity (relative to the FP) may amplify its inhibitory effect on the FP compartment, reducing the FP's counter-regulatory influence on the LM system. This imbalance creates a vicious cycle, stabilizing into the hyper-LM/hypo-FP state characteristic of MDD. For a detailed formulation of the RSM theory of MDD, please refer to (Lee 2016; Lee and Xue 2018b; Lee 2025).

Conclusion

This study provides empirical validation of the framework of imbalanced reciprocal suppression between the FP and LM compartments, designed to address the central neuropathology of MDD. This inter-compartmental imbalance perspective—mediated by abnormal RSM—extends and refines the limbic-cortical dysregulation model, explaining the observed hypoactivity in the FP and hyperactivity in the LM system. Additionally, the resulting neural compensatory changes and reorganization through plasticity may account for individual differences in symptomatology and subtypes of MDD, which can be empirically examined in future studies. Furthermore, this study highlights

a caveat: the neural metric ALFF should be interpreted with caution and in conjunction with nodal strength, given their strong negative correlations and possible disease-related deviations.

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Author contributions

Tien-Wen Lee (Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing—original draft, Writing—review & editing).

Supplementary material

Supplementary material is available at *Cerebral Cortex* online.

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APPLICATION OF AN ANALYSIS-SYNTHESIS FRAMEWORK TO EXPLORE THE PATHOGENIC LOCUS OF BIPOLAR DISORDER

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ABSTRACT

Bipolar disorder (BPD) is a major and complex psychiatric disease, clinically characterized by euthymic, depressive and manic phases. Despite diversity in various bio-psycho-social observations, neuroimaging studies have suggested a relatively consistent neural pattern of BPD – hypofrontality and limbic hyperactivity, similar to the neural manifestation of major depressive disorder (MDD). The shared cortico-limbic imbalance obviously cannot explain the two distinct clinical entities. BPD is different from MDD in many perspectives, such as the bipolar nature, reward sensitivity (especially in the manic phase), trend for enlarged amygdala and striatum, pharmacological choices (lithium / anticonvulsants and antipsychotics), antidepressant-induced polarity switch, and organic mania caused by heterogeneous medical conditions. This study applied an analysis-synthesis framework, which

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was designed to manage complicated issues and has been used to decipher MDD, to investigate the pathogenic foci of BPD. A good candidate synthesis is expected to satisfy three criteria: comprehensiveness, rationality and parsimony. The synthetic results demonstrated that the ventral tegmental area (VTA) is the most likely pathogenic locus of BPD. Incorporated with several well-established large-scale network mechanisms, an over-driving VTA (and its closely related networks) may account for many features of BPD that are difficult to integrate in extant models/theories. The analysis-synthesis hybrid approach provides a simple and useful framework for investigating psychiatric disorders. Similar to MDD, it is postulated that BPD is a brain organization “bug” that is the consequence of having several positive auto-feedback loops that may support sustained goal-directed or motivational behaviors. The dialectic processes between analysis and synthesis are explicated and discussed (dialectic neuroscience).

Keywords: analysis-synthesis, antidepressant, antipsychotic; bipolar disorder, dialectic neuroscience, mood stabilizer, ventral tegmental area

ABBREVIATIONS

ACC	anterior cingulate cortex
BPD	basal ganglia (BG), bipolar disorder
CRF	corticotrophin-releasing factor
fMRI	functional magnetic resonance imaging
MDD	major depressive disorder
mPFC	medial PFC
NAc	nucleus accumbens
OFC	orbitofrontal cortex
PFC	prefrontal cortex
RN	raphe nucleus
RSM	reciprocal suppression mechanism
SSRI	serotonin-selective reuptake inhibitor
vmPFC	ventral medial PFC
VS)	ventral striatum
VTA	ventral tegmental area

INTRODUCTION

Psychiatric disorders are complicated and heterogeneous. Although a consensus has been reached in several clinical perspectives (e.g., diagnosis and classification, although still being subject to refinement) [1], the disease mechanisms are largely unknown. To address this difficulty, an analysis-synthesis hybrid has been developed, which was applied to explore the psychopathology of major depressive disorder (MDD), and a jigsaw puzzle is used to illustrate the tenets [2, 3]. In brief, the analytic results from various studies are the surrounding pieces of the jigsaw puzzle, while the central missing piece is what the synthetic endeavor intends to discover; see Figure 1B. In contrast to the linear thinking that is frequently used in analysis, synthesis usually demands non-linear and creative thinking. “Synthesis” has been employed in several scientific disciplines to solve complicated issues, but it is still not well-acknowledged in neuroscience research [2]. To protect the rigorous standard of science, liberal abuse of synthesis is discouraged. A good synthetic result is one that accounts for analytic evidence from various perspectives (as many as possible), which is also expected to be simple and biologically plausible—the three criteria of comprehensiveness, parsimony and rationality. The spirit of these three standards is akin to the Bayesian scheme of model selection, in which the posterior probability is determined by the given models (e.g., plausible network mechanisms; rationality) and the explained observations (comprehensiveness), and a penalty is charged on the number of chosen mechanisms (parsimony). Analogous to the broadly accepted “ $P < 0.05$ ” that indicates the probability of a discovery by chance (null hypothesis) is lower than 0.05, Fisher’s combined probability test (a meta-analysis statistic) reveals that the likelihood for five observations (the cutoff for a “good” synthesis, described in the next paragraph) to be contemporaneously valid by chance (i.e., $P < 0.05$) is approximately 0.001 in a single synthesis [4]. In other words, the validity of synthetic results can be “quantified,” similar to the analytic counterpart.

With the application of an analysis-synthesis hybrid, Lee demonstrated that a cortico-limbic reciprocal suppression mechanism (RSM) could be the central missing piece of MDD [3]. The cortico-limbic RSM, together with several well-documented network mechanisms, may account for a substantial portion of the understanding of MDD [2]. The issue of how to formulate a synthesis has never been formally articulated in previous scientific literature. Lee further suggests that an analysis-synthesis research obey the following formats: In the *Methods* section, part I summarizes the main analytic results

related to the target illness (or issue), and part II lists the cardinal features that the synthetic endeavor attempts to integrate (the peripheral pieces of the jigsaw puzzle). In the *Results* section, part I proposes the synthetic result (the central piece of the jigsaw puzzle), which is expected to be simple (parsimony) and biologically plausible (rationality), and part II explains how the synthetic product may account for the features described in part II of the *Methods* in a one-to-one correspondence (comprehensiveness). The performance of a synthesis can be evaluated by a scale, where an explained observation number of 1–2 is poor, 3–4 is fair, 5–7 is good, 8–10 is very good, and > 10 is excellent. Both the analysis (linear thinking) and synthesis (creative or non-linear thinking) capabilities are human talents [3, 5], and there seems to be no reason to prohibit the application of synthesis to neuroscience. This research will show the power of an analysis-synthesis hybrid by using it to identify the disease foci of another major psychiatric disorder, bipolar disorder (BPD). The authors believe that every psychiatric illness can be deciphered in a similar way. Notably, analysis-synthesis is a general framework to assess complicated issues that is not limited to psychiatry.

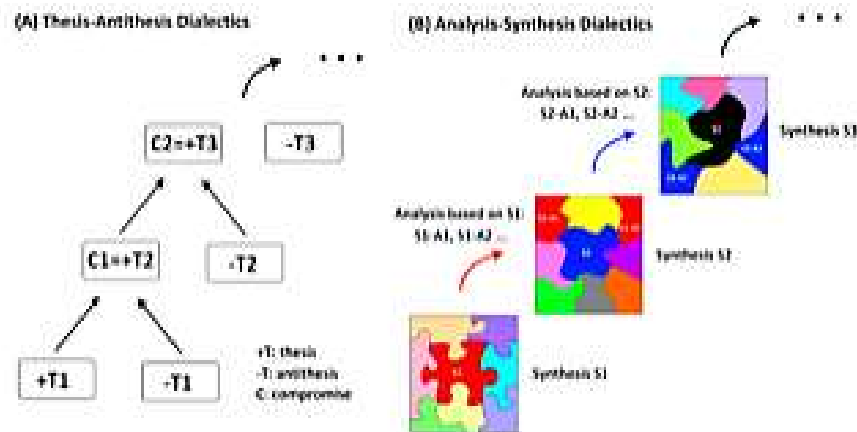


Figure 1. Two different dialectics are contrasted. Left: the dialectics based on thesis and antithesis. Right: the dialectics substantiated by analysis and synthesis. A jigsaw puzzle is used to illustrate the ideal theory/mechanism that may underlie complicated issues. In this study, the central piece represents the candidate brain model (synthesis) that fits well the convoluted outline formed by the observations from different perspectives (analysis) of BPD. The proposed VTA theory of BPD may account for (and hence, integrate) the various important features of BPD.

BPD is also known as manic-depressive illness and is characterized by periods of depressed and elated moods. BPD in general has three phases: depressive, manic and euthymic. The clinical manifestation of the depressive phase of BPD is similar to that of MDD, including symptoms of depressed mood or lack of interest, inattention, self-depreciating or suicidal thoughts, and fatigue, and disturbances in psychomotor activity, circadian rhythm, appetite and weight [1]. Manic phase may present with elevated, expansive, or irritable mood, inflated self-esteem or grandiosity, decreased need for sleep, hypertalkativity or pressured speech, flight of ideas or racing thoughts, distractibility, increased goal-directed activity or psychomotor agitation (sometimes violence), and excessive pleasure-seeking behaviors (e.g., buying sprees, hypersexuality, irrational investments) (DSM-IV) [1]. Both depressive and manic phases may be accompanied by marked impairments in psychosocial and occupational functions and may be associated with psychosis. There are several variants of BPD, which together affect approximately 2.4 percent of the population [6]. For instance, hypomania (less severe than mania) and mixed episode (mixed manic and depressive mood) may occur. Concordant rates for BPD in monozygotic twins can be as high as 80 percent (65 to 80 percent), which reduce to 20 percent in dizygotic twins [7], suggesting that BPD is a disorder with strong biological and hereditary underpinnings. A wide range of neuropsychological domains are affected in patients with BPD [3, 8-10]. Some deficits may persist in remitted BPD or BPD with residual symptoms, such as those in sustained attention, inhibitory control, verbal memory and executive function [10]. Reward abnormality in patients with BPD is of particular interest. It has been proposed that there is a competition between the desire for an instant reward (reflexive or immediate reward gain) and the delayed satisfaction of a long-term goal (reflective reward or temporary reward dismissal) [11]. Bipolar mania may have abnormalities in both reflexive and reflective processes, with a propensity for the former and less proficiency for the latter. It is important to note that patients with BPD in the euthymic phase also show reward sensitivity and negative risk-taking behaviors [12], indicating that the abnormalities in the reward-related circuitry and basal ganglia (BG) are an enduring neural feature of BPD. The persistent neuropsychological deficits during euthymia resonate with the claim of a strong biological component for BPD arising from genetic research.

For bipolar mania, mood stabilizers (in a strict sense [13, 14]) and antipsychotics are the two main classes of pharmaceutical agents. The most frequently used mood stabilizers are lithium and anticonvulsants (e.g.,

carbamazepine, valproate). Since mood stabilizers may take longer to exert a therapeutic effect, dopaminergic antagonists (antipsychotics) are often combined to allow for a faster sedation (note: tranquilizers may also be prescribed but are not a focus of this study). Up to 50 percent of BPD patients may experience psychotic symptoms, and dopamine antagonists are effective at relieving psychosis [15]. In addition, the prevalence of psychosis in patients with BPD depression is much higher than that in MDD counterparts [16]. Although the combination of mood stabilizers and antipsychotics has been prescribed to treat bipolar mania, antipsychotic monotherapy is also effective in a substantial number of cases [17]. It is well established that reward processing and motivational dopaminergic circuits in the brain are closely relevant [18-21]. Various studies have reported abnormalities of reward-related tasks and neural networks in patients with BPD [12, 22-30]. Bipolar mania is accompanied by increased goal-directed behaviors, hypertalkativity and psychomotor agitation. Animal studies have also indicated that increased brain dopamine levels are highly correlated with increased psychomotor activity [31]. Combining the evidence from neuropsychology, pharmacology and brain science, it is reasonable to assume that BPD, especially in the manic phase, is associated with a hyperdopaminergic state.

For patients with bipolar depression, the response to antidepressants such as serotonin-selective reuptake inhibitors (SSRIs) alone is not always satisfactory, which may lead to the risk of reversing the polarity from depression to mania [32]. In contrast to unipolar depression, the treatment of bipolar depression usually relies on combined mood stabilizers and antidepressants (note: the role of antidepressants in the treatment of bipolar depression has been questioned recently) [32, 33]. The discontinued use of mood stabilizers may result in the reappearance of BPD symptoms within half a year in 50 percent of patients [34]. Although bipolar depression and MDD share clinical presentations, it is interesting to note that compared with the treatment of MDD, antipsychotics seem to be more effective in the treatment of bipolar depression [35-37]. In summary, both mood stabilizers and dopaminergic antagonists/modulators may benefit BPD, either in the depressive or manic phase. Dopaminergic agents such as levodopa and amphetamine are well known for their side effect of inducing mania or depression, even for non-bipolar patients [38-40]. Convergent evidence thus indicates that aberrancies in the dopaminergic pathway may underlie BPD.

The brain activation maps are similar between bipolar and unipolar depression [41], and the neural pathology (psychopathology) of MDD mainly involves a cortico-limbic imbalance and aberrancies in the subgenual anterior

cingulate cortex (ACC) [42-44]. In the execution of a working memory task, all three phases of BPD (depressive, manic, euthymic) show a pattern of reduced and increased neural activities in dorsal (cortical) and ventral (limbic) compartments, respectively [45, 46]. By applying different experimental designs to assess various frontal and limbic functions, a considerable number of neuroimaging studies have also replicated the findings of limbic hyperactivity and hypofrontality [47-59], including during the euthymic period [49, 60, 61]. This persistent trend across different phases, even in euthymia, is consistent with the observations that BPD is a disease with a strong genetic component and that the associated neuropsychological deficits may persist even in the symptom-free period. There is other (indirect) evidence supporting limbic hyperactivity and frontal hypoactivity in patients with BPD: the healthy relatives of patients with BPD may have abnormal event-related potentials for target detection [62]; similar to patients with MDD, patients with BPD are also reported to have volume reductions in the subgenual cortex (probably also mediated by prolonged over-excitability to compensate for limbic hyperactivity) [63]. Patients with bipolar mania were observed to have increased baseline metabolism in the limbic region and striatum (including the ventral striatum; VS) and decreased metabolism in the dorsolateral prefrontal cortex (PFC) [51, 64, 65]. Limbic disinhibition, indicated by failed de-activation in a working memory challenge, was reported in patients in both depression and mania phases [66, 67]. The above research seems to indicate that the fronto-limbic RSM in patients with BPD is eschewed toward the limbic side and that the BG is more important in bipolar mania than in bipolar depression. In addition to the subthalamic nucleus, the globus pallidus is also a common target of deep brain stimulation to treat Parkinson's disease. A PET study (using oxygen-15 labeled water), however, revealed that the mania induced by globus pallidus stimulation was associated with enhanced activity in the BG and PFC and decreased activity in the limbic system (68). This pattern is partly opposite to that of the previously reported limbic hyperactivity and hypofrontality in bipolar mania (and the other two phases). In the case of globus pallidus stimulation, the cortico-limbic RSM is deviated toward the dorsal compartment, most likely via striato-frontal connections. The trend of hypofrontality and limbic hyperactivity itself is thus not essential for mania to occur, and the key structure is the BG, concordant with the clinical evidence of hyperdopaminergic states. In brief, the major deviation in the neural functions of patients with BPD has been related to frontal and limbic regions and the BG/VS (motivational dopaminergic circuitry).

It is notable that previous admirable efforts and investigations into BPD seem to be hard to integrate, echoing the complexity of psychiatric disorders. Furthermore, despite the summarized “peripheral pieces” above, there are many questions left unanswered. For example, what are the pathogenic foci of BPD? Why do the two different diseases of BPD and MDD share a similar neural manifestation (i.e., hypofrontality and limbic hyperactivity)? How can a single disease present opposite (bipolar) clinical manifestations? What is the neural underpinning that mediates the polarity change in BPD? The current analysis-synthesis research reveals that the ventral tegmental area (VTA) is the most likely pathogenic locus of BPD and is the “central missing piece” of the jigsaw puzzle of BPD, which may account for (and hence, integrate) a substantial portion of the findings of previous studies and explain the bipolar nature of BPD. The readers are encouraged to refer to the original analysis-synthesis report to obtain a holistic understanding of the methodology, underlying philosophy and network mechanisms of MDD [2, 3].

MATERIALS AND METHODS

This section addresses the analytic phase and is divided into two parts following the recommended format of synthesis as a scientific report [2]. In the first part, the analytic results from previous research are briefly reviewed (mainly from adult patients with BPD). The network abnormalities of patients with BPD (compared with healthy controls) and relevant network mechanisms are briefly summarized. In the second part, the defining (neuro-) features of BPD that the synthesis attempts to integrate are proposed (the peripheral pieces of the jigsaw puzzle). Since the depressive phase is similar to MDD, which has already been investigated by the analysis-synthesis hybrid [2], this section mainly focuses on the manic and euthymic phases of BPD.

Part I: Analytic Results

Frontal Abnormalities in Patients with BPD

- Decreased frontal metabolism in the manic state has been consistently replicated by independent research groups (review) [65].
- Decreased activation in the fronto-parietal network while performing working memory tasks was observed across the three BPD phases [45, 46].

- During a response inhibition task, decreased neural activity in the right inferior PFC (or lateral orbitofrontal cortex [OFC]) was reported in the manic phase [47, 48].
- While performing a decision-making task, manic patients showed decreased activation in frontal regions (e.g., the frontal pole and inferior PFC) [53].
- During a continuous performance task, mania (and mixed type) was observed to be associated with decreased PFC activation [55].
- Decreased activation in the ventrolateral prefrontal cortex during motor response inhibition was reported during mania [54].
- Euthymic BPD patients exhibited attenuated PFC activity during a working memory task [69].
- Euthymic BPD patients exhibited attenuated PFC responses to affective stimuli [59].
- The successful treatment of mania was associated with increased activities in the PFC and OFC during sustained-attention tasks [70, 71].

Limbic Abnormalities in Patients with BPD

- Increased limbic metabolism in the manic state has been consistently replicated by independent research groups (review) [65].
- Increased metabolism in the ACC or cingulo-opercular network was observed during the manic state [51, 52].
- Amygdalar hyperactivity to (both positive and negative) affective stimuli has been observed in the manic phase [56-58, 72].
- While performing a decision-making task, manic patients showed increased activation in limbic regions (e.g., the ACC) [53].
- During a continuous performance task, mania (and mixed type) was observed to be associated with increased amygdalar activation [55].
- When processing negative affect, euthymic BPD patients showed a neural pattern of limbic hyperactivity (the amygdala and hippocampus) [60].
- Limbic nodes (amygdala, hippocampus, OFC, insula) showed enhanced neural responses to affective stimuli in the euthymic phase [61].
- Neural responses in the amygdala and OFC increased during motivational processing in the euthymic phase [30, 49].

- Remission from mania was reported to be associated with a decrease in amygdalar activation during a motor response inhibition task (Go/NoGo) [73].

Other Subcortical Abnormalities in Patients with BPD

- Increased metabolism in the caudate was reported in the manic state [51].
- Increased amplitudes of low frequency fluctuations in the putamen and caudate were observed in the manic phase [74].
- Increased activities in the caudate and thalamus while performing affect generation were noticed during hypomania [75].
- Increased activity in the putamen in response to negative facial stimuli was reported across all three BPD phases [52].
- Increased activity in the caudate in response to affective stimuli was observed in the euthymic phase [59, 61].
- Increased activity in the VS while anticipating a reward was reported in the euthymic phase [29, 30].
- Increased caudate volume was correlated positively and negatively with executive performance in healthy controls and euthymic BPD patients (within three months of sustained remission), respectively [76].

Neurophysiological Understanding and Facts

- The cortico-striato-thalamo-cortical circuit is the fundamental structure for the functionally segregated parallel networks of the BG, with cortical areas including the motor, PFC, oculomotor and limbic regions [77].
- The VS is a relay station in the limbic-striato-thalamo-cortical pathway. However, unlike other parallel pathways of the BG, the connections around the nucleus accumbens (NAc, a major structure of the VS) are more complicated. The inputs may comprise afferents from the PFC, limbic structures (ACC, amygdala, hippocampus, parahippocampal cortex), thalamus and mesencephalon (VTA, raphe nucleus [RN]), and the efferents may project to the BG (ventral pallidum, substantia nigra), hypothalamus and mesencephalon. In addition to the classical striatal-thalamo-cortical organization, the VS has innervations from and to deep nuclei.
- The VTA has connections with the medial PFC (mPFC), limbic system (ACC, hippocampus, amygdala), BG (VS, ventral pallidum),

hypothalamus, lateral habenula, and bed nucleus of the stria terminalis. In contrast to the BG and other deep nuclei, almost all areas that receive afferents from the VTA project back to it. VTA dopaminergic neurons also receive inhibitory input from GABAergic neurons within the VTA.

- Diverse information may integrate in the VS. The information flow from the PFC to NAc may be influenced by contextual constraints (e.g., the hippocampus), motivational saliency (dopaminergic neurotransmission from the VTA), physiological state (e.g., arousal indicated by the midline thalamus) and affective significance (e.g., the amygdala) to generate adaptive goal-directed behaviors [78].
- The dopaminergic neurons in the VTA are phasically active. If there are coincident excitatory inputs from the limbic region (such as the amygdala, hippocampus or ventral medial PFC [vmPFC]) and the VTA to the NAc (i.e., the limbic afferents are activated in the context of increased dopamine transmission), the information flow from the NAc to the mediodorsal nucleus in thalamus and then to the cortical division of the limbic forebrain will be reinforced [78].
- The VTA is located close to the floor of the midbrain and consists of approximately 60 to 65 percent dopaminergic neurons and 35 percent GABAergic neurons, with the latter modulating the firing of the former. The anatomical location of the VTA is adjacent to the substantia nigra, which is also rich in dopaminergic neurons. The substantia nigra projects to the dorsolateral caudate/putamen while the VTA projects to the VS and PFC; the former is the starting point of a mesostriatal pathway that is related to movement (and reward to a lesser degree), and the latter is the origin of mesocortical and mesolimbic pathways that are particularly implicated in reward circuitry and addiction [79, 80].
- The principal neurons of the ventral striatum are GABAergic, medium-sized, densely spiny projection neurons that form more than 95% of the total population [81]. The projections from the NAc to the VTA are generally onto GABAergic neurons, and hence the net effect is a disinhibition of the firing of VTA dopaminergic neurons (inhibition of inhibition via GABAergic neurotransmission) [79].
- The glutamatergic projections from the PFC to the VTA increase the firing of VTA dopaminergic neurons [79].
- The glutamatergic projections from the limbic system to the VTA increase the firing of VTA dopaminergic neurons [82].

- The VS/NAc may exert dopaminergic impact on other parts of the striatum by projecting to the VTA and substantia nigra compacta through the repeated spiraling striato-nigro-striatal circuitry [83].
- The distribution of the locations of brain lesions that may cause mania is very diverse and includes the mesencephalon, diencephalon, BG, frontal cortex and medial temporal lobe, to name a few [68, 84-94].

Part II: Cardinal (Neuro-) Features of Patients with BPD

The candidate brain theory of BPD is expected to be able to explain diverse prominent phenomena of BPD, tentatively including the following:

1. The occurrence of mania;
2. The occurrence of depression;
3. The occurrence of mixed mania and depression;
4. The enhanced limbic activity and hypofrontality [65, 95];
5. The reward abnormalities [26-28];
6. The therapeutic effects of anticonvulsants and lithium in both depression and mania;
7. The therapeutic effects of antipsychotics in mania;
8. The therapeutic effects of antipsychotics as one of the potentiation strategies in bipolar depression and refractory depression;
9. Antidepressants alone may not be effective for the treatment of bipolar depression;
10. The antidepressants may switch bipolar depression to mania; and
11. Diverse brain lesion locations that may cause mania, including the neocortex, limbic cortical structures, diencephalon and mesencephalon [84, 85, 88-90, 96-99].

RESULTS

This section describes the synthetic phase (the analytic phase is in the *Materials and Methods* section) and is divided into two parts. The VTA is proposed to be the pathogenic site of BPD and is the central missing piece of the jigsaw puzzle. The evidence for the role of VTA in BPD is depicted in the first part (biological rationality), whereas the performance of the synthetic result is scrutinized in the second part (accountability/comprehensiveness).

Part I: Synthetic Product – Evidence for the Role of VTA in BPD

There are several points derived from previous research/observations that underlie the reasoning and the determination of the pathogenic foci of BPD:

- BPD can be viewed as a single disease or as a single pathology characterized by two potential abnormal states, mania and depression.
- Since the manifestation of depression in patients with BPD is similar to that in patients with MDD, exacerbated limbic hyperactivity (and hence hypofrontality through an imbalanced RSM) is thought to be the origin of bipolar depression. Limbic hyperactivity alone, and the associated cortico-striato-thalamo-cortical loop, is not adequate to explain the occurrence of a manic phase.
- Mania is associated with a hyperdopaminergic condition that is related to the BG. However, enhanced BG activity alone (i.e., neurological disorders) cannot explain the occurrence of a depressive phase.
- SSRIs may inhibit neural activity in the limbic region [100-104]. If the core pathology of BPD is in the abnormally hyperactive limbic system, SSRIs will have no chance to switch/activate the brain to the manic state.
- Based on the above, the pathogenic locus of BPD is outside the limbic region and BG yet must innervate both structures.
- Anticonvulsants and lithium can treat BPD, either in the depressive or manic phase. Given that the action of anticonvulsants and lithium is to stabilize neuronal membrane and reduce firing, the neural substrate of BPD is assumed to possess an automatic oscillatory property.

According to the reasoning above and the effort of non-linear thinking, it turns out that the central missing piece of the BPD jigsaw puzzle is the VTA or a VTA-related pathway. Gradually enhanced neurotransmission or firing of the VTA is the very likely neural pathology of BPD, as this satisfies all of the above six points. The VTA is enriched in dopaminergic neurons and innervates both the limbic system and the BG (see *Part I* in *Materials and Methods*). The VTA hypothesis nicely accommodates two potential disease states, depression and mania. On one hand, the limbic

hyperactivity in the depressive phase may originate from both enhanced VTA-limbic interactions and the limbic-VS-thalamo-cortical pathway (the VTA has a strong connection with the VS/NAc). When reaching the breaking point of a cortico-limbic imbalance, BPD presents itself as depression that is nearly indistinguishable from MDD [41]. On the other hand, since the VTA also innervates the mPFC, enhanced VTA activity may increase frontal activity and thereafter increase BG activity via cortical-striato-thalamo-cortical pathways. Importantly, enhanced VTA-VS activity may increase BG activity through the repeated spiraling striato-nigro-striatal circuitry (see *Part I* in *Materials and Methods*). If the cortico-limbic balance is maintained (limbic compartments is not “expanded” significantly by the RSM), the consequence of enhanced activity in the VTA and BG (especially the caudate, VS and pallidum) shall be mania. The treatment of bipolar depression requires mood stabilizers or mood stabilizers plus antidepressants to correct for both VTA over-driving (mood stabilizer) and a cortico-limbic network imbalance (antidepressant) [2, 3]. The treatment of BPD mania demands mood stabilizers, antipsychotics or mood stabilizers plus antipsychotics to ameliorate the increased neural activity in both the VTA and the BG (antipsychotic). Dopaminergic neurons in the VTA and neighboring structures show repetitive burst-like firing that is closely related to its physiological function [105]. Other deep brain structures with dopaminergic activity are not considered in the generation of BPD (even though they could be the foci of iatrogenic mania) since they are mainly involved in motor functioning (and to a lesser degree, in reward). BPD is obviously not a movement disorder. The candidate physiological mechanisms that may over-drive the VTA are explicated in the *Discussion*.

In this report, “hyperdopaminergic” does not mean an over-secretion of dopamine but rather an enhanced function or efficiency in the neurotransmission of VTA-BG structures. Presynaptic dopamine function, as reflected by 18F-DOPA (18F is an isotope of fluoride) uptake and the concentration of dopamine metabolites in cerebrospinal fluid, is not altered in mania; however, presynaptic dopamine function is decreased after treatment with anticonvulsants [106]. The VTA hypothesis, therefore, should not be simply viewed as an increase or decrease in dopamine secretion but should be regarded as augmented network function and electrophysiological efficiency of VTA-related pathways that is shaped through plasticity during development (recall that BPD has substantial genetic component). Of course, the BG- and VTA-pathways can be enhanced by the external administration of dopaminergic agents that may cause organic mania. Although the VTA

projects to the BG, PFC and limbic regions, the influence on the limbic system in patients with BPD seems stronger than that on the PFC, such that during euthymia, the cortico-limbic balance is relatively biased toward the ventral compartment but does not reach an imbalance.

Part II: Evaluation of the parsimonious VTA model (accountability or comprehensiveness) that can be used to explain the BPD profiles (note: the contents are in a one-to-one correspondence with the core features summarized in the *Materials and Methods* section, part II)

1. In the case of bipolar mania, the cortico-limbic balance is not breached. The hyperdopaminergic state of the BG is the main neural manifestation, which has at least three sources: direct VTA inputs, frontal inputs via the fronto-striatal pathway, and limbic inputs via the VS-VTA pathway. The abnormalities in BG activity may be sustained by several positive auto-feedback loops (see *Discussion* for detail).
2. In the case of bipolar depression, the main neural manifestations is an unbalanced hypofrontality and limbic hyperactivity. Since the limbic hyperactivity may attenuate frontal activity via the RSM, the reduced frontal input to the BG may neutralize the increased limbic input to BG. In addition, the compensatory feedback from the vmPFC/ACC to the RN may quench the reward system [42-44], including the VTA. This explains why BPD may manifest as pure depression (nearly indistinguishable from MDD) without mania-related symptoms and neurobiological findings [41].
3. Following (1) and (2), mixed type of BPD is a state where a cortico-limbic imbalance and a hyperdopaminergic BG co-exist. The hyperactive BG may result from a particularly strong/efficient VTA-VS drive (which is not diminished by hypofrontality and negative feedback from the RN), or from the mPFC input (fronto-striatal) that is not completely suppressed by the RSM, or from both.

Based on the above, the VTA model of BPD may accommodate opposite polarities within a single disease.

4. The prolonged VTA drive may explain the enhanced limbic activity (and hypofrontality via RSM).
5. The reward abnormalities can be accommodated by the VTA and VTA-VS pathways [79, 80].
6. The anticonvulsant and lithium medications may reduce the firing rate of VTA dopaminergic neurons and, thus, can be used in both depression and mania [107, 108].
7. The VTA hypothesis explains that antipsychotics are useful in mania.
8. The VTA hypothesis explains that antipsychotics are one of the strategies of potentiation in bipolar depression and refractory depression.
9. Why is the treatment response to antidepressants alone not effective for bipolar depression? This is because the VTA abnormalities, the source of the limbic hyperactivity, are not corrected.
10. How can antidepressants switch bipolar depression to mania? This is because antidepressants confer the effects of limbic suppression and/or frontal enhancement mediated by the RSM that, in turn, may increase the input from the frontal cortex to the VTA and BG [2]. Although serotonin (or SSRIs) may suppress the reward system, decreased limbic activity may also reduce the feedback from the vmPFC/ACC to the RN; the net effect is canceled out such that the VTA is still active. Together, mania occurs.
11. The scattered lesions that cause organic mania all seem connected to the VTA.

The accountability of the synthesis is briefly summarized in Table 1, and a detailed explanation is expounded upon in the *Discussion*. The self-evaluation scale shows that the performance of the synthesis is excellent (>10 items in terms of accountability). The VTA-related pathways are illustrated in Figure 2.

Table 1. Summary of the BPD Phenomena that May Be Explained by the Theory of an Over-Driving VTA

Queries/Phenomena	Explanations
<i>Neuroscience perspective</i>	
The enhanced limbic activity and hypofrontality?	Enhanced VTA firing and cortico-limbic interactions mediated by RSM
The occurrence of mania?	Enhanced VTA and BG activity, and balanced cortico-limbic interactions
The occurrence of depression?	Enhanced VTA firing and imbalanced cortico-limbic interactions
The occurrence of mixed mania & depression?	Enhanced VTA and BG activity, and imbalanced cortico-limbic interactions
Why does a manic episode last?	Persistent over-driving VTA and several self-reinforcement loops
Why does a depressive episode last?	Cortico-limbic imbalance via RSM is a stable attractor
The reward/dopaminergic abnormalities?	VTA is a dopaminergic tank and a center of reward circuitry
Therapeutic effect of electrical convulsive therapy?	Resetting the abnormal VTA firing
High prevalence of BPD?	Positive feedback design is a potential bug in brain organization
Opposite vegetative manifestations?	VTA may influence deep brain nuclei through limbic system or VS
<i>Pharmacological perspective</i>	
The therapeutic effects of anticonvulsants and lithium?	Both agents may attenuate neuronal firing (i.e., VTA oscillations)
The therapeutic effects of antipsychotics in mania?	Antipsychotics may decrease the neural activity in VTA and BG
Antidepressants alone not ideal to treat BPD depression?	Over-driving VTA is not corrected
The therapeutic effects of antipsychotics in depression?	Modulation of abnormal VTA firing
SSRIs may switch bipolar depression to mania?	Decreased limbic hyperactivity may increase activity of VTA, BG and PFC
<i>Other Perspectives</i>	
Why may an acute stress trigger disease episode?	VTA is sensitive to stress hormone modulation
Why is obesity associated with disease severity?	VTA theory may explain abnormal food rewards
Diverse brain lesions may cause organic mania?	These lesions seem all connected to VTA (and related network)
The trend of enlarged amygdala and striatum?	Dopaminergic neurotransmission may carry neurotropic effects
Deep brain stimulation may cause mania?	Deep brain stimulation may “hack” the auto-feedback pathways

Abbreviations: basal ganglia (BG), reciprocal suppression mechanism (RSM), serotonin-selective reuptake inhibitor (SSRI), ventral tegmental area (VTA), ventral striatum (VS).

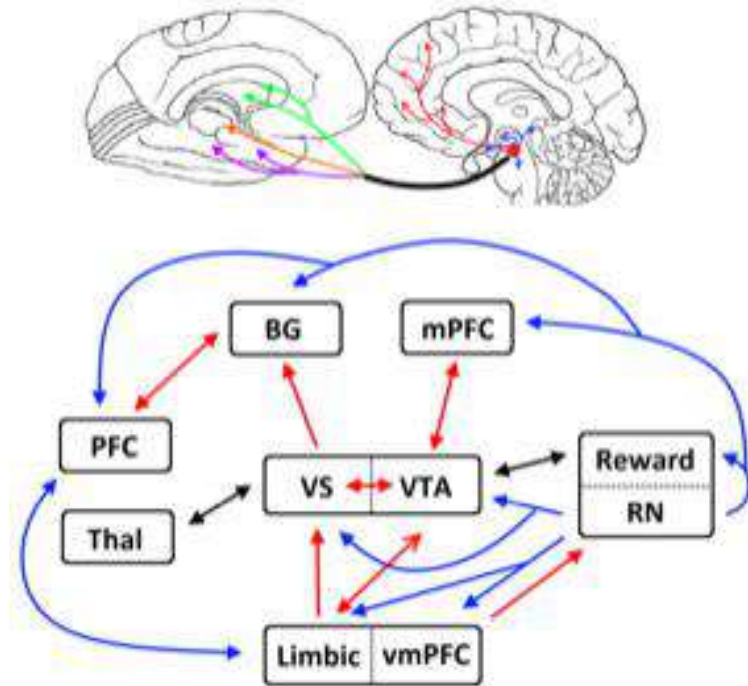


Figure 2. VTA-related pathways are illustrated. *Upper subplot*: neuroanatomical description of the VTA-related pathways, demonstrated using two medial views of the brain. The filled red circle in the midbrain (right side) is the approximate position of the VTA. Color arrows indicate different brain regions that the VTA projects to. Blue: reward network; Red: medial prefrontal cortex; Purple: limbic system; Brown: thalamus; and Green: basal ganglia. *Lower subplot*: a simplified schematic diagram of the interacting neural nodes, centered on the VTA. There are five different relationships: (1) Red unidirectional arrow: excitatory feedforward input; (2) Blue unidirectional arrow: inhibitory feedforward input; (3) Red bidirectional arrow: bidirectional interaction with positive auto-feedback (note: there are three different classes of positive auto-feedback; please refer to the main text); (4) Blue bidirectional arrow: bidirectional interaction with negative auto-feedback (i.e., cortico-limbic reciprocal suppression), and (5) Black bidirectional arrow: bidirectional interaction without forming a positive auto-feedback loop. Some detailed information is not depicted in the diagram, such as the interacting deep nuclei in the mesencephalon, diencephalon and hypothalamus. Abbreviations: basal ganglia (BG), medial PFC (mPFC), prefrontal cortex (PFC), raphe nucleus (RN), thalamus (Thal), ventral medial PFC (vmPFC), ventral striatum (VS), ventral tegmental area (VTA).

DISCUSSION

Although convergent evidence has indicated dopaminergic hyperactivity in mania, BPD is complicated by the intervening depressive and euthymic phase(s), making the precise location of the core abnormality ambiguous. Previous research has invested admirable efforts to investigate BPD from different perspectives, such as from the domains of emotion regulation and behavioral activation systems [25, 109]. However, many characteristics of BPD still cannot be accounted for satisfactorily. By applying the analysis-synthesis framework, which has been employed to decipher MDD [2, 3], the synthetic results unraveled that the VTA is the mostly likely pathogenic locus of BPD. The superiority of the VTA model is endorsed by this region's unique neuroanatomical properties, i.e., strong innervations to both the BG and the limbic system, rendering an "over-driving VTA" as a preferred candidate for the psychopathological mechanism that may accommodate the two potential (opposite) disease states, mania and depression. The abnormality of the VTA (or VTA-VS) may persist throughout the lifetime given its strong genetic component, its abnormal neural responses in the euthymic phase, and the high risk of recurrence of symptoms/episodes after a discontinuation of mood stabilizer. The onset of mania could range from early childhood to very old age, and the severity of the abnormal VTA may fluctuate with time [110]. Only when the severity reaches a breaking point may depression or mania occur (through either a cortico-limbic RSM or several sustained auto-feedback loops, see the sub-sections of *Network Mechanisms*). The further inspection of the pertinent neural pathways revealed that the VTA hypothesis may account for the remarkable defining features of BPD, whereas, the underlying physiological abnormalities at the tissue or cellular levels are still not clear. The details are elaborated below.

Summary of VTA-Related Pathways

The majority of the VTA-related pathways can be summarized into four categories; please refer to Figure 2. First, the VTA interacts with the VS/NAc, which is a relay station in the limbic-striato-thalamo-cortical pathway. The input connections to the VS/NAc include the PFC, limbic structures (ACC, amygdala, hippocampus, parahippocampal cortex), thalamus and mesencephalon (e.g., VTA and RN), and the outputs may project to the BG (ventral pallidum, substantia nigra), hypothalamus and mesencephalon.

The VS/NAc may thus integrate information from cognitive (PFC), motivational (VTA), contextual (hippocampus), emotional (amygdala) and arousal (midline thalamus) sources [78] and adjust the behavioral and physiological states [80]. Through the VS and the repeated spiraling striato-nigro-striatal organization, the VTA may also modulate other parts of the BG (i.e., not limited to the VS). Second, the VTA has direct connections with the mPFC, named the mesocortical pathway, and the afferents are excitatory and glutamatergic in nature [79]. Third, the VTA has direct connections with the limbic system, named the mesolimbic pathway, which mainly includes the ACC, hippocampus and amygdala. The afferents to the VTA-VS are also excitatory and glutamatergic [82]. Last, the VTA is a central node of a distributed reward-related network, which comprises the RN, lateral habenula, supramammillary nuclei, rostromedial tegmental nucleus, and bed nucleus of the stria terminalis, among others [111]. A unique feature of the VTA is that almost all areas that receive afferents from the VTA feedback to this region.

Frontal and Limbic Abnormalities in BPD (Synthetic Results 4)

Across the three phases, BPD tends to present limbic hyperactivity and hypofrontality [45, 46, 65, 95], which is similar to MDD [41-43]. Limbic hyperactivity prevails in baseline metabolism and in neural responsivity across a wide range of psychological domains, such as emotion, attention, response inhibition, reward processing and decision making [49, 51-53, 55-58, 60, 61, 72, 73]. In contrast, decreased frontal metabolism was reported in baseline conditions, and attenuated frontal responses were observed in several psychological tasks, including response inhibition, decision making, working memory, affective processing, and sustained-attention tasks [45, 47, 53-55, 59, 70, 71]. Phenomena that more reliably differentiate MDD and BPD include the manic phase (hyperdopaminergic neurotransmission), volumetric/morphometric changes in brain structures (amygdala and BG), increased neural responsivity in the BG, abnormal reward processing, and therapeutic choices (discussed in later sub-sections). Similar to MDD, the conjoint manifestation of limbic hyperactivity and hypofrontality may be mediated by the RSM [2, 3]. Since antidepressants may reverse the polarity from depression to mania, the critical pathogenic neural substrate of BPD is not within the limbic system (i.e., the limbic hyperactivity is not the primary disease mechanism); otherwise, the distinction between MDD and BPD would not exist. The VTA is known to project to both the limbic system and the BG, which renders the

VTA a suitable pathogenic candidate for BPD. It is imperative to note that mania is accompanied by hypofrontality, negating a naïve assumption that frontal hyperactivity and limbic hypoactivity mediated by the RSM (i.e., a reversal of the pattern of hypofrontality and limbic hyperactivity observed in depressive disorders) is the core neural mechanism of mania.

Among the different studies that probe frontal dysfunction in mania, the ventrolateral PFC and neighboring lateral OFC are of particular importance, as they are responsible for attentional shift and action inhibition and are also implicated in stimulus-reward/motor linkages [112-114]. Inadequate function in the lateral OFC during the manic state may result in disinhibition and reduced stimulus-outcome associations and hence, impairments in judgement [47, 48, 54]. Nevertheless, sporadic studies have reported increased activity in the lateral OFC during affective tasks [61, 115]; this inconsistency could result from the fact that the lateral OFC is situated at the junction of the limbic system (hyperactive) and the PFC (hypoactive) and, hence, is influenced by both neural substrates. The observation that the neural nodes at the cortical and limbic junction may show inconsistent directionality in terms of neural responses has been summarized in a previous report regarding MDD psychopathology [2].

The patterns of volumetric changes in brain structures in affective disorders are heterogeneous. However, there seems to be a trend that both BPD and MDD are associated with reduced volumes in several limbic structures, especially the subgenual ACC, OFC and hippocampus [63, 116]. There are various pathways that may lead to the limbic volume reduction, such as cytotoxicity due to prolonged over-excitation, immunological factors and stress hormones [2, 3]. However, in adults with BPD, enlarged amygdalae have been observed in several reports [116], which could be mediated by the long-term VTA-to-limbic input since the stimulation of dopamine receptors may increase neurotrophic factors derived from glial cells [117]. The neurotropic effect is supported by the observation that the administration of levodopa may enhance functional recovery after experimental stroke.

Reward Circuitry and BG Abnormalities in BPD (Synthetic Results 5)

It has long been acknowledged that mania/hypomania is a dysregulated state associated with hypersensitivity to potential future rewards that is accompanied by increased goal-directed activities and excessive pleasure-

seeking behaviors [1, 25]. In addition to clinical observations, psychological studies have also confirmed that BPD patients have elevated sensitivity to reward-related stimuli [22, 23]. Furthermore, heightened reward sensitivity predicts a more deliberate disease course [24]. Concordant with the clinical and psychological assessments, neuroimaging research has disclosed enhanced reward-related neural responses in manic/hypomanic patients or mania-prone people (26-29). Increased activity in the VS while anticipating a reward was also observed in the euthymic phase [29, 30]. However, several studies did not replicate these findings in the VS [11, 118], which will be further elaborated in the sub-section *Inconsistent Results of Previous Neuroimaging Research*. Reward circuitry is closely related to dopaminergic neurotransmission [19, 119-121], which cannot be accommodated by previous theories of emotion dysregulation or abnormal behavioral activation systems [25, 109]. Nevertheless, these important neuroscientific and psychological insights may complement the framework of the VTA theory to account for the clinical profiles and inter-individual differences.

Since the VTA powerfully modulates the activity of the BG (80, 83), the VTA (or VTA-VS) theory is also ideal to account for the observed BG abnormalities in patients with BPD. Increased metabolism and increased amplitudes of low frequency fluctuation in the striatum have been reported during the manic state [51, 74]. Enhanced neural responses to affective stimuli were reported in the striatum across all three BPD phases [52, 59, 61]. While performing affect generation, the caudate and thalamus show increased activity during hypomania [75]. Concordant with the VTA hypothesis, there is a strong trend of enlarged BGs in BPD patients [116]. It is interesting to note that for healthy controls, increased caudate volume was correlated positively with executive performance, whereas for BPD patients, the relationship is reversed, with a negative correlation between the caudate volume and executive performance [76]. The enlarged BG in patients with BPD is thus the consequence of pathological influences (via the abnormal firing of the VTA) and not an adaptive development.

Given that the abnormalities in BPD involve a broad range of cortical, subcortical and deep structures, neural computations over many neuropsychological domains are affected. This article does not cover this important topic, and interested readers may refer to the materials published elsewhere for a review of the neuropsychological impairments in BPD and MDD [3, 8, 9, 122, 123]. There are other interesting phenomena in BPD not addressed by this report. For instance, it has been noted that obesity is associated with a more severe illness course of BPD. Enhanced dopaminergic transmission in the

VTA may mediate an abnormal food reward and contribute to this relationship [124]. The impairments in vegetative functions seen in depressive and manic phases may be modulated via the limbic system and the VTA/NAc on the hypothalamic-pituitary-adrenal axis, respectively (79, 80). Although the detailed network mechanisms of the above associations are still not clear, the VTA theory of BPD seems to possess face validity to account for these observations.

Network Mechanisms of BPD: Manic Episodes (Synthetic Results 1)

Bipolar mania is accompanied by increased goal-directed behaviors, hypertalkativity and psychomotor agitation. Animal studies also indicate that increased brain dopamine levels are highly correlated with increased psychomotor activity [31]. Since the VTA is abundant in dopaminergic neurons, the VTA hypothesis is concordant with the observed correlation. Although transient sadness and clinical depression appear to be similar in psychological presentations and neural features [42], depression is characterized by a prolonged course. There must be a mechanism to maintain the depressive state, which is believed to be an unbalanced cortical-limbic interaction mediated by the RSM [2, 3]. Analogously, the neural network abnormalities in mania must be locked into a stable attractor/mode to sustain the symptoms and to exert substantial influence on the patients. VTA-related pathways may satisfy this critical constraint via two possible mechanisms: abnormal oscillatory rhythms in the VTA (see the sub-section *Possible Physiological Mechanisms of Over-driving VTA in BPD* for details), and positive auto-feedback. As to the latter, three classes of auto-feedback are explicated here. First, the NAc projections to the VTA may result in a disinhibition of VTA dopaminergic neurons (inhibition of inhibition, mediated by NAc GABAergic projections to GABAergic neurons in the VTA). Second, mPFC/limbic projections to the VTA may result in an activation of VTA dopaminergic neurons (glutamatergic projections from the mPFC/limbic system to the VTA or VTA-VS). Recall that almost all areas that receive afferents from the VTA project back to it, which potentially may form a positive-feedback self-enforcement loop around the VTA (please also refer to *Neurophysiological Understanding and Facts, Part I: Analytic Results in Materials and Methods*). Third, positive self-feedback is also a potential trajectory of the fundamental BG pathways — the cortico-striato-thalamo-

cortical loop. The advantage of the positive auto-feedback design lies in its capability to support prolonged goal-directed and/or motivation-triggered behaviors, relayed by the NAc (motivation), caudate (plan) and putamen (implementation) [125]. However, a potentially disastrous consequence is “over-heating”. In the case of mania, the BG is over-heated because of direct and indirect effects driven by the VTA (and/or VTA-VS), which are magnified and maintained through positive auto-feedback cycles. The consequences of the over-heated VTA-BG structures may comprise the characteristic symptoms of hypertalkativity, racing thoughts, increased goal-directed activities and excessive pleasure-seeking behaviors. The accompanying cognition of an expanded “self” may lead to inflated self-esteem or grandiosity. Deep brain stimulation, as introduced earlier, may also “hack” the auto-feedback pathway and cause iatrogenic mania [91, 92]. Akin to MDD, BPD also reflects a “bug” in brain organization. In summary, MDD is the price paid for expanded and integrated mental capabilities that compete with each other (i.e., cortico-limbic interactions via the RSM) [2, 3], and BPD is the consequence of having neuroanatomical design that aims to support sustained actions and explorations (for minutes or even for hours). The VTA-related pathways that may lead to mania are summarized in Figure 3.

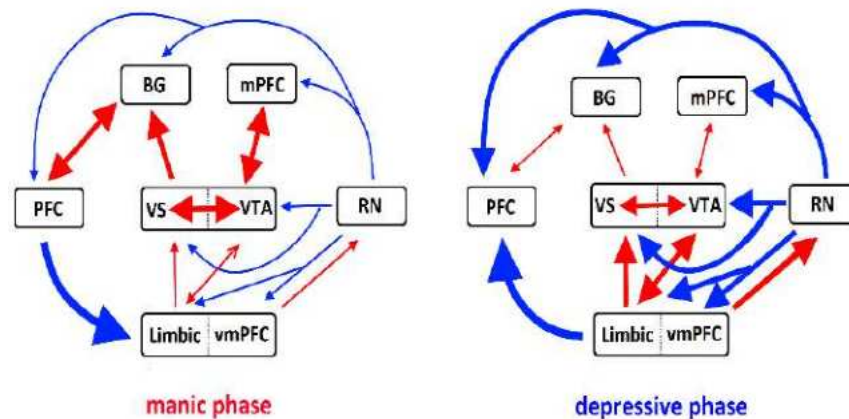


Figure 3. VTA-related pathways that may lead to mania and depression are summarized in the left and right sub-plots, respectively. Please note that the demonstration is a simplified scenario and there may be many variants. For example, some BPD patients may not show strong cortico-to-limbic suppression in the manic phase. Please refer to the legend of Figure 2 for abbreviations.

It is noted that positive auto-feedback interactions also exist between the VTA and the limbic system [82]. People might argue that the over-driving VTA and BPD could be caused by limbic hyperactivity (i.e., taking limbic hyperactivity as the primary disease mechanism of BPD). However, limbic hyperactivity alone is not enough to cause mania for several pathway reasons. First, limbic hyperactivity is accompanied by negative feedback from the vmPFC/ACC to the RN that may prevent the limbic and reward systems from over-excitation [42-44, 111]. Second, the dynamic balance of brain networks is assured by very complicated mechanisms such that the influence from the limbic system to the VTA/VS and then to other BG nuclei should be less and less along the information propagation trajectory. The VTA theory is a better candidate for BPD because the influence of (abnormal) VTA activity on either the limbic system or the BG is direct. Importantly, SSRIs may attenuate limbic hyperactivity (abnormality) [100-104], which makes limbic hyperactivity itself unable to reverse the polarity of depression to mania.

Relevant to the neural mechanisms of mania, the manipulation of the BG and reward circuitry may initiate a quick recovery from clinical depression (e.g., deep brain stimulation of the NAc, lateral habenula, subthalamic nuclei, globus pallidus) [126, 127]. The effects of NAc stimulation may spread to the other parts of the BG via the repeated spiraling striato-nigro-striatal circuitry [83]. The therapeutic effects may be mediated by all three auto-feedback pathways summarized above (directly by the first and the third routes and indirectly by the second route after frontal activity is enhanced). The consequent increased metabolism in the PFC may correct the cortico-limbic imbalance within a short period of time and improve refractory depression [126, 127].

Antidepressants may ameliorate the cortico-limbic imbalance in BPD depression and, therefore, may enhance the frontal input to the BG and VTA and reduce the inhibition of the RN feedback onto the VTA (VTA-VS). Given that the pathology of an over-driving VTA is still not corrected, one possible sequel is a switch from depression to mania. Similarly, the discontinuation of mood stabilizers may lead to the risk of the reappearance of BPD symptoms in a substantial portion of BPD patients, implying that symptom resolution in patients with BPD does not indicate a full recovery of the underlying etiology. A true convalescence from bipolar mania (or depression) is associated with a resetting/cooling of the over-driving VTA-related or VTA-VS network.

Network Mechanisms of BPD: Depressive and Mixed Episodes (Synthetic Results 2, 3)

Limbic hyperactivity has been consistently reported in BPD [45, 46, 49, 51-53, 55-58, 60, 61, 65, 72, 73, 95]. The over-driving VTA may enhance limbic system activity through the mesolimbic pathway (ACC, hippocampus and amygdala) and the limbic cortico-striato-thalamo-cortical pathway. The design of positive auto-feedback loops between the VTA and the limbic system may further accentuate the limbic hyperactivity [82]. When the cortico-limbic balance is breached, bipolar depression may occur, similar to the depressive phase of MDD [2]. In the case of bipolar depression, since limbic hyperactivity may attenuate frontal activity via the RSM, the reduced frontal input to the BG may cancel the increased limbic input to BG. In addition, the compensatory feedback from the vmPFC/ACC to the RN may diminish the activity of the reward system [42-44, 111], including that of the VTA. In contrast to the above inference about mania, the network designs explain why BPD may alternatively present pure depression (nearly indistinguishable from MDD [41]) without obvious hyperdopaminergic manifestation and manic symptoms. In other words, the consequent interactions between the networks associated with the over-driving VTA (or VTA-VS) have a tendency to compete with each other, forming the neurobiological basis of the depressive presentation of BPD. This competition is mediated by the cortico-limbic RSM and compensatory designs that cool down neural hyperactivity or, to put it simply, the inhibitory interactions between the large-scale networks. The VTA hypothesis may also account for mixed manic-depressive episode, in which a cortico-limbic imbalance and a hyperdopaminergic BG may co-exist. The hyperactive BG may result from either a particularly strong/efficient VTA-VS drive (which is not cooled down by hypofrontality and RN), from PFC input (fronto-striatal) that is not completely suppressed by the RSM, or from both. The neural consequences of an over-driving VTA may therefore contain the frequently reported abnormalities in the limbic system, PFC and BG, and hence may also explain the broad neuropsychological deficits, encompassing sustained attention, inhibitory control, verbal memory, executive function, emotion processing and reward sensitivity [3, 8-11, 56, 57, 58, 59, 72]. Together with the psychopathology of mania depicted above, the network mechanisms centering on the VTA (VTA-VS) may inherently carry a bipolar property. The VTA-related pathways that may lead to depression are illustrated in Figure 3.

The VTA is a heterogeneous structure, and the constituent dopaminergic neurons can be organized into clusters according to different projection profiles [19]. It is a misconception that the VTA or VTA-VS participates only in rewarding (positive) situations and not in aversive (negative) situations, although the latter has been less addressed in previous literature. Animal research has demonstrated a trend that the VTA dopaminergic neuro-transmission to the mPFC is modified by aversive stimuli, whereas such transmissions to the NAc are modified by reward (or both aversion and reward) [119]. Susceptibility to depression has been reported as being associated with an opposite trend in phasic firing by mPFC-projecting and NAc-projecting VTA neurons [120], a finding that is largely compatible with the distinction between cortical and limbic compartments in the cortico-limbic dysregulation model of MDD [128]. Conversely, as stated above, the VTA receives glutamatergic feedback and GABAergic feedback from the mPFC and from the NAc, respectively. Hypofrontality and limbic hyperactivity may modulate the bursting activity of the projected VTA neurons. In addition to reward signals, stress-related neuroendocrine molecules, such as cortisol, cortisol-releasing factor and dynorphin, also substantially impact the neurodynamics of the VTA [79]. Previous neuroscientific research thus provides strong support for a bipolar property “within” the VTA. In summary, the bipolar nature of BPD may originate from within the VTA itself and from the/its large-scale network interactions. Whether depression or mania is presented is dependent on the network interactions at the moment, which could be partly pre-determined within the VTA, i.e., the overall electrophysiological behaviors of the different neuronal subpopulations in the VTA.

Considering the VTA and BG to account for the occurrence of depression is reminiscent of neurodegenerative conditions involving the BG, such as Parkinson’s disease and Huntington’s disease [129, 130], which are frequently complicated with clinical depression and hypofrontality [131-133]. It is interesting to contrast comorbid depression in neurological conditions with bipolar depression. For the former, the primary network mechanism that triggers a cortico-limbic imbalance may be the hypofrontality that is the consequence of the decreased striato-cortical input. For the latter, limbic hyperactivity excited by the VTA may be the initiator of the network imbalance. Either hypofrontality or limbic hyperactivity may perturb the cortico-limbic interaction via the RSM and may result in depressive disorder after reaching a breaking point [2, 3].

Stress Response System and VTA

Stress is an important factor that may propel BPD patients to leave the euthymic phase. The previous sub-section describes the differential projections of the VTA to distinct neural substrates in response to rewarding and aversive stimuli. Herein, the possible mechanisms regarding how an acute stress may trigger a manic or depressive episode is further elaborated. The dopaminergic neurons in the VTA are susceptible to the modulation of the stress response system (also named the hypothalamic-pituitary-adrenal axis). Both excitatory and inhibitory synapses on VTA dopaminergic neurons and their long-term potentiation characteristics can be altered by exposure to acute stress [134, 135]. Note that unless otherwise specified, the term “stress” hereafter designates acute stress. Conceptual issues, such as the differentiation of stressful versus aversive stimuli/events and whether a reward is also a kind of stress, are beyond the scope of this report. The physiological mechanisms that urge patients with BPD to spontaneously progress to disease episodes is discussed later (*Possible Physiological Mechanisms of an Over-driving VTA in BPD*).

The stress-related molecules include (not exclusively) glucocorticoids (a class of steroid hormones), corticotrophin-releasing factor (CRF) and dynorphin. It has been observed that glucocorticoids may modify the AMPA/NMDA receptor ratio on the dopaminergic neurons that synapse with glutamatergic axon terminals (e.g., from the mPFC) [134]. The increased AMPA/NMDA ratio underlies the stress-induced dopamine efflux in the PFC [136]. How fast can the VTA neurons respond to a stressor? It has been reported that the AMPA/NMDA ratios are potentiated as soon as two hours after stress and remain potentiated for at least one day [137]. CRF is a hypothalamic peptide that signals stress throughout the brain. The projections (mainly glutamatergic) from the amygdala, hypothalamus and several deep nuclei to CRF-containing VTA neurons (i.e., CRF has bound to the receptors) may enhance the expression of NMDA receptors and the firing of dopaminergic as well as GABAergic neurons [138]. Dynorphins (a class of opioid peptides) and κ -opioid receptors are distributed broadly in the brain, with the highest concentration in the deep subcortical structures, including the VTA. Dynorphin levels and κ -opioid receptor phosphorylation are increased after stress and are thus implicated in stress-related behaviors and may profoundly alter VTA synapses [139]. The activation of opioid-associated pathways may attenuate the release of GABA from the GABAergic terminals that project onto VTA dopaminergic neurons and may change the

electrophysiological properties of VTA neurons, including excitatory and inhibitory postsynaptic currents and long-term potentiation at GABAergic synapse [79]. It is notable that several of the electrophysiological consequences of stress tend to enhance dopaminergic neurotransmission or firing, such as increased AMPA/NMDA ratios, enhanced expression of NMDA receptors, decreased GABAergic release and so on. The VTA response to chronic stress is complicated and may even show opposite bursting patterns compared with those of acute stress [140].

Since the VTA responds to stress drastically and quickly, it seems appropriate to position VTA in a central position that may trigger the relapse/recurrence of psychiatric disorders. Given the bipolar nature of the VTA (and its associated networks), stress-associated aberrancies imposed on the original VTA abnormalities may induce either a depressive or manic episode in patients with BPD and may induce a depressive episode in patients with MDD by exaggerating limbic hyperactivity. It is interesting to note that depression and mania are both well-known side effects of the administration of steroids (sometimes the mood symptoms may occur within several hours after taking steroids). This “bipolar” side effect can also be accommodated using the stress-VTA framework described above [141]. In addition, VTA-VS and mesolimbic abnormalities may cause psychosis and are some of the major foci that antipsychotics target at [78, 142]. Put together, the stress-VTA framework may account for the deleterious effect of stress on (at least) two major categories of psychiatric conditions, i.e., affective and psychotic disorders. Other biological factors may also modulate the VTA-VS dynamics in an acute or chronic manner, such as immunological abnormalities (e.g., through the kynurenine pathway) and decreased levels of brain-derived neurotrophic factor [143-145], which require further studies to clarify. In summary, the phenomenon of a euthymic phase transitioning to a disease episode after stress exposure may be mediated by the interaction between the stress response system and the VTA [142].

Medical Conditions Associated with Mania (Synthetic Results 10, 11)

As described in the *Introduction*, dopaminergic agents may cause iatrogenic mania even for non-bipolar patients [38], which is concordant with the proposed VTA hypothesis. The medical conditions that are associated with mania are quite diverse and are categorized as follows:

1. PFC stimulation or lesions: One potential side effect of transcranial magnetic stimulation and electrical stimulation of the PFC is mania [84, 85]. Surgical resection of frontal region was also reported to induce mania [86].
2. Lesions in the limbic/paralimbic system: Medial temporal lobe and OFC lesions (or resection) may be associated with mania [88-90].
3. Deep brain stimulation: Electrical stimulation of the NAc, globus pallidus and subthalamic nucleus may cause mania (electrical stimulation of deep nuclei in the motor pathway is a neurosurgical procedure to alleviate motor symptoms of later stage Parkinson's disease) [68, 91-93].
4. Deep brain lesions: Mesencephalic and diencephalic lesions may be associated with mania [96-99].
5. Medications: Steroids and dopaminergic agents may elicit mania (141). Antidepressants may switch a depressive phase to a manic phase in patients with BPD.
6. Seizure: Mania was reported to be related to seizure activity in epileptic patients [88, 146].

The reported brain lesions associated with organic mania are distributed quite diversely, ranging from the neocortex and limbic cortical structures to deep nuclei. It seems difficult to reconcile such a scattered distribution of pathogenic loci within a simple framework. However, a careful inspection of the above regions reveals that most of them are pertinent to a VTA-associated network, such as the PFC, limbic/paralimbic regions, BG and deep nuclei (the lesions may affect the distributed reward circuitry or mediodorsal nucleus in the thalamus, which receive information flow from the NAc). The exact physiological mechanisms underlying organic mania are not clear; nevertheless, we conjectured that it could be mediated by a loss of negative feedback (recall that the VTA receives feedback from nearly every target it projects to) or a reorganization of the VTA network elicited by a retrograde degenerative/apoptotic signaling. Seizures may affect the VTA via the propagation of epileptic activity, and the values of seizures in localizing the origin of organic mania is limited. The condition of delirious mania is not considered here because the associated consciousness change may involve global disturbances in the brain that are thus not informative for pathway clarification. In terms of the network mechanisms of secondary depression that result from various medical conditions, please refer to a previous report [2].

Mechanisms of Pharmacological Treatments for BPD (Synthetic Results 6–9)

Several classes of medication have been proven to be effective in the treatment of BPD, including lithium, anticonvulsants, antipsychotics, antidepressants and others (e.g., benzodiazepines). Lithium is one of the oldest medications used to treat BPD; however, its mechanism is still not fully understood. Many biochemical mechanisms have been proposed, such as inhibition of the second messenger enzyme inositol monophosphatase, modulation of G-proteins, influence on the signal transduction cascade, interaction with nitric oxide signaling pathway, protection of mitochondria from oxidative stress, competition with magnesium to reduce glutamatergic neurotransmission, and the release of neuro-protective proteins [147]. Various anticonvulsants used to treat epilepsy have also been shown to possess therapeutic effects on BPD. The therapeutic mechanisms may include interference with voltage-sensitive sodium channels, enhancement of the inhibitory effects of GABA, and regulation of signal transduction cascades. Although the actions of various mood stabilizers differ, they have one thing in common: they stabilize neuronal membrane and decrease neuronal firing [107, 108]. It is noteworthy that the therapeutic effects of lithium and anticonvulsants are not universal but show regional preferences, especially in the limbic region and reward circuitry (including the VTA) [107, 148, 149]. Lithium treatments may decrease frontal activation during working memory tasks, which is likely to be mediated by decreased striato-frontal dopaminergic transmission [150, 151]. It has been noted that mood stabilizers have therapeutic effects for both bipolar mania and depression and may also prevent euthymic BPD patients from relapse. Based on the summarized network mechanisms above, the attenuation of the firing of VTA neurons may decrease limbic and BG hyperactivity in depressive and manic phases, respectively. Electroconvulsive therapy for acute mania may work by resetting the abnormal oscillations of the VTA [152].

It has been verified that antipsychotics (i.e., modulators of dopamine pathways) help treat not only bipolar mania but also bipolar depression [17, 35-37]. Although the manifested symptoms of bipolar depression appear to be similar to those of MDD, one critical difference lies in the differential therapeutic efficacies of antidepressants and antipsychotics. In BPD depression, the treatment response to SSRIs alone may not be satisfactory and may lead to the risk of reversing polarity from depression to mania. However, SSRIs are among the first-line treatment choices for MDD,

and antipsychotics are generally not recommended for MDD that is not complicated by psychosis. Regarding the use of antipsychotics, the distinction between MDD and bipolar depression is concordant with the proposed dopaminergic aberrancies in patients with BPD. Without the correction of the underlying pathogenic mechanisms of BPD (e.g., the abnormal VTA drive), antidepressant treatments (e.g., SSRIs) will not suffice to convert the associated limbic hyperactivity and frontal hypoactivity (the neural manifestations of clinical depression). The VTA hypothesis thus also draws support from the therapeutic perspective. It is interesting to note that the pharmaceutical options for treatment-resistant depression (potentiation strategy) include mood stabilizers and antipsychotics [153]. It is an open question whether treatment-resistant depression is actually an under-diagnosed variant of BPD and not a subtype of MDD [154]. The VTA hypothesis does not exclude the possibility that a BPD patient may present only depressive episodes for his/her life time.

From the VTA theory, the disease mechanisms of BPD mainly involve an over-driving VTA or VTA-VS that exerts its influence through various downstream dopaminergic pathways. It appears reasonable to infer that lithium/anticonvulsants may attenuate VTA neuron firing, whereas antipsychotics may modulate the downstream systems that are affected by the dopaminergic neurotransmission. Concordant with the above inference, a combination of mood stabilizers and antipsychotics may result in a better treatment response than either one alone in several clinical cases or situations [155]. The combined use of different anticonvulsants may reduce the VTA influence more effectively and may benefit some BPD patients [156]. Based on the distinct pharmacological routes that lithium/anticonvulsants and antipsychotics separately operate through, we temporarily retain the nomenclature that differentiates mood stabilizers (i.e., lithium/anticonvulsants) from antipsychotics in this article [13, 14], rather than incorporating lithium/anticonvulsants and antipsychotics under a broad concept of “mood stabilizers”. We acknowledge that the above distinction is over-simplistic and is for the convenience of discussion. For example, antipsychotics may affect VTA firing through the NAc-to-VTA feedback projection and the dopaminergic auto-receptors on VTA neurons [157]. In other words, both lithium/anticonvulsants and antipsychotics may stabilize VTA and, hence, mood. Nevertheless, a previous fMRI study supports the idea that an anticonvulsant (divalproex) and an antipsychotic (risperidone) exert differential effects on brain networks [158].

Inconsistent Results of Previous Neuroimaging Research

In psychiatry research, the interpretation of neuroimaging findings warrants particular caution. For example, either decreased or increased frontal activation to cognitive tasks can be regarded as supporting evidence for hypofrontality (e.g., in MDD or schizophrenia); the former may reflect the frontal abnormality itself, and the latter might indicate an extraordinary/compensatory effort to cope with the hypoactivity and maintain task performance. These two accounts oppose each other but are both popular in the interpretation of neuroimaging findings. In addition, reduced frontal reactivity may imply either insufficient engagement or higher efficiency (less energy to finish neural computations). Other more complicated scenarios are also worthy of consideration. For instance, the baseline neural activity in patients may be different from those in healthy controls, and there is a negative interaction between the pre-stimulus baseline and subsequently evoked neural activity [159, 160]. If the patient group has abnormal (either higher or lower) baseline activity in region X, then the neural reaction in region X to stimuli could be similar for both patient and control groups, explained below. In the condition of hyper-metabolism in region X, the neural response is expected to be higher, but at the same time, the increased evoked activity is offset by the negative interaction with the increased baseline activity. Similar inferences can be applied to the condition of hypo-metabolism. The VS is a key structure in reward circuitry that is implicated in BPD. The VS responses of euthymic BPD patients to reward-related signals have been reported to increase [29, 30] and decrease [11], compared with healthy controls. In manic/hypomanic states, the neural response of the VS to reward-related stimuli may increase, decrease or show no differences [27, 118, 161]. In other words, the summed effect of the contrasted, evoked responses may be unpredictable and could originate from all three possible causes discussed above (though not exclusively). This complicated interaction may mask real psychopathologies in psychiatric disorders. Although the inconsistencies in neural responsivity in the reward system seems to negate the role of the VTA-VS as a “reliable” disease locus, patients with BPD are well known as being less capable of suppressing the automatic activation of the mesolimbic system when having to reject a reflexive reward to obtain a reflective reward, i.e., to sacrifice instant pleasure to fulfill a long-term goal [11]. This raises the concern of whether the reported structures with high variability across studies actually indicate pertinent disease foci in the neuroimaging research of psychiatric disorders.

Discrepancy and unreliability could be a façade, and the variability between reports might also provide valuable information.

From the above explication, it becomes clear why the VTA has been largely ignored in previous BPD research. The VTA is small and lies deep in the mesencephalon, which cannot be adequately assessed by modern neuroimaging tools (e.g., electroencephalography or fMRI). Furthermore, in depressive states, the dopaminergic abnormalities are masked by an inhibitory projection from the RN to the reward circuitry (a compensatory mechanism to reduce limbic hyperactivity) and by the decreased frontal feedback to the BG and VTA. In addition, the most consistent neural manifestation of BPD across the three phases is limbic hyperactivity and hypofrontality [46, 60, 65]. Together with the inconsistent reports of the NAc, it is no wonder that the VTA or VTA-VS has not been broadly recognized as a candidate pathogenic locus for BPD. It is noteworthy that the prominent role of the VTA (or VTA-VS) in BPD can be reasonably unveiled by the current “synthesis”. Despite inconsistent neuroimaging reports, the evidence of reward/BG abnormalities in patients with BPD is very strong [22-24, 26-30]. It is thus recommended to use a fine resolution fMRI that focuses on the mesencephalon or a beamforming approach (e.g., synthetic aperture magnetoencephalography that applies spatial filters to gain access to deep brain structures) to elucidate the neural properties of the VTA (VTA-VS) in patients with BPD [162]. As to other causes of inconsistent reports, please refer to the discussion about the lateral OFC (in the sub-section *Frontal and Limbic Abnormalities in BPD*).

Possible Physiological Mechanisms of an Over-Driving VTAIN BPD

Dopaminergic neurons in the VTA fire spontaneously in a pacemaker-like manner. In the previous discussion (*Network Mechanisms of BPD: Manic Episodes*), three classes of auto-feedback pathways were contrived based on neuroanatomical/neurophysiological knowledge. This sub-section addresses another BPD mechanism, i.e., an over-driving VTA. Concordant with the strong genetic component, the euthymic state of BPD also presents abnormalities in neural responsivity [46]. The BPD psychopathology itself will not impair normal daily functioning in the euthymic phase. It is noteworthy that manic or depressive episodes may occur spontaneously, not necessarily preceded by a stress. The neural underpinnings of BPD must undergo a progressive or accumulative process. It is when the pathology accumulates to a

certain threshold that a large-scale network balance is breached, and depression or mania emerges. These two features (i.e., persistent and fluctuating abnormalities and episodic disease manifestations) differentiate BPD from other neuropsychiatric disorders that are accompanied by long-lasting and significant psychosocial impairments, such as schizophrenia. The kindling phenomenon (i.e., shortened disease-free intervals over time) of BPD further indicates that the abnormality accrues with age or with number of episodes. Then, what are the physiological and molecular mechanisms underlying this gradually augmented, fluctuating neurotransmission in the VTA?

This issue is grossly unknown, and the VTA is still not a hotspot for BPD research [65, 109]. In addition, the VTA is small, and the electrophysiological responses of the VTA to external stimuli varies quite a bit (depending on the studied contexts) [79], which together make previous non-invasive large-scale neuroimaging tools less suited to investigate its abnormalities. It seems reasonable to assume that the proposed gradual fluctuations of VTA oscillations may be related to chronobiological control. The chronobiology spectrums comprise daily (diurnal), tidal, weekly, seasonal, and annual rhythms. The physiology and behavior of an organism may change drastically according to different phases of the biological rhythm. A substantial portion of BPD patients do show seasonal patterns [163, 164]. Below the critical point that would lead to a radical large-scale network remodeling, the (fluctuating) VTA abnormalities will not handicap the BPD patient and can only be unraveled by neurophysiological or psychological examinations. Beyond a certain threshold, however, the large-scale neural networks will progress to either a cortico-limbic imbalance via the RSM (depression) or an over-active BG-VTA-PFC circuitry due to positive auto-feedback (mania). The suprachiasmatic nucleus has been verified to be a primary circadian oscillator, where gene expression, metabolism and rate of action potentials show daily rhythms in a synchronized manner [165]. Nevertheless, recent research highlights that almost all cells and tissues in the body are biological clocks and may express the “Clock gene” (Clock is an abbreviation of “circadian locomotor output cycles kaput”) [166, 167]. The Clock proteins (activators and repressors) and associated kinases and phosphorylases form the molecular foundation of circadian rhythms. It is interesting to note that an association between Clock genes and BPD has been suggested in human research [168]. Moreover, animal studies demonstrate that a Clock Δ 19 mouse model of mania (mutant-type) is associated with increased activity in VTA dopaminergic neurons. Lithium treatment reduces the VTA firing rate and NAc dopamine

levels in mutant mice (with no effect in non-mutant/wild-type mice) [107, 169].

Other physiological mechanisms are also worthy of consideration for the over-driving of the VTA. The NAc is known to be a coincidence detector, and the dopaminergic neurons in the VTA are phasically active [78]. If there are coincident excitatory inputs from the limbic region (such as the amygdala, hippocampus or vmPFC) and from the VTA to the NAc (i.e., the limbic input is in the context of increased dopamine transmission), the information flow from the NAc to the mediodorsal nucleus in the thalamus and then to the cortical division of the limbic forebrain will be reinforced. Abnormal coincidence firing may also result in a net effect similar to an over-driving VTA. Although the content of this sub-section is largely speculative, it exemplifies a typical dialectic process substantiated by the endeavors of alternate analysis and synthesis. Synthesis is certainly not a stopping point but rather a source of new predictions that can be verified or rejected empirically (entering the next cycle of analysis-synthesis); see below for details on “dialectic neuroscience”.

Analysis-Synthesis Approach: Dialectic Neuroscience

This report aims to identify the pathogenic loci of BPD. The synthetic results indicate that an over-driving VTA or VTA-VS is an “excellent” candidate (number of explained phenomena greater than 10). The phenomena accounted for by the VTA model actually exceed the 11 defining features, and the model (potentially) may also accommodate other important observations, such as the relevance of disease severity to over-weight, abnormal (bipolar) vegetative functions, enlarged amygdala and striatum, pharmacological choices (lithium/anticonvulsants and antipsychotics), network attractors (sustained and prolonged symptoms), influences of stress (stress-VTA pathway) and side effects of steroids. Considering limbic hyperactivity and hypofrontality (the most consistent neural features of BPD and MDD) as the core pathologies of BPD would leave the abnormal dopaminergic/reward evidence unexplained. In addition, due to a compensatory inhibition from the RN (driven by the vmPFC and subgenual ACC), the activities of the reward circuitry are expected to be further attenuated (e.g., resulting in anhedonia in patients with MDD), rendering the limbic hyperactivity theory not ideal in resolving what occurs in the manic phase [2, 3, 22-24, 26-29, 42-44]. The hypotheses based on limbic hyperactivity (and hypofrontality) should

accordingly surrender to the VTA model of BPD. The animal model based on stimulant-intoxication (mania) and -withdrawal (depression) is useful but is not plausible for human BPD since bipolar depression is not associated with clinical withdrawal symptoms. In addition, the animal BPD model cannot explain the defining features of BPD, such as why antipsychotics may benefit bipolar depression [40]. The application of an analysis-synthesis framework may help to solve complicated issues, and the synthetic results may provide theoretically more sound direction for further empirical explorations. The term “dialectic neuroscience” is invented to designate this whole process.

The connotations of the term “dialectic” are two-fold. First, it is used to describe the dialectic process endorsed by the analytic and synthetic endeavors. This dialectic is drastically different from the analog of Fichte (and many others) that is substantiated by the synthesis of “thesis” and “antithesis” [170]; see Figure 1 for illustration. Obviously, the analytic results (i.e., the peripheral pieces of the jigsaw puzzle) are not necessarily antagonistic to each other, and the analysis-synthesis hybrid may accommodate complicated situations. What are the consequences of not having dialectic (synthetic) science? The direct results could be that debates continue to be debated. For example, supporters of the frontal lobe theory of MDD may apply different experimental paradigms, neuroimaging tools and mathematical methods and always confirm the abnormalities in the frontal lobe. Similarly, defenders of the limbic theory of MDD may always verify limbic aberrancies. Likewise, proponents of frontal, limbic or BG abnormalities in BPD can always find strong and persuasive evidence to “prove” that their viewpoints are valid. The most likely scenario is that they all grasp some aspects of a complicated issue; however, a core mechanism is demanded to integrate these aspects. Through the synthetic process, different analytic facts or disciplines can begin to interact in a “non-linear” manner (non-linear thinking is the cognitive capability that supports synthesis) [2, 3]. Under the resultant synthetic framework, the analytic findings actually may annotate each other and become meaningful to each other.

Figure 4 contrasts the integrative endeavors underlain by linear and non-linear (synthetic) attitudes. Linear integration is easily trapped in the pitfall of parochialism, i.e., using one discipline to explain other disciplines or implicitly assuming one discipline is more fundamental than others. This kind of integration may be compelling and useful in some situations but potentially could be superficial and circular reasoning. In contrast, synthesis is a non-linear integration that is difficult to achieve but may be devoid of futile endeavors. The quintessence of synthesis is to facilitate (or sometimes coerce)

“true dialogues” between different viewpoints/disciplines, hence, the second connotation of “dialectic neuroscience” — the word root of dialogue. In the beginning, the dialogue might just occur in the synthesizer’s mind. With the distribution of the synthetic results, the dialectic outcome can be examined by the scientific community and supplemented by other researchers, and finally, a consensus could be reached. Since the terms analysis and synthesis have been applied in very diverse contexts, it is recommended to use “dialectic neuroscience” when appropriate to confine the semantics of analysis and synthesis.

The methodology of “dialectic neuroscience” has been applied in the exploration of fundamental neuroscience issues and the psychopathology of MDD and BPD [2, 3]. Its power is enhanced by the user’s proficiency in the managed topic. There are several points to be reminded and advised of. If researchers want to apply the analysis-synthesis framework to solve complicated issues, it will be helpful to collect peripheral pieces of the jigsaw puzzle that are pertinent to the defining features and are equipped with higher differentiability, and then follow the suggested format (i.e., *Methods* for analysis and *Results* for synthesis) as demonstrated in this article (and in a previous report [2]). As to the synthesis endeavor, non-linear thinking is strongly recommended to actively integrate, not passively agglomerate, fragmented information. The synthetic results with lower accountability should succumb to the one with the highest accountability. Since a synthesis demands non-linear thinking, there is no fixed brain theory format for psychiatry illnesses. We would like to ensure that every psychiatry disorder can be deciphered by dialectic neuroscience.

Dialectic neuroscience may progress following the stages below [3]; please refer to Figure 1:

1. In the initial stage, neuroscientific evidence is accumulated from various disciplines and perspectives. The reliability of the evidence is assured by sound experimental designs even though false positives and false negatives are unavoidable. At this stage, researchers generally resort to linear thinking design experiments and to interpret analytical results. Many hypotheses may be examined, and some will survive. True cross-talk is not common.
2. In the second stage, an endeavor is directed to determine whether the diverse analytical findings can be integrated into an insightful, simplified and usually mechanistic framework. This attitude is synthetic, and the researchers usually need to rely on non-linear

thinking and creativity to fulfill this “synthetic science”. The synthesizer behaves like an active organizer that may force the dialectic to commence and the non-linear integration to be achieved. At this stage, the constructed theory should conform to the criteria of parsimony, plausibility and comprehensiveness so that the synthetic account may conceptually pass stringent statistical challenges. The statistical/scientific validity of the synthetic outcome should be acknowledged, like the analytic counterparts.

3. In the third stage, the synthetic outcome may provide predictions for further analytical experiments to either verify or deny. Generally, if a synthetic story is based on many analytical facts, further experiments shall not only prove its correctness but also refine or supplement its tenets or contents. If there are two synthetic stories for related topics, it is possible to integrate the two into a higher-order synthesis. Contradictory syntheses can also be resolved by examining their predictions.
4. New predictions and their relevant analytical experiments may result in the generation of new issues. Then, the cycle repeats and goes back to the first stage.

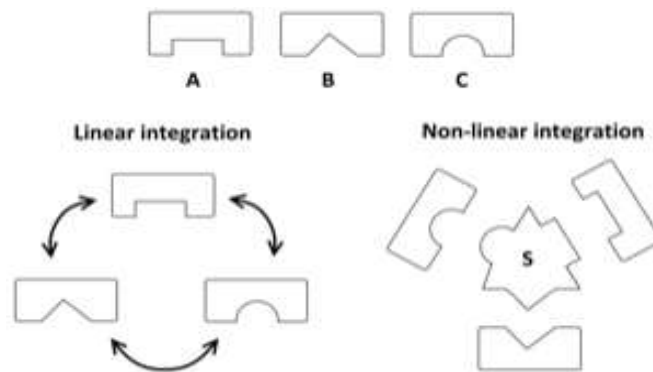


Figure 4. Integrations by linear and non-linear attitudes are contrasted.

Assume A, B, C are three different disciplines (A, B and C could be emotion, cognition and attention, among others). Left: Linear (analytic) integration and the possible consequence of circular reasoning. The arrow indicates the direction that uses one discipline (origin) to account for the other disciplines (end). For example, using A to explain B and then using B to explain C. Right: Non-linear (synthetic) integration attempts to determine the central missing piece S that satisfies the observations from A, B and C.

CONCLUSION

This synthesis work attempts to localize the pathogenic locus of BPD. The synthetic results demonstrate that a VTA model of BPD may accommodate the confusing nature, i.e., opposite polarity, of this single disease. This model is biologically reasonable (rationality), the explained phenomena are broad (comprehensiveness, not limited to the 11 defining features but also encompassing other relevant domains, such as neurophysiology, pharmacology, vegetative functions and metabolic profiles), and the model itself is simple (parsimony, only 1 structure), satisfying the three proposed criteria for synthesis. The bipolar presentation may originate from network interactions and the VTA itself. To date, the analysis-synthesis framework has been applied in the investigation of two major psychiatric disorders, MDD and BPD. The factors that affect psychiatric disorders are surely diverse and heterogeneous, involving neurochemical and neuroendocrine pathways, genomic expression, glial and neuronal pathology, abnormal synaptic neurotransmission, immunological reactions, apoptotic and degenerative changes, and derangement in the intra-cortical plexus, among others. The holistic influence of all the neurobiological correlates of BPD will manifest itself together in the brain's dynamics, and there must be a simple platform to accommodate all the complexity at a large-scale neural network level [2, 3]. The analysis-synthesis hybrid approach therefore is not faulty reductionism of complicated issues and avoids an arbitrary dichotomy of simplicity and complexity. It is important to note that the research into the reciprocal suppression mechanism and ventral tegmental area is not new. Without dialectic neuroscience, both would be embedded among many other studies like a droplet in a cup of water, and their significance in MDD and BPD would not stand out. In addition, the true pathology could be masked by various neural interactions, such as between baseline abnormalities and evoked neural activity. Regarding the disease mechanisms of psychiatry disorders, we may have already known much more than we thought. What is lacking is a suitable framework to fully utilize previous analytical results and build theoretically sound hypotheses based on (if not all of, at least a substantial portion of) them. An analysis-synthesis hybrid was invented to serve this purpose and to integrate the seemingly irrelevant peripheral pieces of the jigsaw puzzle by determining the central missing piece. Dialectic neuroscience may help to provide "biological definitions" of major psychiatric disorders in the future, enabling psychiatry to become comparable to other medical disciplines.

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Competing Interests

No conflicts of interest to declare.

Author Contributions

TW Lee and SW Xue provided intellectual input to this work. TW Lee wrote the first draft.

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Ventral Tegmental Area as the Core Pathophysiological Hub of Bipolar Disorder: Evidence from Resting-State fMRI

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Abstract

Objectives: Bipolar disorder (BPD) is a major and complex psychiatric condition, clinically characterized by euthymic, depressive, and manic phases. Through the implementation of the “dialectic neuroscience” approach, the ventral tegmental area (VTA) has been proposed as a potential key hub in BPD. This study utilized resting-state functional magnetic resonance imaging to investigate functional connectivity (FC) changes seeded by the VTA in BPD.

Methods: MRI data from 98 participants in a publicly available dataset were analyzed (49 stable BPD patients and 49 healthy controls). Using the dopamine receptor D1 distribution template from JuSpace, the representative voxel of the VTA in the midbrain was identified based on the highest correlation with the D1 template. This voxel served as the seed for FC map construction. The FC maps were Fisher-transformed and compared statistically using an independent two-sample t-test.

Results: Significant deviations in BPD were observed in brain regions that were highly consistent with the projections of the VTA, including the ventral and medial prefrontal cortex, orbitofrontal cortex, anterior cingulate cortex, and nucleus accumbens.

Conclusions: The FC analysis provided empirical support for the VTA theory in BPD. The role of VTA abnormalities in contributing to the manifestation of opposing polarities within a single disorder was discussed, offering insights into the potential neuropathological mechanisms and genesis of BPD. The framework of dialectic neuroscience may provide a valuable approach for developing guiding brain theories in psychiatric disorders.

Key Words: Bipolar disorder (BPD), functional magnetic resonance imaging (fMRI), medial PFC (mPFC), nucleus accumbens (NAc), orbitofrontal cortex (OFC), ventral tegmental area (VTA).

Running Title: Ventral Tegmental Area and Bipolar Disorder

Introduction

Bipolar disorder (BPD), as its name suggests, is characterized by two opposing phases: mania and depression, and is also known as manic-depressive illness. Brain science research has significantly contributed to identifying consistent patterns of decreased frontal and enhanced limbic neural activities across all three states of BPD (depressive, manic, and euthymic) [1-5]. Additionally, bipolar mania has been associated with increased baseline metabolism in the striatum, including the ventral striatum (VS) [5, 6], while euthymic BPD is also linked to reward sensitivity and negative risk-taking behaviors [7]. These findings suggest that abnormalities in the reward-related circuitry and basal ganglia (BG) also constitute an enduring neural feature of BPD. However, the underlying disease mechanisms that account for the holistic picture remain elusive. It is evident that neither limbic hyperactivity, including the associated cortico-striato-thalamo-cortical loop, nor a hyperdopaminergic state with enhanced BG activity alone sufficiently explains the occurrence of manic and depressive phases, respectively. Consequently, the pathogenic locus of BPD likely resides outside the limbic region and BG, while still exerting influence over both structures.

Psychiatric disorders are inherently complex, posing substantial challenges in deciphering their fundamental nature. To address this complexity, the author developed the framework of “centralized dialectics” and its application to brain science—termed “dialectic neuroscience.” This approach was previously applied to explore the neuropathology of major depressive disorder (MDD) and has recently received empirical support [8-10]. Building on this framework, a guiding theory was proposed, identifying the ventral tegmental area (VTA) as a key hub in BPD [11]. Notably, the neural pattern of hypofrontality and limbic hyperactivity and clinical manifestation of depression are shared by both MDD and BPD [12-15], highlighting a potential transdiagnostic mechanism. Insights gained from deciphering MDD have paved the way for investigating BPD within this theoretical VTA model. This study utilized resting-state fMRI to examine the functional connectivity (FC) patterns centering on VTA in individuals with BPD.

Located near the midline on the floor of the midbrain, the VTA serves as the primary source of dopaminergic cell bodies within the mesocorticolimbic dopamine system [16]. As an inherent dopaminergic hub, the VTA is a plausible candidate for explaining the dopaminergic dysregulation implicated in BPD [17-20]. Additionally, the VTA interacts with the ventral striatum (VS) and nucleus accumbens (NAc), which function as relay stations within the limbic-striato-thalamo-cortical pathway [21]. The rationale for the VTA-centered theory of BPD is briefly outlined below from two perspectives: (1) the projection distribution of the VTA and (2) its physiological properties. Firstly, the VTA has direct connections with the medial prefrontal cortex (mPFC) and the anterior cingulate cortex (ACC), forming the mesocorticolimbic pathway [22, 23]. Moreover, the VTA exhibits strong reciprocal interactions with the VS/NAc, where information from cognitive (PFC), motivational (VTA), contextual (hippocampus), emotional (amygdala), and arousal-related (midline thalamus) sources is adaptively integrated [24, 25]. These VTA-associated pathways robustly modulate neural activity within both the limbic system and the BG, positioning the VTA as a key structure for modeling the opposing poles of BPD. For a more detailed discussion on network interactions in manic and depressive states, see [8, 11]. Secondly, similar to the VS/NAc, the VTA has also been implicated in reward and reinforcement processes [26, 27]. It serves as a central node within a distributed reward-related network, which includes raphe nucleus (RN), lateral habenula, supramammillary nuclei, rostromedial tegmental nucleus, and bed nucleus of the stria terminalis, among others [27]. Beyond its traditional functions, the VTA is also involved in aversion regulation [22, 28]. Aversive and stressful experiences, such as social threats, foot shock, physical restraint, resource limitation, and suboptimal caregiving environments, have been shown to enhance dopaminergic activity within the mesolimbic system [22, 29, 30]. In summary, the VTA is engaged in both rewarding and aversive processes, also mirroring the bipolar nature of BPD. Notably, the projection and physiological profiles exhibiting “bipolarity” are features that the neural nodes in the limbic system or BG lack, despite strong evidence linking abnormalities in these regions to BPD.

Since directly localizing the VTA using structural MRI is challenging, the author utilized JuSpace, which provides nuclear imaging templates derived from radiolabeled ligands of various neurotransmitter systems. The foundational paper on JuSpace demonstrated that drug-induced spatial alterations in brain activity

correspond to the distribution of specific receptor systems targeted by the respective compounds [31]. Specifically, receptor density distributions detected by Positron Emission Tomography or Single Photon Emission Computed Tomography have been shown to correlate with neural metric maps obtained from functional MRI (fMRI). The validity of JuSpace has been established in neurological conditions, such as Parkinson's disease [31], and in the localization of small subcortical nuclei [32]. Similar to the latter approach, the author utilized a D1 receptor density map to identify the VTA within the midbrain [33]. The VTA-seeded FC maps of BPD and healthy controls (HC) were then compared to examine potential deviations in the interaction with mPFC, ACC, and NAc [21-23, 27].

Materials and Methods

Subjects, MRI data, and preprocessing

MRI data from 98 participants from the University of California, Los Angeles (UCLA) Consortium for Neuropsychiatric Phenomics LA5c study was obtained [34], including 49 BPD patients and 49 HC. At the time of scanning, all BPD patients were in a stabilized condition for at least four weeks. This publicly available dataset can be accessed via OpenNeuro (<https://openneuro.org/datasets/ds000030>). The sample size provides adequate statistical power based on prior neuroimaging literature [35]. Whole-brain functional and structural MRI (sMRI) images were acquired using 3.0 Tesla MRI scanners (Siemens Allegra) with a TR of 2s, a voxel size of 3×3×4 mm³, and 152 volumes.

rsfMRI preprocessing was conducted using the Analysis of Functional NeuroImages (AFNI) software package [36]. The preprocessing pipeline included despiking, slice-time correction, realignment (motion correction), registration of T1 anatomy, transformation to Talairach space (TT_N27+tlrc; both functional and structural MRIs), spatial smoothing, and bandpass filtering at 0.01–0.10 Hz [37]. The first 4 scans were discarded to allow for signal equilibrium. A smoothness kernel of 6 mm was applied to the rsfMRI data. For anatomical segmentation, FreeSurfer was employed to delineate gray and white matter from T1-weighted images and to parcellate the cortical surface into 68 regions of interest (ROIs) using the Desikan-Killiany Atlas [38-40]. The segmented results were also transformed to align with standard template. This approach facilitated the identification of the midbrain and VTA. To account for motion and physiological noise, 12 movement-related parameters, as well as white matter and ventricular signals, were included as nuisance regressors in the model following established denoising protocols [41-43]. Additionally, second-order polynomials were applied to model baseline drift.

Identification of VTA by D1 receptor map

The brainstem ROI delineated by FreeSurfer served as the initial reference for VTA identification. Given that all MRI images were aligned to the Talairach template, it was reasonable to assume that the midbrain lies above the Z coordinate of -30, as illustrated in Figure 1 (subplot A). The time series of each voxel within the midbrain ROI was extracted and correlated with the rest of the brain. A cortical mask was then constructed based on known VTA projection areas, encompassing the ACC, lateral and medial orbitofrontal cortex (lOFC and mOFC), and ventromedial prefrontal cortex (vmPFC) [22, 23]. The correlation between the D1 receptor map and the VTA-FC map was constrained within this mask. The FC map of the voxel showing the highest correlation with the D1 receptor map was considered a surrogate for the VTA. Notably, the BG was excluded to minimize potential confounds from nigrostriatal projections, which could influence the D1 receptor distribution and reduce the sensitivity of the localization strategy. This approach is consistent with existing methodologies utilizing JuSpace, a toolbox designed for cross-modal correlation of MRI-derived measures with nuclear imaging-based estimates of various neurotransmitter systems [31, 32].

To assess whether there is a significant difference in the distribution of VTA coordinates between the BPD and HC groups, Hotelling's T² test was employed, which is a multivariate generalization of the t-test used for comparing the means of two groups with more than one variable (in this case, the 3D coordinates: x, y, and z). The test involved the calculation of respective sample mean and covariance matrix. The pooled covariance matrix of the two groups was computed. Hotelling's T² statistic was then calculated using the

formula, which incorporates the difference between the group means, the pooled covariance matrix, and the sample sizes of both groups. This statistic quantifies the multivariate distance between the two group means, adjusted for the variance and covariance structure. A P-value less than 0.05 indicates that the two groups' distributions of VTA coordinates differ significantly.

FC map construction and statistical comparison

The voxel values of the VTA-centered FC maps were transformed into Fisher's z-scores prior to group-level statistical comparisons (where a Fisher's z-score of zero corresponds to a correlation coefficient of zero). A two-sample independent t-test was conducted to identify significant brain regions with scores showing between-group differences using the AFNI module 3dttest++ [36]. The statistical threshold for the t-test was set at a corrected P-value < 0.05 (non-parametric alpha permutation) with an extent threshold > 30 voxels. Given that the BPD patients were not in active disease states and hence that the between-group differences were expected to be less robust, a more lenient uncorrected P-value < 0.005 was also reported.

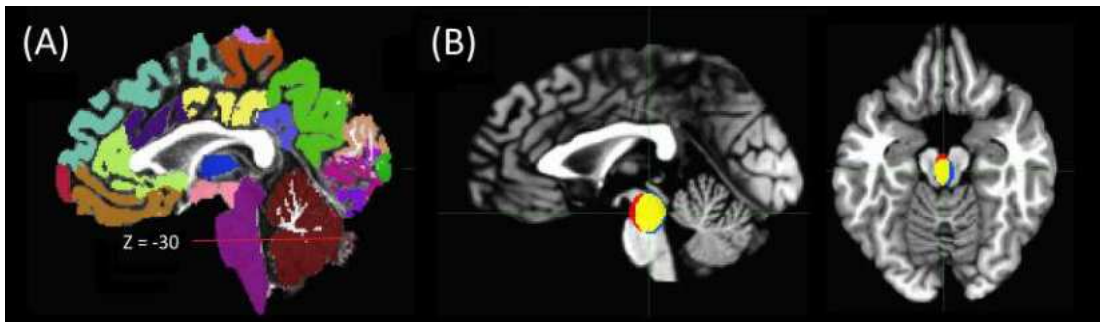


Figure 1. (A)

Segmented structural MRI image from a selected case for demonstration. The purple ROI indicates the brainstem, and the red line marks the Z coordinate at -30, with the midbrain structure located above the line. (B) Target VTA voxel positions represented as ellipsoids with dispersion of 1 SD along the three axes for the BPD and HC groups, superimposed on a standard Talairach template. Blue: BPD, Red: HC, Yellow: overlapped. Sagittal and axial views are centered at [0.2, 23.1, -15.1], the global mean coordinate of the target VTA voxels across all participants. This distribution aligns with the elongated structure of the VTA in the midbrain.

Results

The mean ages of the BPD and HC groups were 35.3 years (SD = 9.0) and 35.3 years (SD = 8.4), respectively, with no significant between-group difference ($P = 0.991$, $t = 0.012$, $df = 97$). The gender distributions for the BPD and HC groups were 28/49 and 26/49, respectively, with no significant distribution difference (Chi-Square statistic = 0.165, $P = 0.685$). As for other protocol details, please refer to the data source [34].

The average coordinates of the representative VTA for the BPD and HC groups were [-0.34, 23.8, -15.3] and [0.75, 22.3, -14.8], respectively, following the RAI convention, on the Talairach brain template (TT_N27+tlrc provided by AFNI), as shown in Figure 1 (subplot B). The square roots of the eigenvalues of the respective covariance matrices, which represent the spatial dispersion, are [6.2, 7.4, 10.3] and [4.6, 8.8, 9.6]. It is noteworthy that one major contribution to the dispersion comes from the imperfect (which is a fact) alignment of fMRI to sMRI and to the template. The distribution of the identified VTA loci did not show any group differences, with the mean coordinate difference approaching zero, with Hotelling T^2 statistic: 2.0806 and P-value 0.563.

The VTA-centered FC maps demonstrated significant differences in the vmPFC (including the frontal pole), bilateral OFC (including pars orbitalis), anterior cingulate cortex (ACC), and NAc, which were in good concordance with the major cortical and subcortical projections of the VTA. The results are illustrated in Figures 2 and 3 and summarized in Table 1.

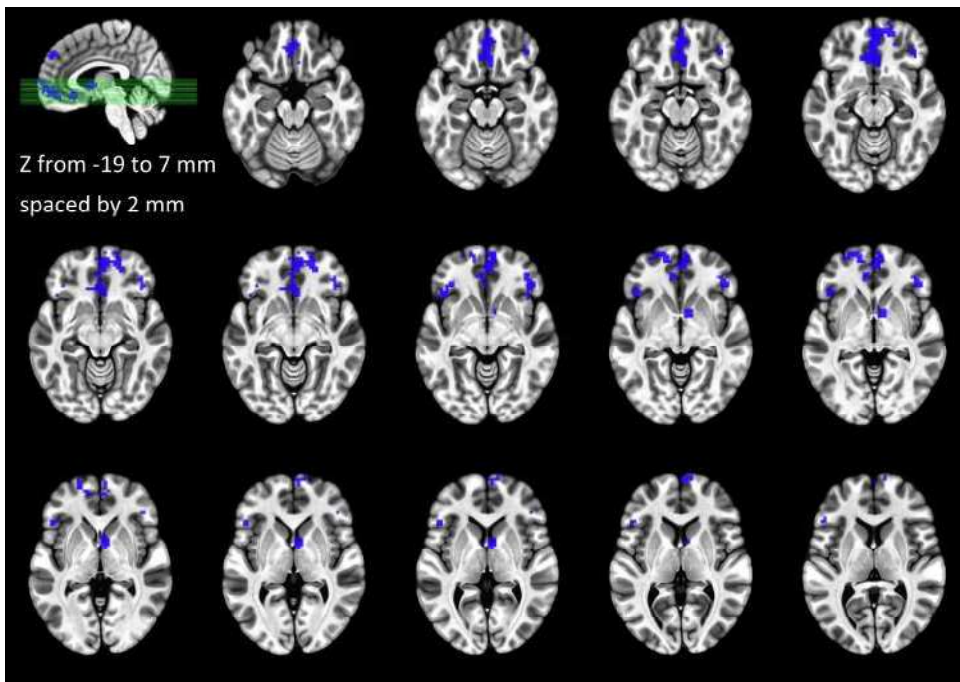


Figure 2. Mosaic axial views depicting the abnormal clusters of the VTA-seeded FC map. Blue indicates decreased functional connectivity in the BPD.

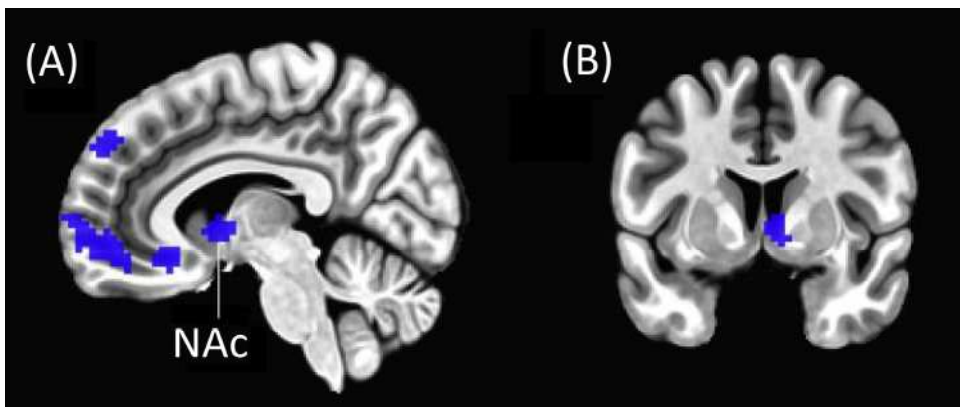


Figure 3. Sagittal and coronal views for better illustration of the abnormal clusters in the medial PFC (subplot A) and NAc (subplots A & B) in BPD. Please refer to Table 1 for the detailed information of the coordinates and statistics.

Table 1 Brain regions showing significant functional connectivity changes in BPD compared to HC.							
Brodmann Area	Region	Peak x	Peak y	Peak z	Z-score	Voxel Number	Cluster Details
*11	R IOFC	-16.5	-55.5	-12.5	-4.23	265	involving Bil mOFC, vmPFC & R FP
47	R pars orbitalis	-43.5	-31.5	-6.5	-3.73	49	
	L cerebellum	43.5	58.5	-27.5	-3.61	44	
47	L pars orbitalis	46.5	-25.5	-0.5	-3.63	38	crus
	R Naci	-4.5	-4.5	2.5	-4.29	35	
9	R superior frontal	-1.5	-49.5	38.5	-3.77	35	
11	L lateral OFC	16.5	-58.5	-3.5	-3.51	34	mPFC
							close to L FP

*Multiple comparison correction with $P < 0.05$. Other results: uncorrected $P < 0.005$. Spatial extent threshold: 30 voxels.
Peak coordinates are reported according to the RAI convention: negative for right, anterior, and inferior.
Z-scores represent Fisher's transformation of the functional connectivity with the VTA (correlation coefficient).
Abbreviations: R = right, L = left, Bil = bilateral, IOFC = lateral orbitofrontal cortex, mOFC = medial orbitofrontal cortex,
NAc = nucleus accumbens, FP = frontal pole, vmPFC = ventromedial prefrontal cortex.

Discussion

While substantial evidence supports dopaminergic hyperactivity in mania, the presence of intervening depressive and euthymic phases in BPD complicates the identification of the core abnormality's precise

location. Hyperdopaminergicism alone seems insufficient to explain the observed decrease in frontal activity and increase in limbic activity across the three phases. Previous research has made commendable efforts to investigate BPD from various perspectives, including emotion regulation and behavioral activation systems [17, 44]. However, a comprehensive explanation of the disease mechanism and pathogenesis has been lacking. This research provides empirical evidence supporting the theory that the VTA serves as a central hub in the pathogenesis of BPD [11]. Verification of this hypothesis has been hindered by two major factors. First, the challenge of localizing the VTA using in vivo neuroimaging tools. Second, the complexity of depression pathogenesis. Recent advancements integrating functional and neurochemical imaging techniques, along with a deeper understanding of MDD pathogenesis from a brain science perspective (the latter to be elaborated later), have addressed these obstacles [9, 31]. With the D1 receptor template provided by JuSpace, a surrogate VTA position was elucidated, and the FC map with VTA as a seed was constructed and compared. Interestingly, the brain regions showing significant deviations in BPD were highly concordant with the projections of VTA, including mPFC, vmPFC, OFC, ACC, and NAc. The decrease in connectivity strength may reflect compensatory adaptations to prolonged VTA overactivity (elaborated below). These findings persuasively support the role of VTA in BPD. In addition, samples from stabilized BPD patients suggest that abnormal VTA activity could be an enduring feature of the disorder. However, among the diverse neuroimaging findings of BPD, why is the VTA qualified to be the key hub (a proposal derived from the efforts of dialectic neuroscience [10, 11])? This question is addressed through an exploration of several key points outlined below.

Summary of neural abnormalities in BPD from neuroimaging research

A wide range of neuropsychological domains are affected in patients with BPD [45-48]. Some deficits, such as impairments in sustained attention, inhibitory control, reward sensitivity, verbal memory, and executive function, may persist even in remitted BPD or BPD with residual symptoms [7, 48]. The persistence of these neuropsychological deficits during euthymia aligns with genetic research suggesting a strong biological basis for BPD [49]. This broader perspective reinforces the view that BPD has a substantial genetic component, with neuropsychological impairments persisting even in symptom-free periods [50].

Despite diversities in neuroimaging findings, three major categories of neural abnormalities have been observed in BPD: reduced frontal activity/responsivity, along with heightened activity/responsivity in the limbic system and BG. For example, during the execution of a working memory task, all three BPD phases exhibited a consistent pattern of reduced neural activity in dorsal (cortical) regions and increased activity in ventral (limbic) regions [1, 2]. The findings of hypofrontality and limbic hyperactivity have been replicated across a wide range of cognitive and affective experimental paradigms [3, 51-55].

Reward abnormalities in BPD are of particular interest. It has been proposed that a competition exists between the desire for an immediate reward (reflexive or instant gratification) and the delayed satisfaction of a long-term goal (reflective reward or temporary reward suppression) [56]. In bipolar mania, both reflexive and reflective reward processes appear to be impaired, with a stronger inclination toward the former and reduced proficiency in the latter. Motivational and reward-based tasks in BPD have been associated with heightened neural responses in the BG (BG), particularly VS [51, 55, 57]. Even in the euthymic phase, BPD patients exhibit reward sensitivity and negative risk-taking behaviors [7], suggesting that dysfunctions in reward-related circuitry and the BG are enduring features of the disorder. Notably, the BG also show an exaggerated response to affective stimuli [51, 58], a pattern that persists across all three BPD phases [59]. From clinical perspective, up to 50 percent of BPD patients may experience psychotic symptoms, and dopamine antagonists are effective at relieving psychosis [60]. These findings align with the concept of hyperdopaminergicism and BG dysfunction in BPD.

VTA theory to account for the depressive phase in BPD

As summarized above, the primary neural dysfunctions in BPD involve the frontal and limbic regions, as well as the BG/ventral striatum (BG/VS), which are central to the motivational dopaminergic circuitry. Notably,

these three categories of abnormalities appear to be distinct and independent, with no clear explanatory link between them. This suggests that the core pathology of BPD likely extends beyond these systems. With the recent understanding that depression arises from a compartment-level network imbalance between the frontoparietal and limbic systems, the findings of hypofrontality and limbic hyperactivity can be integrated into a unified framework [8, 10]. Specifically, a reciprocal suppressive mechanism (RSM) between the frontoparietal and limbic compartments enables dynamic switching between external engagement and internal processing. A disruption of this balance drives the system into an attractor state, manifesting as depression—characterized by limbic hyperactivity and hypofrontality. The cortico-limbic RSM, together with several well-documented network mechanisms, may account for a substantial portion of the understanding of MDD and secondary depression (e.g., post-stroke depression) [8]. How, then, does VTA theory account for the occurrence of depression in BPD?

Limbic hyperactivity in the euthymic state may stem from both enhanced VTA-limbic interactions and the limbic-VS-thalamo-cortical pathway, given the strong connectivity between the VTA and the VS/NAc. Through the reciprocal suppressive mechanism (RSM), this hyperactivity leads to hypofrontality. When the cortico-limbic imbalance reaches a critical threshold, BPD manifests as depression. Clinically and neurologically, depression in BPD is nearly indistinguishable from MDD due to their shared neuropathological mechanisms [12]. However, from a therapeutic standpoint, strong evidence suggests that depression in BPD and MDD differs. Antidepressants are a primary treatment for MDD; however, their efficacy in bipolar depression is often limited when used as monotherapy and carries the risk of inducing a switch from depression to mania. Instead, several classes of medications have been shown to be effective in treating BPD, including lithium and anticonvulsants, collectively referred to as mood stabilizers. Lithium, one of the oldest treatments for BPD, has an incompletely understood mechanism of action. Proposed mechanisms include inhibition of inositol monophosphatase, modulation of G-proteins, regulation of signal transduction cascades, interaction with nitric oxide signaling, mitochondrial protection from oxidative stress, competition with magnesium to reduce glutamatergic neurotransmission, and promotion of neuroprotective protein release [61]. Additionally, several anticonvulsants used for epilepsy have demonstrated therapeutic efficacy in BPD. Their mechanisms may involve interference with voltage-sensitive sodium channels, enhancement of GABAergic inhibition, and modulation of signal transduction pathways. Despite differences in their specific mechanisms, mood stabilizers share a common function: stabilizing neuronal membranes and reducing neuronal excitability [62, 63], which aligns with the overactive VTA theory. Furthermore, antipsychotics may influence VTA firing through the NAc-to-VTA feedback projection and the dopaminergic autoreceptors on VTA neurons [64]. The efficacy of antipsychotics in bipolar depression supports the role of dopaminergic dysfunction in BPD, reinforcing the hypothesis that an overactive VTA underlies its pathology. Correcting the overactive VTA and the imbalance between the frontoparietal and limbic compartments may be achieved through a treatment approach combining mood stabilizers and antidepressants. The VTA theory thus offers a compelling framework for understanding the differential pharmacological responses to depression in MDD and BPD.

VTA theory to account for the manic phase in BPD

The BG are among the primary regions implicated in BPD, particularly the VS in mania. Since the VTA powerfully modulates the activity of the BG [25, 65], the VTA theory is also ideal to account for the observed BG abnormalities in patients with BPD. It has long been recognized that mania/hypomania is a dysregulated state characterized by heightened sensitivity to reward-related stimuli, increased goal-directed activities, and excessive pleasure-seeking behaviors [17, 66-68]. In line with clinical and psychological assessments, neuroimaging research has revealed enhanced reward-related neural responses in manic/hypomanic patients or individuals prone to mania [18-20, 57]. The cortico-striato-thalamo-cortical circuit forms the core structure for the functionally segregated parallel networks of the BG, with cortical areas including the motor, PFC, oculomotor, and limbic regions [69]. The VS acts as a relay station within the limbic-striato-thalamo-cortical pathway and has reciprocal interactions with the VTA. Unlike other parallel pathways of the BG, the

connections of the VS are more intricate, extending to deep nuclei such as the VTA, hypothalamus, hippocampus, amygdala, and RN. Furthermore, the VS/NAc can modulate dopaminergic signaling in other striatal regions by projecting to the VTA and substantia nigra through the spiraling striato-nigro-striatal circuitry [65]. This organization enables interactions between the parallel cortico-striato-thalamo-cortical circuits, facilitated by projections from the VS-VTA pathway, which may also influence neural activity in other PFC regions beyond the vmPFC. Concordantly, increased PFC activity in bipolar mania compared to the euthymic state has been observed [1]. In addition, the heightened activity in the BG and PFC during mania may mitigate limbic hyperactivity via RSM. This hypothesis aligns with neuroimaging findings showing reduced amygdala responses to negative emotional stimuli in mania relative to the euthymic state [59]. Thus, in bipolar mania, the cortico-limbic balance remains intact due to enhanced BG/PFC activity. Overall, the hyperdopaminergic state of the BG emerges as a key neural signature, driven by multiple sources: direct VTA inputs, frontal inputs via the fronto-striatal pathway, limbic inputs via the VS-VTA pathway, and less RSM from the limbic system.

Under the assumption of an overactive VTA, why might depression occur independently of mania? In depression, pronounced limbic hyperactivity may attenuate frontal activity via the RSM, leading to reduced frontal input to the BG, which in turn may counterbalance the increased limbic input. Additionally, excessive limbic activation could trigger compensatory feedback from the vmPFC and subgenual ACC to the RN, dampening the reward system [13-15], including the VTA. This explains why BPD can manifest as pure depression (nearly indistinguishable from MDD), where the primary neural signature is unbalanced hypofrontality and limbic overactivity, without excessive BG activation. Accordingly, the presentation of depression or mania is shaped by the interaction and competition between large-scale networks or by the dynamic regulation of VTA neuronal subpopulations (see the section *Physiological mechanisms related to the genesis of BPD* for details). Following this reasoning, mixed-type BPD represents a state where cortico-limbic imbalance coexists with hyperdopaminergic BG activity. The hyperactive BG may arise from a particularly strong or efficient VTA-VS drive (which remains uninhibited by hypofrontality and negative feedback from the RN), together with mPFC input via the fronto-striatal circuit. Based on this framework, the VTA model of BPD can accommodate opposite affective polarities within a single disorder.

Increased limbic activity in BPD can be explained by the VTA to limbic projection outlined in the previous section. The heightened VS activity driven by the VTA may further amplify limbic cortical activity via the cortico-striato-thalamo-cortical circuit, providing an additional source of limbic hyperactivity. These pathways of limbic enhancement may account for the cortico-limbic imbalance being biased toward the ventral compartment across all three disease phases and for the greater prevalence of depressive episodes compared to manic episodes in BPD [70].

Physiological mechanisms related to the genesis of BPD: positive feedback circuits and overactive VTA

About 60–65% of the VTA neurons are dopaminergic, while the remaining 35% are GABAergic [26]. The dopaminergic neurons in the VTA are phasically active and exhibit repetitive burst-like firing, which is closely related to their physiological function [71]. Interestingly, the neural circuits surrounding the VTA contain multiple positive feedback mechanisms, which may contribute to the persistence of neural abnormalities in BPD. For instance, projections from the NAc to the VTA primarily target GABAergic neurons, resulting in a net disinhibition of VTA dopaminergic firing (i.e., inhibition of inhibition via GABAergic neurotransmission) [22]. Similarly, afferents from the mPFC and limbic regions to the VTA can enhance VTA dopaminergic activity through glutamatergic projections from the mesolimbic system to the VTA or VTA-VS [22, 72]. Furthermore, the cortico-striato-thalamo-cortical loop, a fundamental BG pathway, may also function as a self-reinforcing circuit, further amplifying these effects (note: the mechanism is complex, with one possibility involving the differential distribution of D1 and D2 receptors in the mPFC and striatum [73]). The advantage of these positive feedback circuits lies in their ability to sustain prolonged goal-directed and motivation-driven behaviors, mediated by the NAc (motivation), caudate (planning), and putamen (execution) [21]. This autofeedback design, with the VTA as a key ignitor, is adaptive and essential for survival and is finely regulated

by a complex array of neural inhibitory processes [74]. However, a potentially disastrous consequence is “overheating.” In the case of bipolar mania, over-activation of the BG may be driven by the VTA (and/or VTA-VS). Additionally, iatrogenic mania can emerge when autofeedback circuits are “hacked” by medical interventions, such as deep brain stimulation or pharmacological treatments like levodopa [75-77]. Overheating of VTA-BG structures may give rise to hallmark symptoms of mania, such as hypertalkativity, racing thoughts, heightened goal-directed activities, and excessive pleasure-seeking behaviors. This dysregulation is often accompanied by an expanded sense of self, potentially manifesting as inflated self-esteem or grandiosity. Notably, while autofeedback mechanisms may contribute significantly to the persistence and expression of BPD, the core pathology of BPD likely lies beyond these adaptive circuits and instead stems from an overactive VTA, further discussed below.

“Bipolarity” is a defining feature of BPD, which not only manifests in network activities, as discussed above, but also exists within the VTA itself. For example, susceptibility to depression has been linked to opposing trends in phasic firing between mPFC-projecting and NAc-projecting VTA neurons [78]. Beyond reward signaling, stress-related neuroendocrine molecules—such as cortisol, corticotropin-releasing factor, and dynorphin—also exert significant effects on VTA neurodynamics, which can occur within several hours [22, 79]. Although an overactive VTA appears to be a promising candidate as a core pathological locus of BPD, its underlying molecular and physiological mechanisms remain unknown. It is noteworthy that manic or depressive episodes can occur spontaneously and are not necessarily preceded by stress. The “kindling” phenomenon of BPD—characterized by progressively shortened disease-free intervals—suggests that the underlying abnormalities accumulate with age or with the number of episodes. Therefore, the neural aberrations in the VTA of BPD follow a progressive or cumulative trajectory.

Dopaminergic neurons in the VTA fire spontaneously in a pacemaker-like manner, a process supported by several mechanisms, including the large h-current (I_h) mediated by hyperpolarization-activated cyclic nucleotide-gated channels [80]. The molecular basis of the sensitization or kindling-like phenomenon could be linked to glutamatergic mechanisms and the plasticity of N-methyl-D-aspartate (NMDA) receptors [81]. Similar to epilepsy, pathology may accumulate to a critical threshold, at which point large-scale network stability is disrupted, leading to the emergence of depression or mania. Below this threshold, VTA abnormalities do not cause overt impairment in BPD patients and can only be detected through neurophysiological or psychological assessments. From an evolutionary perspective, autofeedback mechanisms aiming for active working mode may align with circadian rhythms. It is thus also reasonable to assume that the proposed gradual increase in VTA oscillatory fluctuations could be linked to chronobiological dysregulation. Chronobiology encompasses a range of rhythms, including daily (diurnal), tidal, weekly, seasonal, and annual cycles. The physiology and behavior of an organism can undergo significant changes depending on the phase of its biological rhythm. Notably, a substantial proportion of BPD patients exhibit seasonal patterns [82, 83]. Recent research highlights that nearly all cells and tissues in the body function as biological clocks, expressing the Clock gene (circadian locomotor output cycles kaput), not just the suprachiasmatic nucleus [84]. The molecular foundation of circadian rhythms is built upon Clock proteins (both activators and repressors), as well as associated kinases and phosphorylases. Interestingly, human studies have suggested an association between Clock genes and BPD [85, 86]. Moreover, animal research demonstrates that the Clock Δ 19 mutant mouse model of mania exhibits increased activity in VTA dopaminergic neurons, further implicating circadian mechanisms in the pathophysiology of BPD [62, 87]. Additionally, the VTA is a heterogeneous structure, and its dopaminergic neurons can be organized into clusters based on differential projection profiles [88]. Given the existence of subcircuits originating from the VTA, a reasonable inference is that the disproportional enhancement of activity in the mPFC- and VS-projecting subgroups may respectively contribute to the occurrence of depression and mania. Whether abnormal interactions between these sub-groups of VTA neurons also play a role in the gradual enhancement in VTA warrants further animal and electrophysiological studies to elucidate. While the notion of an overactive VTA is well-supported, the precise mechanisms underlying this dysregulation remain uncertain.

In summary, similar to MDD, BPD also reflects a “bug” in brain organization: MDD is the price paid for

expanded and integrated mental capabilities that compete with each other (i.e., cortico-limbic interactions via the RSM) [8, 47], and BPD is the potential consequence of having a neuroanatomical design that aims to support sustained actions and explorations (for minutes or even hours). The neural pathways for the occurrence of depression and mania in BPD are tentatively summarized in Figure 4. Gradually enhanced neurotransmission or firing of the VTA is the very likely neural pathology of BPD. Future studies of BPD may place more emphasis on this midbrain structure that has long been ignored in its brain science research.

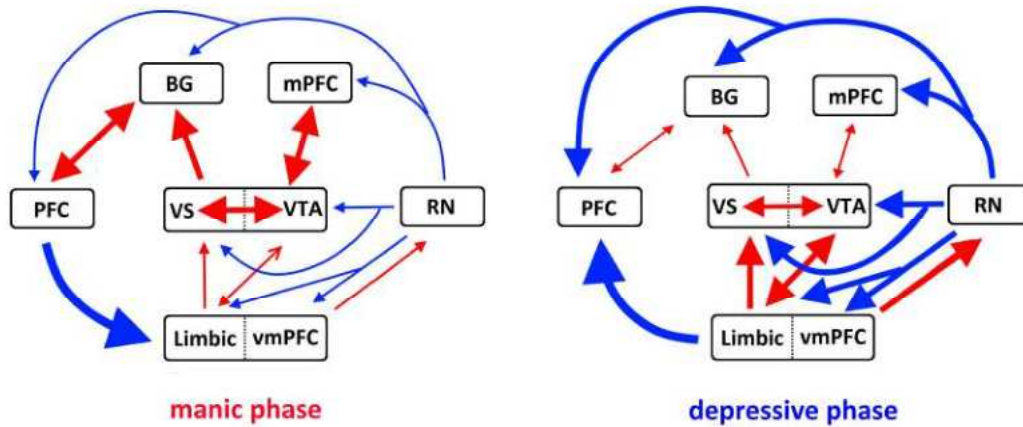


Figure 4. Tentative VTA-related pathways leading to mania and depression are summarized in the left and right subplots, respectively. Reproduced from Figure 3 in [11], with permission from Nova Science Publishers, Inc. Abbreviations: BG = basal ganglia, PFC = prefrontal cortex, mPFC = medial PFC, vmPFC = ventromedial PFC, VS = ventral striatum, VTA = ventral tegmental area, RN = raphe nucleus. Red arrows indicate activation, while blue arrows represent suppression. The thickness of the arrows conceptually reflects the strength of the interaction.

Conclusion

This study provides empirical evidence supporting the theory formulating VTA as a key hub in the pathogenesis of BPD. The superiority of the VTA model is supported by its unique neuroanatomical properties, namely its strong innervation of both the BG and the limbic system. Furthermore, the VTA plays a crucial role in both reward and aversive conditions. These make an "over-driving VTA" a compelling candidate for the psychopathological mechanism capable of accounting for both manic and depressive states. The identification of the VTA relied on the state-of-the-art D1 receptor template from JuSpace, along with functional connectivity analyses of rsfMRI. According to the VTA theory, the bipolar nature of BPD may originate from within the VTA itself and from its large-scale network interactions. Whether depression or mania is presented is contingent on the network dynamics, which may, in part, be pre-configured within the VTA—specifically, the overall electrophysiological activity of its distinct neuronal subpopulations. From theory formulation to empirical verification demonstrated in MDD and BPD, "dialectic neuroscience", in contrast to the dominant psychological or computational approach, could provide a valuable framework for developing guiding brain theories for psychiatric disorders.

Authors Contributions

This report is authored by a single individual.

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Compliance with ethical standards

This research analyzed the databank from a publicly released dataset. The author carried out no animal or human studies for this article.

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Figure Legends

Figure 1. (A) Segmented structural MRI image from a selected case for demonstration. The purple ROI indicates the brainstem, and the red line marks the Z coordinate at -30, with the midbrain structure located above the line. (B) Target VTA voxel positions represented as ellipsoids with dispersion of 1 SD along the three axes for the BPD and HC groups, superimposed on a standard Talairach template. Blue: BPD, Red: HC, Yellow: overlapped. Sagittal and axial views are centered at [0.2, 23.1, -15.1], the global mean coordinate of the target VTA voxels across all participants. This distribution aligns with the elongated structure of the VTA in the midbrain.

Figure 2. Mosaic axial views depicting the abnormal clusters of the VTA-seeded FC map. Blue indicates decreased functional connectivity in the BPD.

Figure 3. Sagittal and coronal views for better illustration of the abnormal clusters in the medial prefrontal cortex (subplot A) and nucleus accumbens (NAC; subplots A & B) in BPD. Please refer to Table 1 for the detailed information of the coordinates and statistics.

Figure 4. Tentative VTA-related pathways leading to mania and depression are summarized in the left and right subplots, respectively. Reproduced from Figure 3 in [11], with permission from Nova Science Publishers, Inc. Abbreviations: BG = basal ganglia, PFC = prefrontal cortex, mPFC = medial PFC, vmPFC = ventromedial PFC, VS = ventral striatum, VTA = ventral tegmental area, RN = raphe nucleus. Red arrows indicate activation, while blue arrows represent suppression. The thickness of the arrows conceptually reflects the strength of the interaction.

SHORT COMMUNICATION

RS-fMRI Evidence of Left Frontal Lobe Developmental Deviation as a Candidate Core Pathology of Autism Spectrum Disorder

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Correspondence: Tien-Wen Lee (dwleeibru@gmail.com)**Received:** 12 May 2025 | **Revised:** 19 February 2026 | **Accepted:** 23 February 2026**Keywords:** autism spectrum disorder (ASD) | frontal lobe | functional connectivity | limbic system | resting-state functional magnetic resonance imaging (rsfMRI)

ABSTRACT

Autism spectrum disorder (ASD) is one of the most prevalent developmental disorders. This study utilized 3-Tesla resting-state fMRI data analysed with the functional parcellation algorithm MOSI (modular analysis and similarity measurement) to investigate cortical functional organization in ASD. Sixty individuals with ASD and sixty healthy controls were selected from the Autism Brain Imaging Data Exchange (ABIDE), with no significant differences in age and gender distribution. The MOSI-derived metrics were compared using independent two-sample t-tests. The findings revealed a significant reduction in the functional volume of the left frontal lobe, a region critical for language, cognitive, and social processing. This reduction appears to be accompanied by compensatory expansion in other brain regions, suggesting a reallocation of neural resources that may contribute to ASD heterogeneity. These results support the notion of left frontal lobe developmental deviation (LFDD) as a parsimonious neural mechanism underlying key ASD features. The accountability of LFDD in various cognitive, symptomatic and behavioural characteristics of ASD is briefly discussed, along with its implications for male predominance and evolutionary relevance. Overall, the study provides a novel brain-based perspective on ASD, moving beyond traditional psychological models to offer a neurobiological explanation for its defining characteristics and possible underlying developmental origins.

1 | Introduction

Autism spectrum disorder (ASD) is a developmental disorder that is characterized by difficulties in social interaction and social communication, as well as repetitive, restricted and inflexible patterns of behaviour, interests and activities, along with cognitive deficits and atypical sensory processing (American Psychiatric Association 2013). Several psychology-oriented brain theories of ASD have been proposed, each addressing a particular cognitive domain or characteristic manifestation, such as theory of mind (ToM, in part linked to potential mirror neuron dysfunction), executive function, central coherence, social motivation and “extreme male brain” (Baron-Cohen 2002; Baron-Cohen 1991; Chevallier et al. 2012; Silva et al. 2013).

Recent research has emphasized neural connectivity abnormalities and hyper-functioning of local neurocircuits in ASD (Goodwill et al. 2023; Markram and Markram 2010). The complexity inherent in ASD (and other major psychiatric conditions) has been a significant challenge in constructing comprehensive mechanistic models.

In contrast to the neural node- or circuitry-based approach, which largely draws from psychological (and with the help from computational) perspectives, the author proposed major depressive disorder (MDD) as a compartment-level disorder (Lee and Xue 2018), which not only possessed higher accountability and was recently empirically verified (Lee 2025a). ‘Compartment’ here refers to the frontoparietal mantle or limbic system as a

neural entity (Lee et al. 2014), not confined to a specific region, network, or psychological construct. The theory formulation of MDD exemplifies the process of ‘dialectic neuroscience’, which seeks to integrate diverse evidence into a parsimonious disease mechanism (Lee 2025b). The treatment of neural compartments requires functional parcellation of the cortex as a pre-processing step, achieved through a relatively novel algorithm—modular analysis and similarity measurement (MOSI) (Lee and Tramontano 2021). Then, akin to the case of MDD illustrated above, is it possible to move beyond psychological approaches and employ a similar framework to decipher ASD?

Previous psychological theories of ASD, although each supported by empirical evidence, have limited explanatory power. Take ToM as an example: While it provides an appealing construct for examining social dysfunction in ASD, it fails to account for abnormalities in executive control, restricted interests and central coherence. Furthermore, ToM deficits are not unique to ASD but are also observed in other psychiatric conditions, such as schizophrenia (Bora et al. 2009). Taking a more holistic view, language deficits, communication difficulties, executive dysfunction, intellectual disability, repetitive behaviours, restricted interests and features associated with the extreme male brain hypothesis may be more cohesively understood through the concept of left frontal lobe (LFL) dysfunction as a unifying factor—or more precisely, developmental abnormalities of the LFL (elaborated in the Section 4).

This study applied MOSI to resting-state functional magnetic resonance imaging (rsfMRI) data to investigate the brain lobes (frontal, temporal, limbic and parietal) as the subjects of analysis, with LFL as the main research target. The resulting lobar metrics of ASD patients will be statistically compared with those of age- and gender-matched neurotypical controls.

2 | Methods

2.1 | Subjects, MRI Data and Preprocessing

MRI data from 120 participants, all over 18 years old, were obtained from the Autism Brain Imaging Data Exchange I (ABIDE I) to minimize variance associated with the maturation process that occurs before adulthood (Di Martino et al. 2014). The cohort included 60 individuals diagnosed with ASD and 60 healthy controls (HC), with written consent collected from all participants. Sample size selection was informed by prior resting-state fMRI studies using similar analytic frameworks and by field-level evidence regarding typical sample sizes (Lee 2025a). Szucs and Ioannidis showed that the majority of highly cited fMRI studies employed considerably smaller samples. The present sample size therefore represents a relatively well-powered dataset for hypothesis-driven analyses (Szucs and Ioannidis 2020). Functional and structural MRI (sMRI) images of the entire brain were acquired using 3.0 Tesla MRI scanners, with rsfMRI parameters set to TR = 1.5 s, voxel size = $3 \times 3 \times 4$ mm³ and a total of 200 volumes.

The echo planar imaging (EPI) data were processed using the Analysis of Functional NeuroImages (AFNI) software package (Cox 1996). The preprocessing pipeline for rsfMRI included

steps such as despiking, slice-time correction, motion re-alignment, T1 anatomical registration, spatial smoothing and bandpass filtering in the range of 0.01–0.10 Hz. To ensure magnetization equilibrium, the first six scans (9 s) were discarded. A spatial smoothing kernel of 6 mm was applied to the EPI data. The FreeSurfer software was used for segmenting grey and white matter from T1-weighted sMRI data, as well as for parcellating the cortical mantle into 68 regions based on the Desikan-Killiany Atlas (Dale et al. 1999; Desikan et al. 2006; Fischl et al. 1999), which served as the initial partition for the subsequent MOSI analysis. Following the recommended analytic pipeline (Jo et al. 2010; Lee et al. 2014), 12 movement parameters were included in the regression model, whereas global signal regression was not performed. Additionally, second-order polynomials were applied to account for baseline drift. Functional connectivity was calculated by computing the Pearson correlation coefficient (CC) between the temporal traces of voxel pairs or the mean temporal traces of partitioned clusters by MOSI.

2.2 | MOSI Analysis

The connectivity map constructed from CCs serves as the basis for modular analysis. In this platform, modules—also referred to as communities—are sets of nodes within a network that exhibit higher intra-group connectivity compared to intergroup connectivity, as determined by CCs in this study. MOSI integrates both modular analysis and similarity measurements, iteratively dividing modules into smaller submodules and merging similar submodules into larger ones. The parcellation process in MOSI adheres strictly to two principles: spatial proximity and functional similarity. Adjacent voxels with comparable neural activity are grouped together, aligning with the fundamental logic of functional parcellation in cortical signal processing. This iterative split-merge process continues until the computation reaches convergence. The current implementation of MOSI employs the Louvain community detection algorithm, where the granularity of modular partitioning is adjustable via the Gamma parameter. Higher Gamma values yield a greater number of modules, refining the resolution of the analysis (Lee and Tramontano 2021). The author examined 12 different resolutions, with Gamma values ranging from 0.30 to 0.85. Each segmented module was assigned to a specific brain lobe based on majority voting when it spanned two or more lobes. The MOSI-derived metrics, including module count and size, were compared between the ASD and HC groups using independent two-sample *t*-tests. Since the outputs from different Gamma values exhibit some dependency, applying a Bonferroni correction would be overly stringent, potentially inflating the risk of false negatives. Therefore, statistical thresholds were set at *p*-values < 0.01 and < 0.005 to reflect varying degrees of stringency.

3 | Results

The mean age of the HC and ASD groups was 21.0 years (SD = 4.2) and 20.9 years (SD = 4.0), respectively, with no significant difference between the groups ($t(118) = -0.1323$, $p = 0.895$). Both groups had identical gender distributions, each comprising 57 male participants.

In alignment with the multiresolution feature of MOSI, higher Gamma values led to an increase in the number of clusters while reducing the voxel count per cluster; see Figure 1. In the HC group, the cortical module count reached 132.3 at Gamma 0.30 and 319.9 at Gamma 0.85. Similarly, in the ASD group, the module count was 137.4 at Gamma 0.30 and 331.4 at Gamma 0.85. The initial partition, based on the Desikan-Killiany Atlas, comprised 68 modules.

For the between-group comparisons, *t*-tests indicated no significant between-group differences in the partition numbers derived from MOSI across the 12 resolutions (Gamma values). Likewise, the voxel counts of the four cortical lobes did not show any group differences in the atlas-informed anatomical volumes. Notably, however, ASD participants exhibited a statistically significant reduction in the 'functional volume' of the LFL, particularly at lower Gamma values (0.30–0.65). Given that MOSI-derived

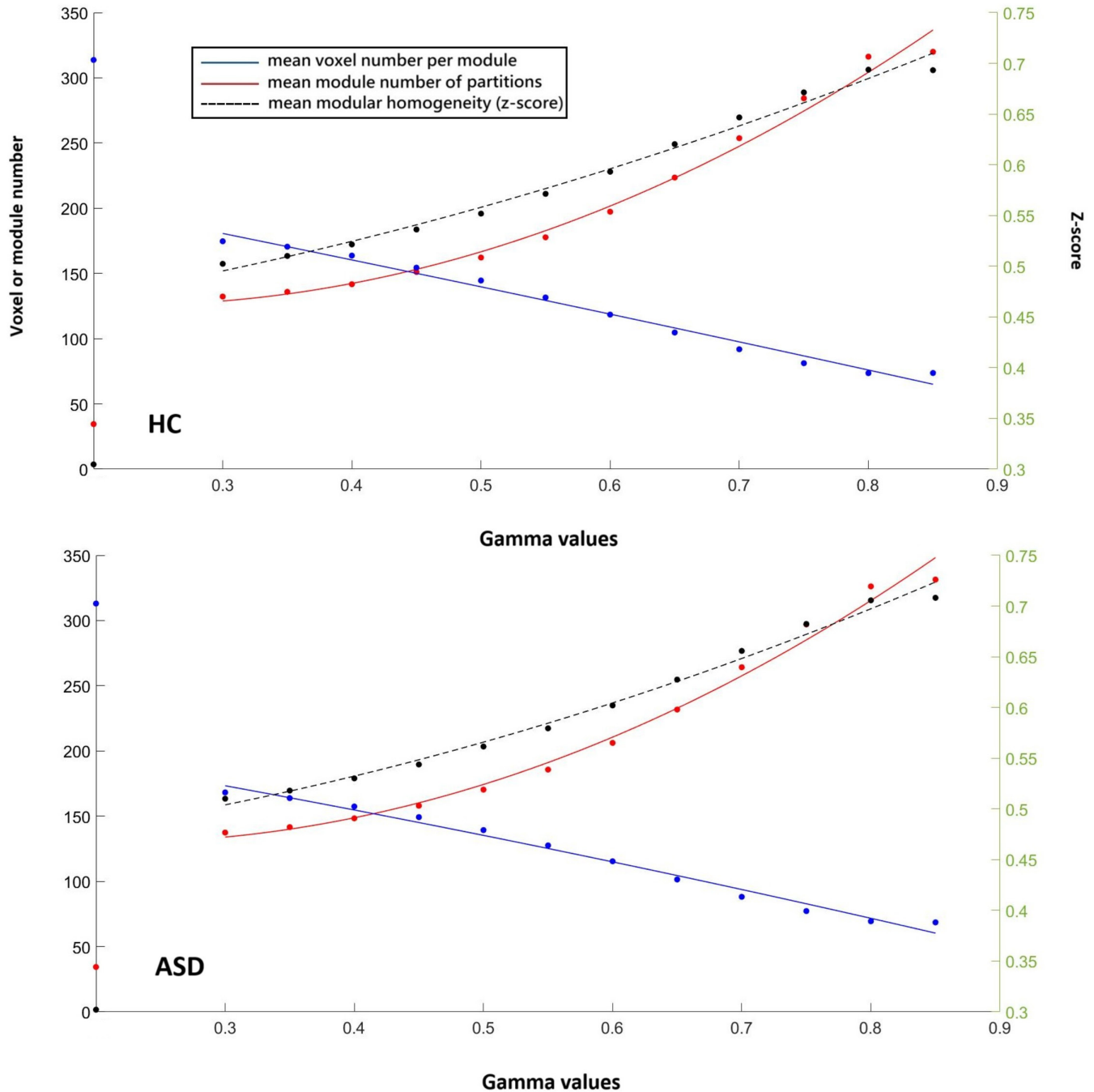


FIGURE 1 | Scatter plots of three indices derived from MOSI, with the X-axis representing 12 Gamma values (resulting in 12 data points per index) and second-order polynomial regression fits. The top panel corresponds to the HC group, while the bottom panel corresponds to the ASD group. The origin ($x=0$) denotes the initial partition based on the Desikan–Killiany atlas. Red dots and the red regression line represent the mean number of modules derived from varying Gamma values, corresponding to the left Y-axis. Blue dots and the blue regression line indicate the mean voxel count per module, also corresponding to the left Y-axis. Black dots and the black regression line illustrate the mean module z-score (reflecting within-module homogeneity), which corresponds to the right Y-axis.

modules may span across two anatomical lobes, majority voting was employed to assign each module to a specific brain lobe. Accordingly, functional volumes are not equal to anatomical volumes that are predetermined by landmarks but were calculated based on the total voxel count of modules classified within each brain lobe. A summary of the functional volume findings is presented in Table 1.

Further investigation revealed that the significance cannot be solely attributed to single factor, such as the parietal lobe enlargement at the expense of the functional volume reduction in the LFL (statistics not significant). Rather, the reduction appears to be a synergistic outcome resulting from the expansion of brain regions adjacent to LFL (in terms of functional volume). For completeness, exploratory analyses, such as regional power, integrative graph index and power-connectivity relationships were conducted, but all showed negative results. Detailed information is provided in Tables S1–S3.

4 | Discussion

Elucidating the neural mechanisms underlying ASD remains a persistent challenge in brain science. Through the novel functional parcellation scheme MOSI, LFL abnormality emerged as the sole definitive finding. A key advantage of MOSI lies in its individualized and multiresolution approach—the former addressing ASD heterogeneity, while the latter enables examining ASD pathology at optimal scales (resolutions) (Lee and Tramontano 2021). Building on MOSI, the concept of functional volume is introduced to distinguish it from anatomical volume. The reduction in functional volume of the LFL indicates that other adjacent brain regions may expand, highlighting the underdevelopment of the LFL. This suggests a potential shift in neural resource allocation, where compensatory mechanisms in other areas could occur as a result of the developmental

deviation in the LFL, which might be further relevant to some ASD individuals exhibiting exceptional abilities in specialized areas. Notably, at higher resolutions, the partitioned modules become smaller, reducing the likelihood and impact of modules spanning multiple brain lobes—underscoring the value of multi-resolution exploration in psychopathology. Dialectic neuroscience has pursued an integrative approach—synthesizing analyses—to address complex issues via creative thinking (Lee 2016, 2025b), with accountability serving as one of its foundational principles. Conceptually aligning more closely with the Bayesian framework (Lee 2025b), this process of formulating guiding hypotheses stands in stark contrast to simplistic reverse inference, which relies on limited evidence and suffers from restricted explanatory power. In the following sections, an attempt is made to propose LFL developmental deviation (LFDD) as a parsimonious neural mechanism to explain the core features of ASD.

First of all, LFDD theory implies that the developmental abnormalities may spare the posterior cortical regions. This argument generally holds from two aspects. Firstly, perceptual issues in ASD primarily involve abnormal sensitivities, rather than a deficiency in the ability to discriminate sensory stimuli, which may be influenced by top-down control mechanisms. Some ASD cases may exhibit high-functioning skills in areas such as mathematics (arguably related to the parietal region), memory (temporal region) or pattern recognition (perception). Secondly, the cortical development follows a posterior-to-anterior progression, with the perceptual and motor functions maturing first, followed by the frontal lobe, where the left side matures later than the right (Gerván et al. 2017). This developmental sequence aligns with evolutionary patterns, where the expansion of the frontal lobe is considered a later evolutionary event undergoing fewer selection processes, making it, especially the left side, more prone to disruptions (Hoffmann 2013; Pletikos et al. 2014). Interestingly, the LFDD account is concordant with large-scale

TABLE 1 | Statistical comparisons of functional volumes in the left frontal lobe.

Gamma	ASD		HC		<i>t</i> -scores	<i>p</i>
	Mean	Std	Mean	Std		
0.30	2923.3	655.4	3291.1	627.2	−3.14	0.002**
0.35	2903.2	664.4	3298.8	647.9	−3.30	0.001**
0.40	2910.8	712.4	3249.7	626.9	−2.77	0.007*
0.45	2878.8	694.1	3284.1	642.3	−3.32	0.001**
0.50	2807.7	735.6	3283.1	662.2	−3.72	0.0003**
0.55	2809.7	768.6	3210.3	681.5	−3.02	0.003**
0.60	2675.5	773.0	3146.9	666.0	−3.58	0.001**
0.65	2628.4	736.1	2995.0	686.8	−2.82	0.006*
0.70	2597.5	762.2	2897.2	789.5	−2.11	0.037
0.75	2477.6	664.4	2782.4	767.1	−2.33	0.022
0.80	2415.8	682.7	2635.0	728.1	−1.70	0.092
0.85	2438.6	617.8	2530.4	677.4	−0.78	0.439

Note: The contents are voxel number. * and ** indicate *p*-values less than 0.01 and 0.005, respectively.

meta-analytic research identifying risk factors of ASD during the second and third trimesters (Gardener et al. 2009).

Cortical development follows a hierarchical progression in which higher order association regions integrate and regulate lower level sensory and behavioural systems, with the LFL occupying an apex position within this architecture. This hierarchical placement positions the LFL to exert broad top-down influence, providing a parsimonious mechanism to account for the diverse cognitive, social and behavioural manifestations of ASD (Lee 2025b). Consistently, LFDD may underlie a wide range of characteristic impairments in ASD, including social dysfunction, pragmatic and expressive language deficits, executive control abnormalities, atypical sensory perception and motor planning difficulties (American Psychiatric Association 2013). The LFL is essential for executing higher order cognitive functions such as language, abstract reasoning and executive control. Developmental deviation at this level is therefore expected to produce a constellation of downstream alterations across multiple domains rather than a circumscribed deficit. For example, the involvement of LFDD in response inhibition, attention regulation, restricted interests, central coherence and broader behavioural symptoms is well-supported by brain science literature, though a full review lies beyond the scope of this short report (Dichter 2012; Silva et al. 2013). Robust evidence suggests that interhemispheric rivalry and competition play a crucial role in brain development and neurophysiological processes (Carson 2020; Cynader et al. 1981), indicating that LFDD may also modulate right frontal functioning, potentially affecting emotional and social domains. Given the frontal lobe's widespread modulatory role, connectivity abnormalities beyond the left frontal cortex are reasonably expected (Goodwill et al. 2023).

A major limitation of the ABIDE sample is that severely impaired individuals with ASD are underrepresented. In such low-functioning cases, deficits may extend beyond the LFL to posterior brain regions. In contrast, among high-functioning ASD or those with relatively intact structural language skills, expressive language deficits—particularly in pragmatic, organized and socially appropriate verbal output—often exceed receptive deficits (Grossman and Tager-Flusberg 2012; Yang et al. 2022). Although large meta-analytic evidence does not reveal a consistent pattern of expressive relative to receptive language ability across the heterogeneous ASD population, this likely reflects the inclusion of individuals with a wide range of functional levels and cognitive abilities (Kwok et al. 2015). Such subgroup-specific language impairments are consistent with the LFDD framework and underscore its relevance to the ASD phenotype.

There is emerging speculation that autism reflects an exaggeration of male-typical cognitive patterns (a perspective that the increasingly prevalent connectivity doctrine is difficult to reconcile with). While existing literature, such as that by Baron-Cohen, largely attributes the male predominance in ASD to androgen effects (Baron-Cohen 2002), this research suggests that deficits in LFL development may also play a critical role, particularly when considering the gender differences in the lateralization of frontal functions. This insight becomes particularly compelling when considering that sex hormones may exert

a substantial influence on immature neural tissues during development. As a result, delayed or reduced development in the LFL—critical for language and social processing—could result in prolonged and excessive influence from sex hormones, leading to a pronounced gender bias (Van de Cruys et al. 2014). In addition, the LFDD framework, grounded in frontal lobe dysfunction, also integrates alternative explanatory models of ASD, including predictive coding abnormalities suggested by the Bayesian brain theory (Van de Cruys et al. 2014).

The lobe-level abnormalities in ASD align with the compartment-level analogs unveiled in MDD, moving beyond psychological frameworks and interpretations to seek an alternative brain science perspective as the core explanation for major psychiatric disorders. Lobar abnormalities occur at a broader scale, inevitably triggering compensatory plastic changes at finer scales to mitigate dysfunction, processes that are highly individualized (Kanai and Rees 2011; Kolb and Gibb 2014; Poldrack 2000). Varying degrees of LFDD and of compensatory changes may account for the heterogeneity in ASD, and in some cases, exceptional skills may result from compensatory expansion of non-frontal brain tissues, as implied by the analytic results. As this study focuses solely on the cortex, parallel developmental deviations in subcortical structures cannot be excluded (Persichetti et al. 2025). In summary, this research links ASD to LFDD, emphasizing the late evolutionary and ontogenetic development of the LFL and its vulnerability to developmental perturbations. ASD manifestations may thus be viewed as arising from insufficient frontal lobe engagement during development.

Author Contributions

This report is authored by a single individual.

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Ethics Statement

This research analysed the databank from a publicly released dataset. The author carried out no animal or human studies for this article.

Conflicts of Interest

The author declares no conflicts of interest.

Data Availability Statement

The datasets analysed in the current study are openly available and were obtained from the Autism Brain Imaging Data Exchange (ABIDE) repository. These data can be accessed by qualified researchers via the ABIDE collection at the International Data Archive (IDA) hosted by USC: <https://ida.loni.usc.edu/>. No new primary data were generated in this study. Access to these data is subject to the terms and conditions of the ABIDE data use agreement.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** Statistical comparisons of mean regional power (ALFF) in the left frontal lobe. **Table S2:** Statistical comparisons of global efficiency in the left frontal lobe. **Table S3:** Statistical comparisons of power-connectivity relationship in the left frontal lobe.

Application of an analysis-synthesis framework to decipher the core neuropathology underlying attention-deficit/hyperactivity disorder

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Running Title: Delayed frontal-to-VTA maturation in attention-deficit/hyperactivity disorder

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Abstract

Attention-deficit/hyperactivity disorder (ADHD) is a prevalent and complex developmental condition. Beyond the core symptoms, hypoarousal, executive dysfunction, emotion dysregulation, and abnormal reward processing have been consistently observed. Given the broad spectrum of associated psychological and physiological dysfunctions, research findings have been remarkably diverse. Despite the heterogeneous and prominent manifestations of ADHD, therapeutic responses to psychostimulants are often rapid and highly effective, suggesting that gross structural defects are unlikely to underlie its core neuropathology. Following the recommended format of dialectical neuroscience, a hybrid analysis–synthesis approach was adopted to formulate a candidate brain theory of ADHD. A viable theory is expected to satisfy three key criteria: biological plausibility, comprehensiveness, and parsimony. Existing empirical findings (analysis) are integrated into a model positing an innate vulnerability in neural organization during development—namely, aberrant prefrontal–subcortical projections centering on the ventral tegmental area—as the initial core neuropathology of ADHD. By incorporating subsequent network-level adaptations and empirically grounded neurophysiological mechanisms, the proposed model enhances explanatory power across a broad array of seemingly unrelated or even contradictory observations. Multiple aspects of ADHD are reinterpreted in light of this underlying network dysfunction. In sum, the analysis–synthesis framework may provide a simple yet powerful approach for investigating the neural mechanisms of psychiatric disorders.

Key Points

- This study introduces a novel brain-based theory of ADHD, proposing that aberrant descending projections from the prefrontal cortex (PFC) to subcortical structures—especially the ventral tegmental area and subsequently, nucleus accumbens (NAc)—constitute a core developmental vulnerability.
- By adopting a dialectical analysis–synthesis approach, the model integrates diverse and seemingly contradictory empirical findings into a parsimonious and biologically plausible framework, providing coherent explanations for both clinical symptoms and neuroimaging abnormalities in ADHD.
- The theory emphasizes network-level dysregulation, whereby initial PFC–subcortical disconnection triggers downstream alterations in arousal regulation, reward sensitivity, emotion control, and executive functioning.
- The proposed model aligns with Bayesian principles of model selection, highlighting cross-domain explanatory power as a key criterion for theoretical validity in psychiatric neuroscience.
- The next step involves empirical validation focusing on directional network properties and interaction effects at the NAc—a critical gap in current ADHD research.

Introduction

This study introduces a novel variant of the review article—one in which a guiding hypothesis or theoretical framework is generated through the review process itself. Unlike conventional formats such as selective, comprehensive, or critical reviews, this approach enables theory generation to emerge dialectically from the synthesis of existing literature, consistent with the methodology of “dialectic neuroscience” (Lee, 2025b). Importantly, the theory developed through this process is not constrained by existing viewpoints or interpretations; instead, it encourages nonlinear and creative reasoning to address complex questions and generate novel insights. It also contrasts with traditional hypothesis papers, which are often not grounded in systematic literature appraisal and are therefore less favored in rigorous scientific discourse. This relatively new approach has previously been applied to theoretical model development in major depressive disorder and bipolar disorder (Lee and Xue, 2018a, Lee and Xue, 2017), both of which have since gained empirical support (Lee, 2025a, Lee, 2025d). The present article extends this dialectical process to the domain of attention-deficit/hyperactivity disorder (ADHD) (Lee, 2025b).

Following the recommended format of presentation (Lee, 2025b), as exemplified in prior publications (Lee and Xue, 2018a, Lee and Xue, 2017), this process begins with a targeted review, placing particular emphasis on brain science literature (**Introduction**), and proceeds through two distinct phases. The first is the **analysis phase**, which summarizes neuroscientific evidence and outlines the cardinal features of ADHD across multiple disciplines and perspectives (**Materials and Methods**). The second is the **synthesis phase**, in which these heterogeneous findings are evaluated for their potential integration into a coherent and mechanistic framework (see **Results**). The resulting model—rooted in empirically supported network-level operations (biological plausibility)—is anticipated to be structurally simple (parsimony), yet capable of explaining a wide spectrum of ADHD-related phenomena (accountability). These three criteria, as indicated in parentheses, correspond to components of the Bayesian framework, thereby ensuring that the scientific rigor of the proposed model is statistically grounded and scientifically robust (Lee, 2025b). Although being a review, the manuscript adheres to the organization of a conventional research article, comprising sections for **Introduction**, **Methods**, **Results**, and **Discussion**. Through the analysis–synthesis approach, the author proposes that developmental abnormalities in descending projections from the prefrontal cortex (PFC) to subcortical structures, especially ventral tegmental area (VTA), may represent a core neuropathology underlying the emergence of ADHD.

Clinical manifestation of ADHD

ADHD is among the most prevalent neurodevelopmental disorders, characterized by persistent patterns of inattention, hyperactivity, and impulsivity (American Psychiatric Association, 2013). Beyond these core diagnostic features, individuals with ADHD commonly exhibit a broader constellation of cognitive and affective difficulties, including deficits in executive functioning, emotional dysregulation, and atypical reward processing. These impairments often manifest as poor impulse control, difficulties with planning and organizing tasks, problems with time management, and a marked preference for immediate rather than delayed rewards. Emotional instability—such as rapid mood fluctuations and low frustration tolerance—is also prevalent, often contributing to comorbid anxiety or mood symptoms. These cognitive and emotional deficits can lead to significant difficulties in interpreting social cues and in forming or maintaining relationships, which in turn contribute to long-term academic and occupational impairments.

ADHD is estimated to affect approximately 6–7% of children and adolescents, and around 2.5% of adults (Willcutt, 2012, American Psychiatric Association, 2013). Although the onset of symptoms is typically recognized before the age of 12, early signs may be detectable as early as ages 2 to 5. Nonetheless, symptom expression tends to emerge gradually across development rather than being evident at birth or during early infancy (Egger and Angold, 2006). Clinically, ADHD is categorized into three presentations: predominantly hyperactive/impulsive, predominantly inattentive, and combined. Despite this heterogeneity, recent advances in neuroscience have begun to elucidate the neurobiological underpinnings of the disorder, as detailed in the following sections.

Re-evaluation of hypodopaminergic hypothesis

Reduced dopaminergic neurotransmission within the mesocorticolimbic system remains one of the most widely cited neuropathological hypotheses of ADHD. This view is primarily supported by two key lines of evidence: the robust therapeutic efficacy of dopaminergic agents and findings from positron emission tomography (PET) studies. The human brain contains four major dopaminergic pathways, each with distinct anatomical projections and functional domains (Hou et al., 2024). The mesolimbic pathway, originating in the VTA and projecting to the nucleus accumbens (NAc) and associated limbic structures, plays a central role in reward processing and motivation (Alexander et al., 1986, Groenewegen and Trimble, 2007). The mesocortical pathway, also arising from the VTA, projects to the PFC and is essential for executive functions, attention regulation, and working memory (Ikemoto, 2010, Polter and Kauer, 2014). These two pathways—the mesocortical and mesolimbic—together form the mesocorticolimbic system, which constitutes the major focus of the present synthesis. By contrast, the nigrostriatal pathway, extending from the substantia nigra to the dorsal striatum, is primarily involved in motor control and is critically implicated in Parkinson's disease (Alexander et al., 1986). However, this pathway—particularly its projections to the caudate nucleus—also plays an important role in cognitive processes, including action selection, working memory, and goal-directed behavior (Grahn et al., 2008). The dopamine (DA) neurons in VTA and substantia nigra occupy more than 75% of DA neurons in the human brain (Basso et al., 2024). Lastly, the tuberoinfundibular pathway, projecting from the hypothalamus to the median eminence, regulates prolactin secretion via dopaminergic inhibition of the anterior pituitary. Together, these dopaminergic systems underscore the extensive neuromodulatory roles of DA, spanning motor, cognitive, physiological, and affective domains.

A number of PET studies have demonstrated dopaminergic abnormalities in the mesocorticolimbic system in ADHD, including alterations in DA transporter (DAT) binding, DA receptor availability, and DA metabolism (Díaz-Heijtz et al., 2006, Weyandt et al., 2013). Earlier PET research indicated reduced D2/D3 receptor availability and lower DAT levels in the NAc and midbrain (Jucaite et al., 2005, Volkow et al., 2009, Volkow et al., 2011). Blunted DA release was also inferred from attenuated displacement of the radioligand [¹¹C]raclopride following methylphenidate (MPH) administration, suggesting impaired presynaptic dopaminergic function (Volkow et al., 2007). Further, ¹⁸F-DOPA PET, which reflects presynaptic DA synthesis and storage capacity, revealed regional disparities in DA levels: children with ADHD showed decreased accumulation in the PFC, but increased uptake in the midbrain (Ernst et al., 1998, Ernst et al., 1999). However, subsequent studies in adolescents and adults with ADHD reported lower ¹⁸F-DOPA influx rate constants in the midbrain (Forssberg et al., 2006, Ludolph et al., 2008).

Despite its broad impact on cognitive and social functioning, ADHD differs markedly from many other psychiatric disorders in that a substantial portion of its symptoms and cognitive deficits can be rapidly ameliorated by pharmacological intervention—most notably with the DA reuptake inhibitor MPH, which rapidly increases extracellular DA by blocking DAT (and also inhibits the norepinephrine [NE] transporter, thereby increasing synaptic NE), thereby offering both clinical and pharmacodynamic support for the hypodopaminergic hypothesis of ADHD. Neuroimaging studies have demonstrated that MPH normalizes hypoactivation in fronto-striatal and fronto-cingulate circuits during tasks involving response inhibition, interference control, and target detection (Rubia et al., 2011a, Rubia et al., 2011b). Improvements have also been reported in working memory, reaction time variability, delay discounting, and broader executive functions, though these enhancements often fall short of restoring performance to the level of healthy controls (Fuermaier et al., 2017, Kofler et al., 2013, Schweitzer and Sulzer-Azaroff, 1995, Taş Torun et al., 2022). The rapid onset of MPH's effects suggests that ADHD symptoms are unlikely to be driven by major structural abnormalities, which typically do not respond to pharmacological agents on such short timescales. Nevertheless, when considering the broader and sometimes contradictory body of evidence, it appears that ADHD may not be fully accounted for by a uniform hypodopaminergic framework (Nikolaus et al., 2022).

For example, the co-occurrence of reduced DA neurotransmission and decreased DAT expression—without compensatory upregulation—is counterintuitive from a homeostatic perspective. Similarly, the

combination of increased ^{18}F -DOPA uptake signal with a decreased influx rate constant presents a paradox that is difficult to reconcile (Ernst et al., 1998, Ernst et al., 1999, Forssberg et al., 2006, Ludolph et al., 2008). Moreover, heightened reward sensitivity is a well-recognized feature of ADHD (see next section), yet it has traditionally been linked to increased dopaminergic activity in both healthy individuals and clinical conditions such as bipolar mania (Lee and Xue, 2017, Schultz, 1998). A recent review systematically addressed the inconsistencies in PET findings, attributing them largely to methodological and design-related limitations (Yamamoto and Inada, 2023). However, a rarely considered possibility—one that this article seeks to advance—is that dopaminergic abnormalities in ADHD may be secondary rather than primary in nature.

Reward sensitivity and ventral striatum

While a general preference for immediate rewards is common across species, individuals with ADHD exhibit a markedly reduced tolerance for delay, leading to steeper discounting of postponed rewards and heightened impulsivity in decision-making (Barkley et al., 2001). Neuroimaging studies have consistently reported hypoactivation in the ventral striatum and PFC during both immediate and delayed reward processing in ADHD, particularly in the context of delay discounting tasks (Plichta et al., 2009, Norman et al., 2017). In youth with ADHD, lower temporal discounting rates (i.e., a greater willingness to wait for delayed rewards) have been linked to increased activation in the right inferior frontal and premotor cortices. In contrast, healthy controls exhibit broader engagement of the reward and cognitive control networks, including the vmPFC, anterior cingulate cortex (ACC), ventral striatum, superior frontal cortex, supplementary motor area (SMA), caudate, and midbrain (Chantiluke et al., 2014). Furthermore, enhanced functional connectivity between the NAc and PFC has been associated with greater impulsivity, reflected in steeper discounting of delayed rewards (Costa Dias et al., 2013).

By contrast, in adolescents and young adults with ADHD, enhanced frontostriatal activity has been observed during both the anticipation and receipt of rewards, while symptom severity negatively correlates with PFC activation during anticipation (von Rhein et al., 2015, van Dongen et al., 2015, Strohle et al., 2008). Although findings in children are more variable, parent-rated reward sensitivity has been associated with greater anticipatory activity in the ventral striatum (van Hulst et al., 2017). Overall, these findings suggest that altered reward processing and response in ADHD reflects a context-specific dissociation in neural activity: hypoactivation during evaluative judgment phases, and hyperactivation during reward anticipation and receipt. The co-occurrence of diminished evaluative control and exaggerated reward reactivity may together underlie the clinical manifestation of reward-driven impulsivity in ADHD. These context-dependent dynamics observed in reward tasks indicate that ADHD cannot be sufficiently explained by a simplistic hypo- or hyper-dopaminergic model. Moreover, the former and latter patterns may correspond to reduced tonic level and elevated phasic DA responsivity, respectively, as demonstrated by dynamic molecular imaging techniques (Badgaiyan et al., 2015), and further elaborated in the **Discussion**.

Cortical dysfunction with emphasis on the prefrontal cortex

Numerous volumetry studies using magnetic resonance imaging (MRI) have revealed reduced volumes in the PFC and corpus callosum in individuals with ADHD compared to neurotypical controls (Ohno, 2003). Within the PFC, the regions most frequently reported to be affected include the orbitofrontal cortex (OFC), medial PFC (mPFC), inferior, middle, and superior frontal gyri, as well as the frontal pole (Depue et al., 2010a, Norman et al., 2016, Bralten et al., 2016). Meta-analytic findings identified the most consistently reduced regions as those with prominent projections with the NAc–VTA (Groenewegen and Trimble, 2007), notably the OFC, ventromedial, and rostral PFC (Lukito et al., 2020). These volumetric decreases are clinically relevant, showing associations with behavioral outcomes and symptom severity. For instance, reduced inferior frontal gyrus volume has been linked to deficits in processing speed, response inhibition, and variability (Depue et al., 2010a), while lower frontal gray matter volume correlates with greater clinical severity (Castellanos et al., 2002). Findings regarding volume changes in motor-related cortices, such as the precentral gyrus and supplementary motor area, have been inconsistent (Carmona et al., 2005, van Wingen et al., 2013). Overall

brain volume reductions in children with ADHD have been further noticed—including total cerebral, cerebellar, and white matter volume—though these findings have not always been replicated (Castellanos et al., 2002, Depue et al., 2010a). Despite widespread abnormalities, longitudinal volumetric studies confirm that ADHD does not follow a neurodegenerative course (Castellanos et al., 2002).

Functional neuroimaging studies demonstrate attenuated neural responses in the PFC of individuals with ADHD across diverse cognitive tasks, including interference inhibition, attention allocation, task switching, working memory, memory retrieval, and temporal discrimination (Cubillo et al., 2011, Depue et al., 2010b, Burgess et al., 2010, Smith et al., 2008, Smith et al., 2006). These reductions are not limited to a single region but span ventral, dorsolateral, medial, and orbitofrontal areas of the PFC (Weyandt et al., 2013). While some studies report focal hyperactivations in ADHD during task execution, these are often interpreted as compensatory. Supporting this view, a meta-analysis across various inhibition and interference tasks identified the frontal poles—associated with high-level integrative functions—as regions of consistently increased activation in ADHD compared to controls (Dickstein et al., 2006, Koechlin et al., 2003, Eickhoff et al., 2014, Burgess et al., 2007). This pattern suggests that individuals with ADHD may recruit additional executive resources for routine tasks. Overall, the evidence reinforces the hypofrontality hypothesis in ADHD. Meta-analytic results indicate that dorsomedial PFC, inferior frontal gyrus, and dorsolateral PFC are the most recurrently implicated regions (Lukito et al., 2020).

Limbic system dysregulation

The limbic system includes structures such as the amygdala, hippocampus, parahippocampal gyrus, ventral striatum (see subsection *Reward sensitivity and ventral striatum*), hypothalamus, cingulate cortex, and OFC. Although the OFC and vmPFC are anatomically parts of the frontal lobe, their strong functional interactions with limbic regions are acknowledged (Mega et al., 1997). Given that the default mode network (DMN) conveys limbic information, its abnormalities will also be reviewed in this section (Lee and Xue, 2018b).

Volume reductions have been reported in the anterior cingulate cortex (ACC), posterior cingulate cortex, amygdala, hippocampus, parahippocampal gyrus, and paralimbic regions, including the subcallosal cortex and insula (Norman et al., 2016, Bonath et al., 2018, Bralten et al., 2016, Brieber et al., 2007). The precuneus, a key node of the DMN, shows no consistent pattern of volumetric increase or decrease across studies (Bralten et al., 2016, Brieber et al., 2007). Notably, the ACC and insula remained statistically significant in a recent meta-analysis (Lukito et al., 2020).

In contrast to the PFC, where structural and functional alterations tend to align in directionality—typically with reduced volume accompanied by reduced activation—findings in the limbic system are far from consistent. For instance, despite volume reduction in the ACC, both increased and decreased activation during cognitive control tasks have been reported (increase:decrease = 8/43:7/43 for ADHD – Controls contrast; see Table 1 in (Lukito et al., 2020)). Consequently, neural responses in the limbic and paralimbic systems, including ACC, amygdala/hippocampus (3/43:2/43), insula (4/43:5/43), did not reach statistical significance in the same meta-analysis (Lukito et al., 2020). Nevertheless, ADHD-related hyperactivation within the DMN, as revealed by fMRI, was identified in a separate meta-analysis (Cortese et al., 2012). Functional connectivity studies have revealed enhanced interactions between the limbic system and the DMN in individuals with ADHD (Kumar et al., 2021, Peterson et al., 2009, Harikumar et al., 2021).

Functional and structural abnormalities of the dorsal striatum

In accord with the intrinsic organization of the cortico-striatal-thalamo-cortical circuitry, abnormalities in the dorsal striatum frequently co-occur with those in the PFC, collectively referred to as fronto-striatal abnormalities (Schneider et al., 2010, Cubillo et al., 2011, Rubia et al., 2009). Correspondingly, structural and functional MRI studies have respectively revealed volume reductions and attenuated neural responsivity to the cognitive control tasks in the caudate and putamen (Brieber et al., 2007, Ohno, 2003), and both of which have withstood statistical scrutiny in meta-analyses conducted by independent research groups (Lukito et al., 2020, Norman et al., 2016, Frodl and Skokauskas, 2012). As for structural connectivity, current fiber tracking

techniques are more reliable for larger bundles, such as the corticospinal tract, superior longitudinal fasciculus, and cingulum (Peng et al., 2014, van Ewijk et al., 2012). In contrast, thinner fibers mediating the PFC-to-VTA connection in ADHD still pose technical challenges. Nevertheless, evidence has suggested disrupted white matter integrity involving the frontostriatal tracts in individuals with ADHD (Connaughton et al., 2022).

PET research has revealed DA dysregulation in the dorsal striatum in ADHD, including decreased D2/D3 receptor availability and increased DAT levels (Spencer et al., 2007, Dougherty et al., 1999, Krause et al., 2000). Notably, stimulation of the human PFC has been shown to evoke DA release in the caudate nucleus (Strafella et al., 2001), likely mediated by excitatory corticostriatal projections through which glutamate facilitates DA release from adjacent nigrostriatal terminals (Chéramy et al., 1986). This suggests that PFC hypofunction—frequently observed in ADHD—may itself contribute to the DA deficits in the caudate identified by PET. The caudate and putamen receive distinct cortical inputs: the former is primarily innervated by cognitive-related regions such as the dorsolateral PFC and lateral OFC, whereas the latter predominantly receives motor-related afferents (Grahn et al., 2008). These anatomical differences may correspond to dissociable aspects of ADHD pathology.

Beyond dopamine: the role of norepinephrine in arousal regulation

In addition to DA, dysregulation of NE, serotonin, gamma-aminobutyric acid (GABA), and glutamatergic systems has also been implicated in ADHD (Naaijen et al., 2017). This article focuses on NE due to its stronger association with a hallmark symptom of ADHD—hypoarousal, a physiological state that may in turn exacerbate inattentiveness and motivational problems in ADHD (Pliszka, 2005, James et al., 2017). Centrally, hypoarousal is characterized by enhanced slow brain waves, supporting the exploration of the theta/beta ratio as a potential neural marker (Saad et al., 2015, Isaac et al., 2023, Strauß et al., 2018). Impaired regulation of central arousal may hinder the ability to maintain optimal alertness and contribute to inconsistent cognitive performance (Du Rietz et al., 2019). Peripherally, reduced autonomic nervous system activity—reflected in lower skin conductance and diminished vagal tone—has been associated with emotional dysregulation in individuals with ADHD (Souroulla et al., 2019).

Altered NE signaling has been linked to hypoarousal (España et al., 2016). Although the locus coeruleus (LC) is widely recognized as the major principal of cortical NE, particularly to the PFC, recent evidence has identified several deep subcortical neuron clusters that also contribute to NE transmission and provide alternative projections to the frontal cortex (Robertson et al., 2013). Beyond these cortical pathways, the LC receives afferent input from medullary nuclei, including the nucleus paragigantocellularis and the nucleus prepositus hypoglossi (Aston-Jones et al., 1991). Its efferent projections are extensive, innervating broad cortical and subcortical territories (Poe et al., 2020). NE reuptake inhibitors (e.g., atomoxetine) and dual DA/NE reuptake inhibitors (e.g., MPH) may enhance signaling across this distributed NE-related network, thereby helping to alleviate hypoarousal-related symptoms in ADHD.

As summarized above, decades of research have implicated cortico-subcortical circuits in the pathophysiology of ADHD. A recent meta-analysis reported increased functional connectivity between subcortical structures—such as the caudate, putamen, amygdala, and NAc—and frontal, temporal, and parietal cortices, though the observed effect sizes were small (Norman et al., 2024). Together with the rapid symptom relief provided by central stimulants, these findings suggest that ADHD is unlikely to result from major structural lesions or isolated dysfunctions. Instead, its underlying pathology may reflect a subtle yet widespread deviation across multiple interacting networks, highlighting the need for conceptual models that move beyond traditional region-based or neurotransmitter-specific frameworks (Lee, 2025b).

Materials and Methods

This section presents the analytic phase and is divided into two parts (**Materials**). The first provides a summarized review of key analytical findings from prior research. The second outlines the defining

(neuro-)features of ADHD that the subsequent synthesis aims to integrate—conceptually corresponding to the peripheral pieces of the jigsaw puzzle (see Figure 1 in (Lee, 2025b)). The **Methods** involve the application of creative and non-linear cognition to uncover the central missing piece of the puzzle—constituting the core process of centralized dialectics and enabling the construction of a holistic picture from seemingly disparate findings. The confidence of the proposed model will be evaluated by Fisher’s combined probability meta-analytic test (Fisher, 1925). Based on a heuristic standard for synthesis performance, accounting for 1–2 observations is rated as poor, 3–4 as fair, 5–7 as good, 8–10 as very good, and more than 10 as excellent (Lee, 2025b).

Part I: Analytic results

Prefrontal and limbic abnormalities in ADHD

- (1) Reduced volume across multiple regions—including the PFC, corpus callosum, and limbic system—has emerged as a consistent finding in ADHD (Ohno, 2003, Depue et al., 2010a, Norman et al., 2016, Bralten et al., 2016).
- (2) Prefrontal volume reduction has been associated with impairments in neuropsychological functioning and the severity of clinical symptoms (Depue et al., 2010a, Castellanos et al., 2002).
- (3) Functional neuroimaging studies have consistently shown reduced PFC activation in individuals with ADHD across a range of cognitive tasks (Cubillo et al., 2011, Depue et al., 2010b, Burgess et al., 2010, Smith et al., 2008, Smith et al., 2006).
- (4) In contrast to the PFC, functional neuroimaging findings in the limbic system have been inconsistent, with studies reporting both hyperactivation and hypoactivation during cognitive control tasks (Lukito et al., 2020).
- (5) Functional connectivity studies have revealed increased interactions between the limbic system and the DMN in individuals with ADHD (Kumar et al., 2021, Peterson et al., 2009, Harikumar et al., 2021).
- (6) Although not formally part of the limbic system, the (superior) temporal cortex interacts with medial temporal limbic structures and has been shown to exhibit reduced volume and attenuated neural responses during target detection and cognitive control tasks (Smith et al., 2006, Rubia et al., 2007).

Subcortical abnormality in ADHD

- (7) Aberrant dopaminergic transmission within both the mesocorticolimbic and nigrostriatal pathways has been consistently implicated in ADHD (Díaz-Heijtz et al., 2006, Ernst et al., 1998, Ernst et al., 1999, Jucaite et al., 2005, Volkow et al., 2009, Volkow et al., 2011, Volkow et al., 2007, Spencer et al., 2007, Dougherty et al., 1999, Krause et al., 2000).
- (8) Reward processing and response in ADHD exhibit a context-dependent dissociation in neural activities—characterized by hypoactivation during evaluative judgment and hyperactivation during reward anticipation and receipt (Plichta et al., 2009, Norman et al., 2017, von Rhein et al., 2015, van Dongen et al., 2015, Strohle et al., 2008).
- (9) Enhanced functional connectivity within cortico-subcortical circuits has been observed in ADHD (Norman et al., 2024), with increased connectivity between the NAc and PFC linked to heightened impulsivity, as evidenced by steeper discounting of delayed rewards (Costa Dias et al., 2013).
- (10) Structural and functional MRI studies have respectively revealed volume reductions and diminished neural responsivity during cognitive control tasks in the caudate and putamen (Brieber et al., 2007, Ohno, 2003, Lukito et al., 2020, Norman et al., 2016, Frodl and Skokauskas, 2012).

Neurophysiological understanding and some facts

- (11) Both MPH and dopaminergic agents such as levodopa (used in Parkinsonism) enhance dopaminergic neurotransmission (Wood et al., 1982, Langer et al., 1982). However, ADHD is characterized by hyperactivity, while Parkinsonism presents with bradykinesia—an opposite motor phenotype. This dissociation suggests that the main pathological foci of hyperactivity in ADHD

resides outside the traditional nigrostriatal pathway.

- (12) MPH may rapidly alleviate symptoms and rectify underlying disruptions in neural processing (Rubia et al., 2011a, Rubia et al., 2011b, An et al., 2013, Yildiz Oc et al., 2007).
- (13) Dopaminergic neurons in the VTA project to widespread cortical and subcortical regions implicated in ADHD, including the PFC, limbic structures (ACC, hippocampus, amygdala), basal ganglia (ventral striatum, pallidum), hypothalamus, lateral habenula, and bed nucleus of the stria terminalis (Schneider et al., 2013, Neumann et al., 2014).
- (14) DA receptors are widely distributed across the neocortex, with a rostral-to-caudal gradient peaking in the frontal regions (Lidow et al., 1991).
- (15) The VTA and PFC are interconnected via an autofeedback loop, with dopaminergic outputs from the VTA to PFC and glutamatergic inputs from the PFC to VTA (Floresco et al., 2001, Polter and Kauer, 2014).
- (16) Neurons in the VTA that receive afferent input from the PFC and project to the NAc have been consistently identified as GABAergic, rather than dopaminergic, in nature (Carr and Sesack, 2000).
- (17) Reduced tonic DA weakens presynaptic D2-mediated inhibition, thereby relatively enhancing mPFC glutamatergic input to the NAc (Floresco et al., 2003, Goto and Grace, 2005).
- (18) Neurons fire in tonic and phasic modes in both DA and NE systems (Grace, 1995, Devilbiss and Waterhouse, 2011).
- (19) Tonic and phasic DA transmissions are functionally interrelated in a reciprocal manner, whereby a reduction in tonic DA levels enhances phasic dopaminergic responsivity through negative feedback mechanisms to maintain homeostasis (Grace, 1991, Grace, 1995).
- (20) Hypoarousal has been associated with NE system dysfunction, in which the LC serves as a major hub, forming an autoregulatory feedback loop with the PFC (Robertson et al., 2013).
- (21) The development of the temporal cortex is influenced by medial temporal structures (Voss et al., 2017, Duff and Brown-Schmidt, 2012).
- (22) The phenomenon of evoked neural activity exhibiting a negative interaction with ongoing baseline activity has been consistently demonstrated across both animal electrophysiological and human functional MRI studies (Arieli et al., 1996, He, 2013).
- (23) The fronto-parietal compartment and the limbic system interact through a reciprocal suppressive mechanism, and an imbalance in this dynamic has been linked to major depressive disorder (Lee, 2025a, Lee and Tramontano, 2025).
- (24) DA may indirectly support neuronal growth and survival via neurotrophic factor regulation (Küppers and Beyer, 2001, Williams and Undieh, 2009, Iwakura et al., 2011, Roceri et al., 2001), and modulate synaptic plasticity, especially in the hippocampus (Kim et al., 2023).
- (25) Anatomical and functional studies indicate that the VTA and substantia nigra are not isolated structures but components of a highly interconnected midbrain network, linked through reciprocal dopaminergic, GABAergic, and glutamatergic projections. These interconnections support bidirectional communication across dopaminergic circuits, facilitating the integration of reward, motivation, and motor control (Watabe-Uchida et al., 2012, Ferreira et al., 2008).
- (26) The ventral striatum serves as a bridge between the limbic and motor systems (Groenewegen and Trimble, 2007), with the NAc projecting directly to the substantia nigra.

Part II: Cardinal (neuro-) features of ADHD

The proposed brain theory of ADHD is expected to account for a range of prominent features associated with the disorder, including the following:

- (1) ADHD conceptualized as a neurodevelopmental disorder;
- (2) The model's implications for dopaminergic system dysfunction and its potential to reconcile disparate findings from previous neuroimaging studies;
- (3) Abnormalities in reward processing, particularly the differential manifestation of responses to

- judgment versus receipt of rewards;
- (4) Neuroimaging evidence of prefrontal hypoactivity and mixed limbic responsivity;
 - (5) The occurrence of inattentiveness;
 - (6) The emergence of the trait of hypoarousal;
 - (7) The occurrence of hyperactivity symptoms;
 - (8) The occurrence of impulsive behaviors;
 - (9) The mechanisms underlying the pharmaceutical interventions targeting core ADHD symptoms;
 - (10) The occurrence of emotion dysregulation and the frequent comorbidity with depression;
 - (11) The comorbidity between ADHD and tic disorders, the most prevalent neurologically associated condition.

Results

This section presents the synthetic phase of the study (the analytic phase is detailed in the **Materials and Methods** section) and is organized into two parts. A candidate brain theory of ADHD—namely, deviant descending PFC-subcortical projections—is proposed as the central missing piece of the jigsaw puzzle. The “biological plausibility” of this model is articulated in the first part of this section, while the second part evaluates its explanatory power and comprehensiveness (“accountability”).

Part I: Synthetic product—evidence for descending PFC-subcortical projections as a developmental vulnerability

Projections from the PFC cortex to subcortical structures such as the basal ganglia and VTA originate primarily from layer 5 pyramidal neurons. These long-range glutamatergic axons are characteristically slender, sparsely myelinated, and exhibit substantially slower conduction velocities relative to the heavily myelinated cortico-spinal fibers (Firmin et al., 2014, Innocenti et al., 2017, Lemon, 2019). In contrast, subcortical-to-cortical feedback projections are predominantly relayed via the thalamus. Thalamocortical axons benefit from well-established developmental scaffolding, including transient embryonic structures such as the subplate zone, which provides precise guidance for axonal navigation (Kostović and Judas, 2010). This process is further refined by conserved molecular cues—including Netrin, Slit, Wnt, JNK, FGF, and Ephrin—that ensure accurate topographic targeting, typically terminating in cortical layer 4 and thereby minimizing the risk of misrouting (Hayano et al., 2014, Poliak et al., 2015, Stoeckli, 2018, Cunningham et al., 2022). In comparisons, layer 5 corticofugal projections must traverse longer distances and innervate a broader array of subcortical targets, necessitating sustained molecular guidance over extended spatial domains. Collectively, these factors render such descending pathways more susceptible to developmental miswiring. In summary, unlike the spatially constrained cortico-cortical and thalamocortical systems, descending PFC-subcortical tracts—such as PFC-striatal and PFC-VTA projections—are inherently more vulnerable to perturbation due to their distinct anatomical trajectories and reliance on prolonged molecular navigation.

Widespread synaptic pruning following early synaptic overproduction is a well-established feature of mammalian brain development (Rakic et al., 1986). This pruning process begins near birth and continues through adolescence, with certain regions—such as the PFC—undergoing pruning into early adulthood (Stiles and Jernigan, 2010). During early development, abundant redundant neural resources may transiently compensate for, or even correct, initial circuit deficits. One of the most validated mechanisms is through diffuse collateral innervations (Ferino et al., 1987, Hui and Beier, 2022), see Figure 1. However, as pruning advances toward an optimized adult configuration, this compensatory buffer diminishes, along with the alternative routing via collateral connections that would otherwise allow mismatched projections to still reach appropriate targets. Even when pruning is largely adaptive, residual “scars” may remain in systems that are inherently fragile during ontogeny, such as the dorsal striatal and mesolimbic/mesocortical pathways. Although psychostimulants can substantially alleviate symptoms and improve various cognitive deficits in individuals with ADHD, some studies suggest that certain impairments may persist even under pharmacological treatment. These findings indicate that ADHD cannot be simplified to be a

hypodopaminergic condition.

Compared to the PFC-striatal analog, PFC-VTA projections are even more susceptible to developmental disturbances. This heightened vulnerability is not only due to the VTA's location in the midbrain—which results in a longer axonal trajectory from the PFC to the VTA than from the PFC to the putamen and caudate—but is further amplified by the intrinsic auto-feedback loop architecture of the VTA. Specifically, the VTA sends dopaminergic projections to the PFC, which in turn provides glutamatergic feedback to the VTA (Hui and Beier, 2022). Through this reciprocal circuitry, DA neurons in the VTA enhance information processing in the PFC (Mininni et al., 2018), while glutamatergic afferents from the PFC can elevate dopaminergic activity in the VTA (Floresco et al., 2001, Polter and Kauer, 2014). For this bidirectional system to function properly, neurons in the VTA must successfully innervate corresponding targets in the PFC, and vice versa. The development of reciprocal PFC–VTA projections is temporally offset rather than synchronous, supporting a model of adaptive circuit refinement: Dopaminergic axons from the VTA begin projecting to the PFC around gestational weeks 10–13 (Kolk and Rakic, 2022), whereas glutamatergic projections from the PFC to the VTA form later, reflecting the relatively protracted developmental timeline of the PFC compared to subcortical structures. This sequential organization allows PFC efferents to adjust to pre-established dopaminergic inputs, facilitating a closed-loop architecture optimized for precise autoregulatory feedback and motivational control. A mismatch within this auto-feedback loop (see Figure 1) could disrupt VTA function and potentially interfere with its structural organization from early developmental stages through maturation. Once synaptic pruning commences, the consequences of such miswiring in the VTA are likely to become more pronounced.

Accordingly, descending PFC-subcortical projections—especially those targeting midbrain dopaminergic nuclei—constitute structurally and developmentally vulnerable pathways. Their relative fragility, compared to the more scaffolded and molecularly stabilized thalamocortical and cortico-cortical systems, reflects an inherent asymmetry between forward and backward projections. This instability renders the PFC-VTA–NAc axis particularly susceptible to early developmental perturbations, potentially compromising its integrity and leading to abnormal dopaminergic neurotransmission (see **Discussion: The neural consequence of deviant descending frontal-subcortical projections**). Such vulnerabilities may underlie core circuit-level deficits characteristic of ADHD and related neurodevelopmental comorbidities.

The role of frontal-to-thalamus projections in ADHD pathophysiology is not considered central. First, these projections are less directly involved in dopaminergic modulation. Second, thalamocortical and corticothalamic connections represent some of the earliest-developing circuits in the embryonic brain (Grant et al., 2012). Notably, the PFC–mediodorsal thalamus pathway is an evolutionarily conserved projection with tightly regulated developmental guidance, involving molecules such as ephrins, semaphorins, and netrins (Braisted et al., 2000). In addition, key developmental boundaries, such as the pallial-subpallial boundary and the diencephalon-telencephalon boundary, play crucial roles in guiding axonal pathfinding and regional differentiation during brain development, helping ensure proper wiring between the thalamus and cortex. Given the thalamus's critical trophic and guiding role in cortical differentiation, as well as its bidirectional and early-established connectivity with the frontal cortex, this circuit benefits from developmental safeguards. These features—including early formation, structural conservation, and robust molecular regulation—render it less vulnerable to the neurodevelopmental perturbations typically implicated in ADHD.

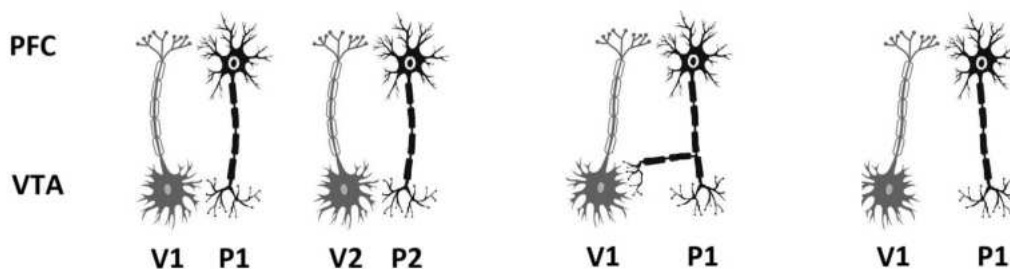


Fig. 1. Developmental trajectories of reciprocal PFC–VTA connectivity and the impact of miswiring and pruning.

Left panel: Normal reciprocal connections are established between PFC and VTA neurons—P1 connects bidirectionally with V1, and P2 with V2.

Middle panel: Miswiring scenario—V1 projects correctly to P1, but P1 fails to form a reciprocal connection back to V1. During early development, redundant collateral pathways still allow access to V1.

Right panel: After developmental pruning removes these early-stage redundant branches, the alternative route from P1 to V1 is lost, resulting in a permanent lack of reciprocal connectivity.

*Part II: Accountability evaluation of the descending PFC-subcortical model of ADHD (note: the contents are in one-to-one correspondence with the core features summarized in the **Materials and Methods** section, part II)*

- (1) The emergence of ADHD may stem from developmental vulnerabilities in descending PFC-subcortical projections, especially those centering on VTA. The consequent impact on mesocorticolimbic and nigrostriatal dopaminergic pathways, the PFC, limbic structures, dorsal striatum, and the NE system may collectively underlie its complex clinical and neurobiological manifestations.
- (2) Impairment in the PFC-to-VTA glutamatergic excitatory pathway may directly result in a reduced tonic dopaminergic state (manifested as hypodopaminergism) (Floresco et al., 2001, Polter and Kauer, 2014), while compensatory and autoregulatory mechanisms may lead to sensitized phasic dopaminergic transmission and the enhanced reactivity of the NAc (Grace, 2016, Goto and Grace, 2005). Further, hypofrontality may disinhibit the NAc (together manifested as hyperdopaminergism) (Carr and Sesack, 2000).
- (3) The altered processing of immediate and delayed rewards in ADHD may reflect a synergistic effect of enhanced NAc reactivity and exaggerated phasic dopaminergic signaling (“hyperdopaminergic”), coupled with reduced tonic dopaminergic transmission and PFC hypofunction (“hypodopaminergic”).
- (4) Prefrontal hypoactivity observed in neuroimaging may stem from reduced frontal volume, inefficient VTA-to-PFC signaling (Mininni et al., 2018), and dysregulated NE modulation. Mixed limbic responsivity may reflect opposing influences: reduced limbic volume and VTA transmission may dampen intrinsic reactivity, while hypofrontality and heightened NAc activity (via mPFC or vmPFC) may enhance it (Lee, 2025a), together producing the heterogeneous findings observed in neuroimaging studies.
- (5) Inattentiveness may arise from at least six factors: hypofrontality due to reduced frontal volume and impaired VTA-to-PFC modulation, hyperactive NAc contributing to distractibility and limbic hyperactivity, dysregulated NE system, reduced caudate volume, and less efficient PFC–caudate interactions. These multiple origins make inattentiveness the most persistent symptom of ADHD.
- (6) The trait of hypoarousal may arise from a similar mechanism of hypodopaminergism, mediated by aberrant descending prefrontal projections to the LC, resulting in lower tonic NE level.
- (7) The occurrence of hyperactivity may be a direct consequence of sensitive and disinhibited NAc.
- (8) The emergence of impulsive behaviors may stem from at least four factors: reduced frontal volume (particularly in the ventrolateral PFC), impaired top-down control from PFC due to hypodopaminergic tone, heightened phasic NE reactivity, and increased NAc activity.
- (9) The therapeutic efficacy of DA and NE reuptake inhibitors may stem from their capacity to elevate tonic transmitter levels, triggering a constellation of neural effects that alleviate ADHD neuropathology—dampening phasic dopaminergic and noradrenergic responses, reducing NAc hyper-reactivity, enhancing PFC function, and attenuating limbic overactivity via decreased NAc drive and strengthened frontal top-down regulation.
- (10) Emotion dysregulation and its common comorbidity with anxiety and depression can be attributed to hypofrontality coupled with limbic hyperactivity, reflecting an imbalance in PFC–limbic system interactions.

- (11) The comorbidity of ADHD with tic disorders may stem from disruptions in descending PFC-subcortical projections affecting the dorsal striatal pathway. In addition, dysfunction in the VTA may directly influence the substantia nigra, pallidum and subthalamic nucleus (Klitenick et al., 1992, Watabe-Uchida et al., 2012, Ferreira et al., 2008, Smith and Villalba, 2008), and impact motor system coordination.

Using Fisher’s combined probability test, the synthetic model incorporating 11 cardinal features yielded a confident result with a p-value below 10^{-7} (chi-square = 65.7), assuming each feature endorsed by previous empirical research by chance at $p = 0.05$. The accountability of the synthesis is briefly summarized in Table 1, and a detailed explanation is elucidated in the **Discussion**.

Table 1 Core manifestations of ADHD and their network-based Interpretations

Queries/Phenomenon	Explanations
The occurrence of ADHD	Miswiring of PFC to subcortical projection (VTA and LC) as developmental vulnerability
Dopaminergic system dysfunction	Deficient PFC-to-VTA glutamatergic signaling; imbalanced tonic and phasic DA transmission
Differential reward responses	Low tonic and exaggerated phasic DA activity; hypofrontality; disinhibited NAc
Prefrontal hypoactivity and mixed limbic responsivity	Reduced volume*; deficient fronto-subcortical network; frontal-limbic interaction
The occurrence of inattentiveness	Reduced volume*; deficient fronto-subcortical network; frontal-limbic interaction
The emergence of the trait hypoarousal	Impaired PFC-to-LC projection; low tonic NE transmission
The occurrence of hyperactivity symptoms	Sensitized and disinhibited NAc
The occurrence of impulsive behaviors	Reduced frontal volume; impaired top-down control; aberrant activity in NAc and LC
Therapeutic effects of psychostimulants	Increased tonic DA/NE transmission; normalization of phasic firing; enhanced PFC function
Comorbidity of emotion dysregulation and depression	Hypofrontality coupled with limbic hyperactivity
The comorbidity between ADHD and tic disorders	Miswiring PFC to subcortical projection involving dorsal striatum

* Reduced volume in the PFC, limbic structure and subcortical nuclei

Discussion

Although traditional review articles that thoroughly summarize previous literature are highly valued and remain an essential part of academic research, systematic attempts to derive novel insights through the review process—and to formalize such synthesis in a scientifically rigorous manner—have been limited. The framework proposed by dialectic neuroscience offers a viable approach to address this limitation. The inherent complexity of psychiatric disorders has long presented a challenge, prompting either blind computational modeling without theoretical grounding or psychological experiments limited in scope and lacking a holistic perspective. In contrast, dialectic neuroscience prioritizes conceptual integration, proposing that the neural essence of complicated issues such as ADHD can emerge through structured and centralized dialectical reasoning over empirical findings and observed phenomena, where these elements are brought into a “dialogue” with one another by the synthesizer (the author in this case, hence the term *dialectic neuroscience*). During this process, the original interpretations of laboratory findings are bracketed (epoché), allowing creative thinking to reinterpret and integrate prior studies, and to flexibly develop new guiding theories. This review adopts such a framework and proposes that the neural pathology of ADHD may originate from aberrant descending PFC-to-subcortical projections and subsequent pruning during development. Interestingly, previous research has shown that synaptic density begins to decline around age 2, and the pruning process may continue into the late 20s (Huttenlocher, 1979, Petanjek et al., 2011), largely corresponding to the onset and eventual stabilization of ADHD symptoms (Henning et al., 2024).

The neural consequence of deviant descending frontal-subcortical projections during development (Synthetic Results 2 and 3)

The impact of deviant descending PFC-subcortical projections can be anatomically and functionally delineated into two principal categories: those directed toward the VTA–NAc system, primarily implicated in the core symptomatology of ADHD and addressed in the present section; and those involving the dorsal striatum, which may contribute to cognitive impairment and motor-related comorbidities (see the section *Comorbidity with other neuropsychiatric disorders*). The former is the primary focus of the article, and its downstream effects can be broadly divided into two parts.

Firstly, less efficient glutamatergic projections from PFC to VTA (mesocortical pathway) may directly

contribute to hypodopaminergism (Floresco et al., 2001, Polter and Kauer, 2014). Conversely, less efficient dopaminergic feedback from VTA may impair neural computation in the PFC (Mininni et al., 2018). In addition, DA can indirectly promote neuronal growth and survival by modulating the expression of neurotrophic factors such as BDNF and various growth factors (Küppers and Beyer, 2001, Williams and Undieh, 2009, Iwakura et al., 2011, Roceri et al., 2001). Hypoactivity in the PFC may also lead to a decreased DA level in the caudate nucleus (Strafella et al., 2001, Chéramy et al., 1986). Reduced volumes of the frontal cortex and striatum (including the ventral striatum) may result from insufficient neurotrophic support of DA signaling (Hesslinger et al., 2002, Seidman et al., 2006, Sethi et al., 2017). Together, these structural and functional impairments may underlie hypofrontality. Notably, the reciprocal loop between PFC and VTA forms an autofeedback circuit, in which dysfunction in one limb (e.g., reduced glutamatergic input from PFC to VTA) can compromise the function of the other (i.e., dopaminergic feedback from VTA to PFC), and vice versa. This mutual dependency renders the system vulnerable to a self-perpetuating cycle of dysfunction.

Secondly, reduced DA release from the VTA may lead to a diminished tonic DA level in the NAc. DA signaling in subcortical regions is governed by two distinct mechanisms: (1) phasic, transient release triggered by behaviorally salient stimuli, and (2) tonic, sustained background release regulated by PFC afferents (Grace, 1991, Grace, 1995). Evidence suggests that tonic activity can modulate phasic responsivity via presynaptic D2 autoreceptors and postsynaptic regulatory mechanisms to maintain homeostatic balance (Grace, 2016). In brief, a reduction in tonic background enhances phasic DA reactivity, and vice versa. Furthermore, it has been shown that VTA neurons receiving PFC input and projecting to the NAc are consistently GABAergic rather than dopaminergic (Carr and Sesack, 2000). In this context, hypofrontality may disinhibit NAc responsivity by reducing GABAergic transmission. Under conditions of reduced tonic DA, presynaptic D2 receptor-mediated inhibition on mPFC terminals is diminished, thereby enhancing glutamatergic transmission from the mPFC to the NAc. This compensatory increase may counterbalance the overall reduction in mPFC-driven excitatory input to the NAc (Floresco et al., 2003, Goto and Grace, 2005). The above physiological mechanisms may jointly account for seemingly contradictory dopaminergic findings in ADHD, as elaborated below.

The diminished DA concentration in the PFC may reflect inefficient utilization and release (Ernst et al., 1999), aligning with reports of attenuated DA release in the subcortical regions (Forssberg et al., 2006, Ludolph et al., 2008). In addition, reduced D2/D3 receptor availability in the ventral striatum may result from chronically lowered tonic DA levels (Jucaite et al., 2005, Volkow et al., 2009, Volkow et al., 2011). Furthermore, the downregulation of DAT expression may suggest that low baseline DA tone represents a developmentally shaped, enduring trait rather than a compensatory mechanism triggered by transient deficiency (Jucaite et al., 2005). Collectively, these findings converge to align with the hypothesis of hypodopaminergism in ADHD.

During evaluative tasks and in the absence of reward delivery, hypoactivation of the ventral striatum and PFC—observed across both immediate and delayed reward conditions—has been interpreted as evidence for DA deficiency in ADHD (Plichta et al., 2009, Norman et al., 2017). However, an alternative explanation is that these response patterns may reflect elevated baseline activity in the NAc due to disinhibition arising from prefrontal dysfunction and dysregulated VTA signaling (Grace, 2016, Goto and Grace, 2005, Carr and Sesack, 2000). The inverse relationship between baseline and evoked activity is well documented in both animal electrophysiology and human fMRI research (Arieli et al., 1996, He, 2013). This interpretation aligns with findings of increased functional connectivity centered on the NAc in ADHD (Costa Dias et al., 2013, Norman et al., 2024).

On the other hand, enhanced frontostriatal activity has been reported during both the anticipation and receipt of rewards (von Rhein et al., 2015, van Dongen et al., 2015, Strohle et al., 2008), with a reported positive correlation with symptom severity. The heightened neural responses may reflect increased phasic dopaminergic activity from VTA that emerges as a compensatory mechanism against a background of low tonic DA levels (Grace, 1991), thereby giving rise to an impression of hyperdopaminergism. Notably, elevated DA storage in the VTA—particularly in children, whose synthesis capacity may not yet be balanced by usage—could represent the other side of reduced DA utilization, e.g., in the PFC (Ernst et al., 1999). Taken together,

by introducing a circuit-level framework grounded in neurophysiology, the apparent contradictions in the literature between hypo- and hyperdopaminergic findings can be reconciled. Specifically, the proposed aberrance in descending PFC-subcortical projections not only integrates these opposing patterns but also point to a core pathophysiological mechanism that may underlie ADHD itself.

The proposed model suggests that ADHD involves erratic or disinhibited phasic firing of DA and NE neurons, subsequent to the hypoactive tonic states of these neurotransmitter systems. Concordantly, one of the most consistent and replicable neuropsychological indices (or endophenotypes) of ADHD is abnormally high intra-individual variability in reaction time across various behavioral tasks, including those measuring motor speed, choice decision, vigilance, behavioral inhibition, cognitive interference, working memory, visual saccade, and visual discrimination (Kofler et al., 2013). In line with this, studies have demonstrated that individuals with ADHD exhibit increased trial-by-trial neural variability across both visual and auditory modalities. This exaggerated variability occurs both during baseline (in the absence of stimuli) and in response to sensory events, indicating a modality-independent instability of ongoing and stimulus-evoked neural activities (Gonen-Yaacovi et al., 2016).

Notably, the neural circuits centered on the NAc are more complex than those of other basal ganglia nuclei. Like other striatal regions, the NAc receives cortical inputs from the mPFC, forming part of the classical cortico-striato-thalamo-cortical loop that projects via the ventral pallidum to the thalamus. However, unlike the relatively confined inputs to other basal ganglia structures, the NAc also integrates dense projections from multiple limbic areas—including the ACC, amygdala, hippocampus, and parahippocampal gyrus—as well as from the thalamus (midline and intralaminar nuclei) and the mesencephalon (VTA, NE and raphe nuclei). It sends outputs not only to ventral pallidum but also to the substantia nigra, hypothalamus and midbrain (Groenewegen and Trimble, 2007). In addition, the VTA maintains strong bidirectional connections with the mPFC and limbic structures (Polter and Kauer, 2014, Reynolds and Flores, 2021, Sesack and Grace, 2010). Given these extensive anatomical links, abnormalities in the VTA–NAc circuit may directly influence both limbic and motor systems, as discussed below.

Frontal and limbic abnormalities of ADHD (Synthetic Result 4)

Volume reduction in both the PFC and limbic system is a consistent finding in the ADHD literature (Depue et al., 2010a, Norman et al., 2016, Bralten et al., 2016). Since both regions receive dopaminergic innervation from the VTA, reduced dopaminergic transmission may indirectly contribute to these morphometric changes, as discussed previously. Supporting this, greater volume loss has been observed in PFC subregions that receive denser VTA inputs (Depue et al., 2010a, Lukito et al., 2020). PET studies further revealed a hypodopaminergic state in the hippocampus and amygdala in individuals of ADHD (Volkow et al., 2007). Animal research underscores the importance of DA in modulating synaptic plasticity, particularly within the hippocampus (Kim et al., 2023). Additional mechanisms may also contribute to these changes: In the PFC, abnormal wiring followed by excessive pruning could further exacerbate tissue loss, while in the limbic system, chronic hyperactivity associated with ADHD may lead to cell loss, likely via calcium overload toxicity (Alberdi et al., 2005).

Concordant with the volumetric changes, hypoactivation in the PFC to cognitive challenges has also been a robust and replicable finding across neuroimaging studies (Cubillo et al., 2011, Depue et al., 2010b, Burgess et al., 2010, Smith et al., 2008, Smith et al., 2006, Dickstein et al., 2006). Beyond diminished frontal lobe volume, impaired DA and NE signaling may further undermine PFC functioning (Mininni et al., 2018). Recent evidence indicates that NE, via $\alpha 2A$ -adrenoceptor activation, enhances the functional connectivity and sustained firing of prefrontal networks, thereby supporting stable working memory representations. In contrast, DA acts on D1 receptors to selectively suppress irrelevant inputs and amplify task-relevant signals, thereby optimizing the signal-to-noise ratio in prefrontal processing (Arnsten, 2011). Collectively, attenuated DA and NE transmission may impair prefrontal operations. Additionally, limbic hyperactivity—despite the coexistence of both hypo- and hyperactivation—may further exacerbate hypofrontality via reciprocal suppression between the frontoparietal system and the limbic network. This mechanism may underlie the

frequently reported failure to adequately suppress the DMN during cognitive tasks in individuals with ADHD (Weyandt et al., 2013, Lee and Xue, 2018a, Lee, 2025a). Another contributor to hypofrontality may involve reduced volume and/or function of the caudate (and putamen), along with compromised structural connectivity within the cortico-striato-thalamo-cortical circuit, manifesting as fronto-striatal hypoactivity (Brieber et al., 2007, Ohno, 2003, Lukito et al., 2020, Norman et al., 2016, Connaughton et al., 2022).

In contrast to the PFC, neural responsivity in the limbic regions exhibits a mixture of hypo- and hyperactivation patterns across various cognitive paradigms (Lukito et al., 2020). While this inconsistency has often been attributed to factors such as small sample sizes, diverse experimental designs, different analytic approaches, and the heterogeneity inherent to ADHD, the proposed model from dialectic neuroscience offers an alternative explanation: two opposing network forces may compete within these circuits, mirroring the coexistence of hypo- and hyperdopaminergic states. Although reduced limbic volume and diminished influence from the VTA would be expected to predispose limbic regions to hypoactivation, increased activity in the NAc, together with hypofrontality (Lee, 2025a), may instead facilitate limbic hyperactivity. Note that while the principal neuron type in the NAc is GABAergic, activation of the NAc—through its integration in the cortico-striato-thalamo-cortical loop—is accompanied by synchronous activation, not deactivation or inhibition, in the limbic cortex (review) (Haber and Knutson, 2010). The limbic cortex further has reciprocal connections with amygdala, subiculum, entorhinal, and perirhinal cortex (review) (Ongur and Price, 2000). Consistent with this, functional connectivity studies have shown enhanced interactions between part of the limbic system and the DMN in individuals with ADHD (Cortese et al., 2012).

The superior temporal gyrus shows reduced volume and attenuated neural responses during target detection, motor inhibition and task switching tasks (Smith et al., 2006, Rubia et al., 2007), exhibiting a directionality of structural and functional alterations similar to that observed in the PFC. There are no substantial projections from the VTA–NAc pathway to the outer temporal cortex. Although not part of the limbic system, the embryonic development of the temporal lobe is closely linked to that of the hippocampus and other medial temporal structures. The alterations observed in the outer temporal cortex in ADHD may thus stem from developmental influences originating in those medial temporal regions (Voss et al., 2017, Duff and Brown-Schmidt, 2012). As a result, the functional and structural features of the outer temporal cortex in ADHD appear more consistent—resembling those of the PFC—rather than showing the mixed patterns associated with the limbic system. Given that the NAc serves as a key subcortical hub for integrating salient information from and to the hippocampus and amygdala (Grace, 2000), aberrant neural responses to target detection and contextual representation, as well as impaired memory encoding may be mediated via these interconnected neurophysiological pathways (Skodzik et al., 2017).

Network mechanisms for symptoms of inattentiveness and hypoarousal (Synthetic Results 5 and 6)

Attention deficit is among the most persistent symptoms of ADHD and may persist even as hyperactivity declines with age (Faraone et al., 2006). This dissociation between the two core symptom domains gives rise to two hypotheses from a brain science perspective: First, inattention and hyperactivity are likely mediated by distinct network mechanisms. Second, the neural underpinnings of inattention appear to be multifactorial and distributed, whereas those underlying hyperactivity may be more circumscribed and unitary in nature.

Hypofrontality—arising from reduced frontal volume, impaired VTA-to-PFC modulation, and dysregulated noradrenergic signaling to the PFC—may compromise the frontoparietal attention network (Ptak et al., 2017, Robertson et al., 2013). The attention system is commonly divided into three functional networks: alerting, orienting, and executive control (Posner and Rothbart, 2007, Fan et al., 2002). The caudate, in interaction with the PFC, is considered essential for executive cognitive processes, including the direction and shifting of attention (Grahn et al., 2008). Recent evidence suggests that the caudate also plays an active role in attention-related visual processing (Herman et al., 2020). This emergent fronto-striatal neuropathology likely disrupts not only attention but also a broader range of cognitive domains (Rubia et al., 2011a, Rubia et al., 2011b, Fuermaier et al., 2017, Kofler et al., 2013, Schweitzer and Sulzer-Azaroff, 1995, Taş Torun et al., 2022). This disproportionate impairment in attention suggests that additional neural

mechanisms may be implicated—most notably, hyperactivity or disinhibition within the NAc, a subcortical hub of the limbic system, and its related limbic structures.

How might the NAc and associated limbic hyperactivity influence attention? First, the cerebral cortex can be broadly divided into two major compartments that support interoceptive and exteroceptive processing, respectively (Lee et al., 2014, Fransson, 2005). The interoceptive compartment is primarily associated with limbic and paralimbic structures, including the DMN. Second, enhanced limbic activity and connectivity may bias attentional resources toward self-referential processing—and possibly toward self-stimulatory behavior—as well as rumination (Nejad et al., 2013). This attentional shift is likely driven by NAc hyperactivity in conjunction with frontoparietal hypofunction in ADHD. Furthermore, the hypersensitive responsivity of the NAc may result in disorganized or non-selective firing in response to low-salience internal or perceptual representations relayed from the hippocampus, amygdala, or mPFC, contributing to distractibility (and hyperactivity, see next session) (Sesack and Grace, 2010, Grace, 2000).

In addition, hypoarousal due to reduced noradrenergic tone may further exacerbate inattention and cognitive inefficiency by disrupting cortical and subcortical computational dynamics (Breton-Provencher et al., 2021, Arnsten, 2011, McCormick et al., 1991). Similar to the distinction between tonic and phasic dopaminergic transmission, NE also exhibits dual signaling modes: tonic levels correspond to baseline arousal, whereas phasic activity reflects transient arousal responses, as indicated by electrodermal measures and LC firing patterns (Boucsein, 2012, Devilbiss and Waterhouse, 2011). The NE system also forms bi-directional autoregulatory loops with the PFC, mirroring similar architecture in the DA counterpart. Analogous to the dopaminergic abnormalities described above, ADHD may involve a comparable dissociation in the NE system—reduced tonic arousal alongside aberrant phasic responses—contributing to both diminished baseline activation and increased intra-individual fluctuation/variability, ultimately leading to impaired state regulation and inattentiveness to relevant stimuli (Du Rietz et al., 2019, Souroulla et al., 2019).

Network mechanisms for core symptom hyperactivity and impulsivity (Synthetic Results 7 and 8)

Traditional animal models have often equated increased locomotor activity with hyperactivity in ADHD (García Murillo et al., 2015, Pandolfo et al., 2007). Some of these models showed that elevating DA level enhances movement, primarily by engaging motor-related circuits within the brainstem and mesencephalon (such as VTA) (Ryczko and Dubuc, 2017, Wang et al., 2023, Juárez Tello et al., 2024, Boekhoudt et al., 2016). However, this pattern contrasts with clinical findings in ADHD, where increasing DA transmission—such as through MPH administration—can reduce hyperactivity. This discrepancy strongly suggests that the neural mechanisms underlying hyperactivity in ADHD are distinct from, and situated outside, those commonly reported to mediate ambulatory locomotion. Other animal research has provided compelling evidence that direct stimulation of the NAc can enhance behavioral output across diverse contexts, including operant performance and spontaneous movement (Bichot et al., 2011, Attachaipanich et al., 2023). These findings suggest that a disinhibited or selectively activated NAc—without markedly elevating dopaminergic transmission, or possibly through excitatory inputs from the ventral subiculum (Bardgett and Henry, 1999)—may be sufficient to generate hyperactivity.

As discussed above, compared to the core symptom of inattention, hyperactivity appears to stem from relatively simpler neural mechanisms. Consistent with this view, the effect size of symptom reduction in response to MPH is greater for hyperactivity/impulsivity than for inattention (Vertessen et al., 2024). Integrating circuit-level models and clinical evidence, dysfunction of the NAc—subsequent to dysregulated dopaminergic transmission—emerges as a key substrate underlying hyperactivity/impulsivity. Approximately 90–95% of neurons in the striatum, including NAc, are GABAergic (not dopaminergic) medium spiny projection neurons (Meredith, 1999, Gerfen and Surmeier, 2011). The NAc, although anatomically part of the limbic system, is widely acknowledged as a key limbic–motor interface that integrates affective, contextual, motive information and transforms it into motor-related processes (Sesack and Grace, 2010, Groenewegen and Trimble, 2007). Through its interactions with the PFC and VTA (Grace, 2016, Carr and Sesack, 2000, Floresco et al., 2003, Goto and Grace, 2005), the NAc may become increasingly sensitized and disinhibited in

the milieu of hypodopaminergism—a state that likely contributes to the behavioral phenotype of hyperactivity and impulsivity in ADHD. Notably, the ventral subiculum–NAc and mPFC–NAc pathways converge on the NAc and compete for control over behavioral output: the former promotes the maintenance of learned behaviors, while the latter facilitates switching to novel associations. In a state of low tonic DA, as observed in ADHD, this balance shifts toward mPFC-driven switching, producing a bias for change over stability (Goto and Grace, 2008). Such a neural bias may also underlie the symptoms of hyperactivity/impulsivity, as the NAc-centered network becomes increasingly biased toward driving novelty-seeking rather than supporting behavioral consistency. Specialized circuit architectures link NAc output to the motor system, as discussed below.

The output of the NAc reaches not only the ventral pallidum and the medial part of the globus pallidus, but also the substantia nigra (see Figure 2 in (Groenewegen and Trimble, 2007)). This organization provides a venue through which the mesocorticolimbic system can modulate the nigrostriatal system, placing the NAc in a position to influence dopaminergic input to other parts of the striatum and, consequently, making it well-situated to account for motor-related abnormalities observed in ADHD. Building on this organization, a spiraling arrangement of the striatonigrostriatal system has been described in primates (Haber et al., 2000). In this architecture, ventral regions of the striatum project to medial dopaminergic cell groups, which not only send feedback to the same ventral area but also forward projections to more dorsal striatal regions. This shift in connectivity recurs along the ventromedial-to-dorsolateral axis, progressively engaging more dorsal striatal territories and increasingly lateral dopaminergic populations in the substantia nigra. In ADHD, abnormal activity in the NAc may hence perturb dopaminergic modulation from the substantia nigra to motor circuits. The spiraling, bidirectional striato-nigro-striatal pathways enable disinhibited NAc activity to propagate within the nigrostriatal system, transforming these disruptions into hyperactivity observed in motor behavior. On this basis, structural and functional deviations in the basal ganglia per se may further accentuate the core symptom of hyperactivity in ADHD (Brieber et al., 2007, Nakao et al., 2011). Based on the proposed model, aberrations in PFC-to-subcortical projections may serve as the primary causal mechanism, with downstream changes in the NAc circuits being secondary. Notably, this framework aligns with statistical evidence suggesting that inattention drives hyperactivity and impulsivity in ADHD (Sokolova et al., 2016).

Although the two-factor model of ADHD has been widely accepted and adopted by the DSM-5 (American Psychiatric Association, 2013), emerging evidence supports a three-factor model that distinguishes hyperactivity and impulsivity as separable dimensions (Panagiotidi et al., 2023). Conceptually, while hyperactivity and impulsivity often co-occur and share overlapping behavioral features—such as increased motor activity and poor regulation of action—they also possess dissociable characteristics. The unique aspect of impulsivity lies in its association with inhibitory control failure, whereas hyperactivity primarily reflects excessive, non-goal-directed motor output. From a brain science perspective, inhibitory control engages specialized neural substrates that are frequently compromised in ADHD, particularly within the inferior frontal cortex (and neighboring lateral OFC) (Chevrier et al., 2007, Rae et al., 2015). Correspondently, neuromodulation techniques targeting the inferior frontal cortex are gaining attention as adjunctive, non-pharmacological treatment strategies for ADHD (Breitling et al., 2016).

Beyond the key role of the inferior frontal cortex, subcortical structures such as the caudate nucleus—also impaired in ADHD—contribute to inhibitory control via cortico-striatal circuits (Peterson et al., 2002, Booth et al., 2003). Alongside dopaminergic input, neuroanatomical evidence highlights that the NAc shell receives substantial noradrenergic innervation (Berridge et al., 1997, Groenewegen and Trimble, 2007). Enhancing NE signaling in this region has been shown to significantly reduce impulsive responding in the five-choice serial reaction time task, supporting the notion that diminished noradrenergic tone in the NAc shell may also contribute to heightened impulsivity in ADHD (Economidou et al., 2012). Thus, impulsivity is likely shaped by multiple interacting factors.

Mechanisms of pharmaceutical treatments (Synthetic Result 9)

MPH, a DAT blocker and the first-line pharmacological option for ADHD, may relieve symptoms by restoring extracellular tonic DA levels and consequently reducing the hypersensitivity of the NAc and aberrant phasic DA signaling (Floresco et al., 2001, Polter and Kauer, 2014, Grace, 1991, Grace, 1995, Floresco et al., 2003, Goto and Grace, 2005). MPH administration has also been shown to elevate DA concentrations in the PFC and caudate, thereby improving related cognitive deficits (Mininni et al., 2018, Strafella et al., 2001, Chéramy et al., 1986). Enhanced PFC function may, in turn, reverse NAc disinhibition via increased GABAergic transmission from the VTA to NAc (Carr and Sesack, 2000). Although MPH is less selective for blocking NE transporter than atomoxetine (Pliszka, 2005), it also increases NE levels, which may contribute to its therapeutic efficacy. By regularizing the phasic firing of DA and NE neurons, MPH may reduce abnormally high intra-individual variability in reaction time, as observed across tasks such as the Continuous Performance Test, Go/No-Go, Stop-Signal, Attention Network, and N-back tasks (Fredriksen et al., 2021, Epstein et al., 2011). However, due to underlying developmental abnormalities, functional restoration is often incomplete (Konrad et al., 2007). Notably, MPH has also been shown to improve sustained attention in low-performing individuals without ADHD (del Campo et al., 2013), underscoring the critical role of DA in cognitive regulation. In contrast, cognitive impairments less responsive to MPH may stem from structural alterations, such as reduced cortical volume or abnormalities within the nigrostriatal system—particularly the caudate nucleus (Herman et al., 2020, Grahn et al., 2008).

Concordant with clinical improvement, various aberrant neural metrics in ADHD can be normalized by psychostimulants across a wide range of cognitive tasks. Brain regions showing robust responses to MPH include the middle and inferior frontal gyri, basal ganglia, and cerebellum, with the frontal gyri particularly engaged during inhibitory control tasks (Czerniak et al., 2013). Underactivation in fronto-striatal and fronto-cingulate circuits— respectively associated with interference inhibition and error processing—has been shown to improve with treatment (Rubia et al., 2011a, Rubia et al., 2011b). Post-imperative negative variation, considered an index of uncertainty, exhibits increased negativity over the ventrolateral prefrontal cortex in children with ADHD, a deviation that appears responsive to stimulant intervention (Werner et al., 2011). Psychostimulants have also been reported to modulate functional connectivity in networks supporting verbal working memory (Wu et al., 2017), as well as to correct fronto-parieto-cerebellar abnormalities observed during the resting state (An et al., 2013).

A potential pharmacological benefit of MPH lies in its indirect neurotrophic effects (Küppers and Beyer, 2001, Williams and Undieh, 2009, Iwakura et al., 2011, Roceri et al., 2001), which remain insufficiently addressed in the current literature. Although midbrain dopaminergic neurons are often categorized into nigrostriatal and mesocorticolimbic groups, this binary classification overlooks important anatomical and functional complexities. For instance, the substantia nigra not only projects to the striatum but also sends distinct fiber subsets directly to cortical areas (Björklund and Dunnett, 2007). Several converging lines of evidence support the potential neurotrophic role of dopamine. First, hypodopaminergicism in ADHD has been linked to regional gray matter volume reductions, particularly in the frontal and temporal lobes, as well as in subcortical structures such as the caudate and thalamus (McAlonan et al., 2007, Jagger-Rickels et al., 2018). The thalamus is especially relevant given its substantial dopaminergic innervation, as demonstrated in primate immunolabeling studies (Melchitzky et al., 2006, Sánchez-González et al., 2005). Second, meta-analyses indicate that brain structural alterations are more pronounced in medication-naïve individuals, and that MPH treatment may exert protective or restorative effects on brain morphology (Frodl and Skokauskas, 2012). These findings have been replicated across diverse brain regions in both human and animal studies (Tebartz van Elst et al., 2016, van der Marel et al., 2014). Third, degeneration of the substantia nigra in Parkinson's disease is accompanied by reductions in both cortical and subcortical gray matter volume, suggesting that midbrain dopaminergic loss has widespread neuroanatomical consequences beyond the basal ganglia (Moradi et al., 2024, Gerrits et al., 2016). Fourth, preliminary evidence suggests that levodopa treatment may increase cortical thickness in patients with Parkinson's disease (Cerasa et al., 2013). Although the use of psychostimulants in ADHD has previously raised concerns, their potential long-term benefits on brain structure warrant renewed attention, given the possible positive clinical implications.

Comorbidity with other neuropsychiatric disorders (Synthetic Results 10 and 11)

Because of the anatomical proximity and developmental interrelation between the VTA and substantia nigra—the two principal sources of midbrain DA—the disrupted descending PFC-to-VTA projections (i.e., ventral fronto-striatal circuit) may be extended to involve the dorsal striatum and nigrostriatal system. Namely, developmental miswiring from the frontal cortex to the dorsal striatum may compromise the integrity of motor control loops and contribute to motor-related symptoms commonly observed in ADHD. Approximately 20% of affected children meet criteria for comorbid tic disorders (Wanderer et al., 2021, Rothenberger and Heinrich, 2022), and many exhibit subtle impairments in gross and fine motor control (Piek et al., 1999). These symptoms implicate dysfunctional dorsal fronto-striatal and/or nigrostriatal circuitry. Reinforcing this connection, longitudinal evidence indicates that individuals with ADHD have a 33% higher risk of developing Parkinson's disease, with an earlier age of onset compared to the general population (Becker et al., 2021, Radomyslsky et al., 2025). Although tau and α -synuclein functionally cooperate during corticogenesis and contribute positively to early brain development (Wang et al., 2022), they are also central to the pathogenesis of neurodegenerative diseases such as Parkinson's disease. However, their potential involvement in Lewy body pathogenesis in individuals with developmental disorders such as ADHD remains unclear. Given that DA neurons in the substantia nigra outnumber those in the VTA by approximately three- to seven-fold—depending on the estimation method—this cellular asymmetry may partly account for the delayed emergence of nigrostriatal hypodopaminergism if it occurs later in life (Basso et al., 2024).

Importantly, the comorbidity of ADHD in individuals with tic disorders has been reported to range from 50 to 60% (Gunturu et al., 2025, Ogundele and Ayyash, 2018), which is substantially higher than the prevalence of tic disorders in individuals with ADHD. This asymmetry in comorbidity not only suggests shared neuropathogenic mechanisms but also supports the notion that the mesocorticolimbic pathways are more susceptible to developmental disruptions than the dorsal striatal analog (see Part I in **Results**). As noted earlier, dopaminergic abnormalities within the caudate nucleus and putamen have also been documented in ADHD (Krause et al., 2000, Spencer et al., 2007, Badgaiyan et al., 2015).

Previous research has shown that excitation of the human PFC can elicit DA release in the caudate nucleus (Strafella et al., 2001). Unlike putamen that mainly received motor-related afferents, frontal inputs to caudate comprise dorsolateral PFC and lateral OFC (Grahm et al., 2008). This effect may be mediated by excitatory corticostriatal projections, whereby glutamate release locally facilitates DA release from adjacent nigrostriatal terminals (Chéramy et al., 1986). Accordingly, hypofrontality itself may also contribute to the reduced DA signaling observed in PET studies of the caudate (Volkow et al., 2007, Volkow et al., 2009). In contrast, enhanced DAT expression has been observed in the striatum (Spencer et al., 2007, Dougherty et al., 1999, Krause et al., 2000). Antipsychotics—pharmacologically antagonistic to MPH—have frequently been the treatment of choice for tic disorders (Weisman et al., 2013). Taken together, these findings suggest that both hyper- and hypo-dopaminergic transmissions may co-exist within the nigrostriatal system in ADHD, paralleling similar patterns observed in the ventral striatum—an intriguing correspondence that lies beyond the scope of the present review. An aberrant dorsal PFC-striatal descending pathway may contribute to the emergence of tics, while dysregulated projections from the VTA to the substantia nigra may affect motor coordination in ADHD (Watabe-Uchida et al., 2012, Ferreira et al., 2008). This notion is endorsed by recent findings showing that MPH treatment may improve motor coordination (Kim et al., 2025). These observations support the proposed model, which posits parallel yet functionally dissociable disruptions in the ventral and dorsal fronto-striatal circuits. Under this framework of descending PFC-subcortical developmental disturbance, abnormalities in both systems arise concurrently. Therefore, although dorsal striatal changes may co-occur and correlate with ADHD symptomatology in imaging studies (e.g., PET or volumetry) (Volkow et al., 2007), such associations should not be misconstrued as evidence of primary causality.

Given that the core neuropathology of ADHD centers on the PFC–VTA–NAc axis, one could argue that the pathological directionality originates instead from VTA-to-PFC projections. However, under the framework of dialectical neuroscience, assigning primary etiology to VTA-to-PFC dysfunction is less tenable,

as it fails to account for comorbid alterations involving dorsal striatal circuits (the criteria of accountability). Taken together, these findings indicate that the neuropathology of ADHD may involve not only the mesocorticolimbic pathways, but also the dorsal striatal system. The developmental disruption of descending PFC-subcortical projections may interact with the intrinsic properties of these two circuits, leading to both shared and distinct consequences that jointly contribute to the complex clinical presentation of ADHD.

In addition to the neurological symptoms discussed above, ADHD is frequently accompanied by psychiatric comorbidities. Commonly reported conditions include major depression (3 to 4 times higher prevalence) (McIntosh et al., 2009), bipolar disorder (4 to 8 times higher) (Schiweck et al., 2021), and autism spectrum disorder. These comorbidities may be interpreted through their respective updated neuropathological frameworks. Major depression, often presenting with emotion dysregulation, can be accounted for by a network imbalance between frontoparietal and limbic systems—originated from hypofrontality and limbic hyperactivity in ADHD (Lee and Xue, 2018a, Lee, 2025a). The VTA, proposed as a central pathological locus in bipolar disorder (Lee and Xue, 2017, Lee, 2025d), may underlie the comorbidity between bipolar disorder and ADHD through maladaptive interactions among distinct neuronal subpopulations within the VTA (Floresco et al., 2001, Polter and Kauer, 2014).

It is estimated that 50% to 70% of individuals with autism spectrum disorder also present with comorbid ADHD—approximately twice the prevalence observed in the reverse direction (Hours et al., 2022). Although a consensus on the precise comorbidity rates has not yet been reached, this pattern is broadly consistent with the view that autism represents a more severe developmental condition than ADHD. A left frontal developmental deviation has recently been proposed as a potential core neuropathology of autism, which may disrupt PFC-to-VTA projections and thereby contribute to comorbid ADHD (Lee, 2025c). While the commonality and uniqueness of psychiatric comorbidities in ADHD warrant further investigation, current mechanistic understandings seem to offer primary and face-valid insights into their underlying basis.

Additional phenomena that may be accommodated by the PFC-to-subcortical model

Several clinical and neuroscientific observations may be preliminarily accounted for by the proposed model, thereby lending it additional credibility. A well-documented gender bias exists in ADHD, with a male-to-female ratio of approximately 2.3–4:1 (Martin et al., 2024, Ramtekka et al., 2010). This disparity may be partly attributed to sex hormone–regulated synaptic remodeling, as males typically undergo more extensive pruning during development (De Bellis et al., 2001). As detailed in Part I of the **Results**, the early developmental period is characterized by an abundance of redundant neural pathways, which may temporarily offset or even rectify initial circuit abnormalities. However, with the onset of large-scale synaptic pruning, this compensatory capacity declines, along with the collateral pathways that could otherwise enable misrouted projections to reach their intended targets. This mechanism may help explain the male predominance in ADHD, and observed sex-related differences in connectivity are consistent with this account (Rosch et al., 2018).

Some individuals with ADHD exhibit sensory over-responsivity and reduced pain thresholds (Lane et al., 2010), which may be partially normalized by MPH treatment (Treister et al., 2015). Recent animal data suggested that enhanced dopaminergic transmission in limbic circuits can attenuate mechanical hypersensitivity under neuropathic pain conditions (Huang et al., 2020). The hypodopaminergic state in the VTA–NAc–limbic network, along with the observed relief of sensory abnormalities following MPH treatment, appears consistent with findings from animal studies. Collectively, these findings indicate that sensory symptoms in ADHD likely stem from dopaminergic dysregulation within the limbic system, rather than from primary sensory deficits. The prominent feature of heightened response variability may also be accounted for by the proposed model, as previously discussed in the sections *The Neural Consequence of Deviant Descending Frontal-Subcortical Projections During Development* and *Mechanisms of Pharmacological Treatments*. Moreover, as discussed above, hyperactivity, impulsivity, and inattentiveness share overlapping yet distinct neural circuitries, providing a preliminary explanation for the three clinical subtypes of ADHD within a unified disease framework.

Conclusion

It is widely recognized that psychiatric disorders leave discernible signatures at the level of large-scale brain networks. Brain science offers the most feasible vantage point for uncovering their underlying mechanisms, as the combined effects of diverse neurobiological underpinnings, nature and nurture, ultimately converge into brain architecture and dynamics. While fronto-striatal abnormalities have long been associated with ADHD, the present work proposes that descending PFC-subcortical developmental aberrations may underlie its pathogenesis—an account grounded in the framework of dialectical neuroscience. This parsimonious model is not only physiologically plausible but also offers a coherent explanation for the observed clinical symptoms, functional impairments, and structural changes. Although statistics are formalized conceptually, the dialectical framework resonates with the logic of model selection and posterior inference, akin to Bayesian reasoning, in which cross-domain explanatory power serves as a key criterion for theoretical validity. Such synthesis serves not as an endpoint but as a foundation for generating new predictions and directing future research along more principled trajectories. As previously outlined (Lee, 2025b), the next essential step is empirical validation. A key challenge lies in establishing directional inferences and characterizing its interaction effects centered on the NAs—critical gaps that previous research has yet to address. Based on the model, two predictions follow: First, the influence from the PFC to subcortical nuclei is weakened. Second, an interaction effect (ADHD vs. neurotypical controls $\times$ PFC-to-NAc vs. NAc-to-PFC) is expected to be reflected in directional neural metrics.

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Figure Legends

Figure 1. Developmental trajectories of reciprocal PFC–VTA connectivity and the impact of miswiring and pruning.

Left panel: Normal reciprocal connections are established between PFC and VTA neurons—P1 connects bidirectionally with V1, and P2 with V2.

Middle panel: Miswiring scenario—V1 projects correctly to P1, but P1 fails to form a reciprocal connection back to V1. During early development, redundant collateral pathways still allow access to V1.

Right panel: After developmental pruning removes these early-stage redundant branches, the alternative route from P1 to V1 is lost, resulting in a permanent lack of reciprocal connectivity.



Asymmetrical frontal–subcortical aberrations in ADHD: evidence for a developmental network model

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Abstract

This study empirically tests a theoretical model of ADHD that identifies aberrant frontal-to-subcortical projections—particularly those involving the ventral tegmental area and, consequently, the nucleus accumbens (NAc)—as a core neurobiological vulnerability. The model predicts reduced frontal influence on subcortical structures and group-by-direction interaction effects, especially at the NAc. Structural and resting-state fMRI data from sixty individuals with ADHD and sixty healthy controls were selected from the ADHD-200 dataset. The cortex was parcellated using MOSI (Modular Analysis and Similarity Measurements). The mean amplitude of low-frequency fluctuations (ALFF) and the mean time series were extracted for each frontal node. Subcortical nuclei—including the caudate, putamen, globus pallidus, NAc, and thalamus—were included in the analyses, with each voxel treated as a neural node. Correlation analyses were performed to examine the relationship between nodal power (ALFF) and nodal strength. Directional metrics were defined as frontal-to-subcortical (F2S) and subcortical-to-frontal (S2F) correlations between nodal strength and nodal power. Group differences and interactions were tested using t-tests and linear mixed-effects (LME) models. Correlation and LME analyses revealed a consistent bimodal pattern, with positive F2S and negative S2F associations across all subcortical nuclei, suggesting a directional excitation–inhibition balance. Reduced F2S slopes in ADHD and a significant group-by-direction interaction in the NAc ($p=0.009$) supported model predictions. These findings are consistent with the proposed developmental model.

Keywords Attention-deficit/hyperactivity disorder (ADHD) · Basal ganglia · Dialectic neuroscience · Frontal cortex (FCX) · Functional MRI (fMRI) · Nucleus Accumbens (NAc)

Introduction

Attention-deficit/hyperactivity disorder (ADHD) ranks among the most common neurodevelopmental conditions, with an estimated prevalence of approximately 6% in children and adolescents and 2.5% in adults [3, 76]. Clinically, ADHD is categorized into three primary subtypes: predominantly inattentive, predominantly hyperactive/impulsive, and combined presentation. In addition to the core symptoms, affected individuals commonly exhibit a broader range of neurocognitive and emotional disturbances. These may include executive dysfunction, emotion dysregulation,

difficulties with planning and organization, impaired impulse control, problems in social interaction, hypoarousal, heightened response time variability, and altered reward sensitivity, which together shape the broader clinical picture [4, 5, 9, 24, 25, 33, 40, 65, 68, 72]. A wide spectrum of psychiatric and neurological comorbidities has also been documented, including tic disorders, anxiety, depression, bipolar disorder, autism spectrum disorder, and, in some cases, an increased risk of Parkinson's disease later in life [39, 53, 59, 63]. Although the formal diagnostic threshold requires symptom onset before age 12, early behavioral signs—such as excessive motor activity, poor sustained attention, and impulsivity—can often be detected during the preschool years, typically between ages 2 and 5. Rather than emerging abruptly, these symptoms usually unfold gradually over the course of development [26].

Consistent with its heterogeneous clinical manifestations, ADHD is associated with widespread neural abnormalities spanning both the dorsal and ventral fronto-striatal

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circuits, limbic structures, and deep brain nuclei—most notably the ventral tegmental area (VTA) and locus coeruleus (LC), which serve as central hubs for dopaminergic and noradrenergic signaling, respectively [10, 11, 13, 15, 17, 18, 20, 22, 27, 28, 32, 51, 55, 57, 62, 64, 70, 73, 74]. While complexity is intrinsic to nearly all psychiatric conditions, dialectic neuroscience—an approach grounded in centralized dialectics—offers a framework for developing integrative theories of psychopathology [43]. This approach has been applied to major depressive disorder, bipolar disorder, and autism spectrum disorder [49, 50], with theoretical models subsequently supported by empirical findings [42, 44, 45]. In the case of ADHD, a candidate theory has recently emerged, positing that aberrant frontal-to-subcortical projections during development constitute a core neurobiological vulnerability (briefly outlined below), offering a unifying framework to reconcile a wide range of seemingly disparate or conflicting findings [41]. The present study aims to empirically evaluate this theoretical account.

Aberrant frontal-to-subcortical projections may initiate a cascade of network-level dysregulations, with the VTA and nucleus accumbens (NAc) highlighted as central foci of neuropathological disruption in ADHD. The involvement of mesocortical and mesolimbic dopaminergic pathways in ADHD is supported by the well-documented therapeutic effects of central stimulants, which enhance dopaminergic signaling by inhibiting dopamine reuptake. Hypoactive glutamatergic signaling from the frontal cortex (FCX) to the VTA may suppress tonic dopamine (DA) levels through mesocorticolimbic circuits, compromise dopaminergic feedback to the FCX, and aggravate hypofrontality [30, 58]. Attenuated frontal input may also lead to sensitization and disinhibition of the NAc [31, 34]. In parallel, reduced tonic DA release from the VTA may enhance phasic responsivity reflected in the NAc [35, 36], collectively contributing to aberrant reward processing and limbic hyperactivity. The latter may further accentuate hypofrontality via reciprocal inhibitory mechanisms between the frontoparietal and limbic systems [42, 50]. A similar dysregulation may affect the dorsal fronto-striatal pathway, as reflected in structural and functional abnormalities in the caudate and putamen [11, 15, 51, 55, 57]. To empirically test the model, it is essential to establish directional inferences—both frontal-to-subcortical (F2S) and subcortical-to-frontal (S2F), with specific emphasis on the NAc. Two predictions were proposed in the previous article [41]: first, the influence from the FCX to subcortical nuclei is weakened in ADHD; second, a group-by-direction interaction should be observable in directional neural metrics centered on the NAc. The first prediction follows directly from the proposed weakening of frontal-to-subcortical projections, which serves as an indirect systems-level indicator of aberrant FCX-to-VTA white

matter connections. The second prediction is grounded in the physiological consequences of reduced tonic dopaminergic activity and the consequent enhancement of phasic responsivity in the NAc, as described above. Enhanced phasic reactivity in the NAc is expected to strengthen FCX-to-NAc signaling (i.e., a more positive F2S slope) and, reciprocally, NAc-to-FCX influence (i.e., a more negative S2F slope), thereby producing a group-by-direction interaction. Importantly, this dynamic bidirectional enhancement may coexist with—and be further complicated by—an overall attenuation of FCX-to-NAc drive due to reduced frontal input efficiency.

Resting-state functional magnetic resonance imaging (rsfMRI) data from the public ADHD-200 dataset will be used to test the proposed hypotheses [16], where causality analysis is essential for this purpose. While correlation is inherently unidirectional, recent research suggests that in cross-modal contexts, certain causal inferences are still feasible [48]. This approach has been employed in major depressive disorder to assess the hypothesis of compartment-level mutual suppression [42]. Specifically, nodal strength (i.e., the total functional connectivity [FC] of a node) appears to influence nodal power (i.e., ALFF), but not vice versa. Following prior studies, two directional metrics were used to characterize the relationship between nodal strength and nodal power within the frontal-subcortical network. Subcortical nuclei were incorporated based on the canonical fronto-striato-thalamo-cortical loops [1, 37], which encompass the caudate (Cau), nucleus accumbens (NAc), globus pallidus (Pal), putamen (Put), and thalamus (Tha), see Fig. 1. The “F2S” index refers to the association between frontal-to-subcortical nodal strength and subcortical ALFF, whereas “S2F” captures the reverse—subcortical-to-frontal nodal strength versus frontal ALFF. Functional parcellation of the cortex will be performed using MOSI (Modular Analysis and Similarity Measurements) [47]. The core neuropathology of ADHD is expected to emerge in reduced F2S index and through a two-way interaction effect, reflecting slope differences between F2S and S2F across ADHD and healthy control (HC) groups (ADHD vs. HC $\times$ FCX-to-NAc vs. NAc-to-FCX).

Materials and methods

MRI datasets and preprocessing

Data from 120 participants (60 with ADHD and 60 HC) were obtained from the ADHD-200 dataset (New York University Child Study Center) [6, 16], with written informed consent provided by all individuals. At the time of data acquisition, 77 combined-type ADHD individuals were available in the

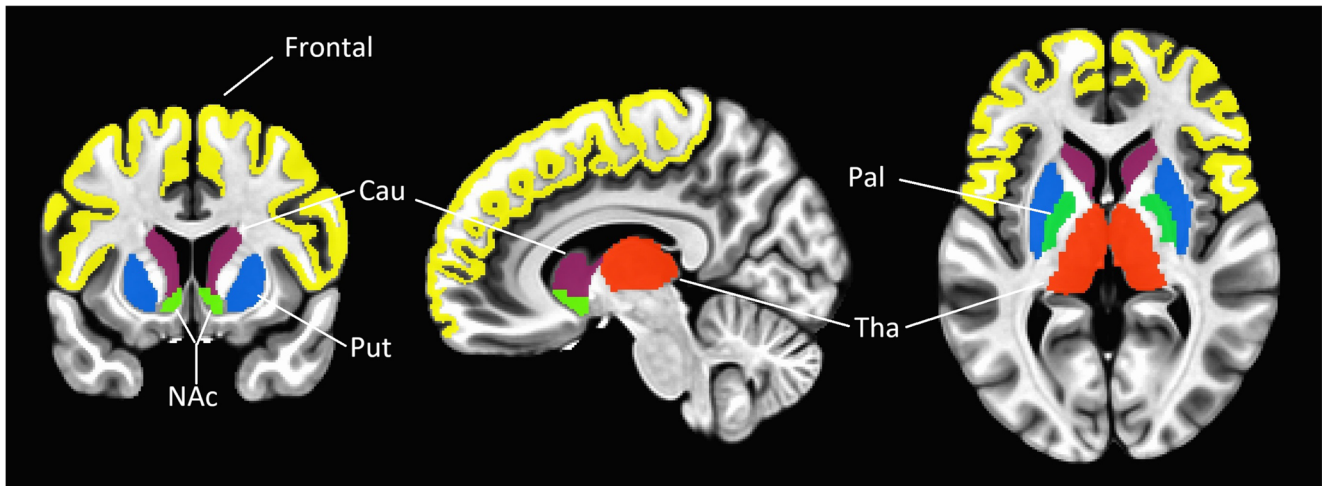


Fig. 1 An illustration of the frontal lobe and subcortical nuclei—Cau (caudate), NAc (nucleus accumbens), Pal (globus pallidus), Put (putamen), and Tha (thalamus), each highlighted in a distinct color

early release of the dataset. From this pool, 60 participants were retained based on data completeness, imaging quality, and compatibility with the analytic framework, in line with typical sample sizes reported in prior resting-state fMRI studies using similar methods [42]. Szucs and Ioannidis showed that the majority of highly cited fMRI studies employed considerably smaller samples, indicating that the present sample size represents a relatively well-powered dataset for hypothesis-driven analyses [71]. The functional and structural MRI images of the entire brain were recorded using 3.0 Tesla Siemens MRI machine (fMRI: TR=2s, TE=15ms, Flip Angle=90°, voxel size=3×3×4 mm³, 33 slices, 170 volumes).

rsfMRI preprocessing was performed using AFNI [19]. Steps included despiking, slice timing correction, motion realignment, coregistration to structural T1 images, spatial smoothing with a 6 mm FWHM kernel, and temporal bandpass filtering (0.01–0.1 Hz) via the 1dPort function, which generates sinusoidal regressors for frequency isolation. The first four volumes were discarded to ensure magnetization stabilization. Head motion was controlled using a multi-step procedure consistent with current resting-state fMRI recommendations. First, volumes with framewise displacement > 0.20 mm or with more than 10% outlier voxels were censored (scrubbing) prior to model estimation. Outlier voxels were identified using standard AFNI-based procedures. Second, 12 motion-related regressors were included in the nuisance model, comprising the six rigid-body motion parameters and their first temporal derivatives. This approach reduces residual motion-related variance beyond censoring alone. T1-weighted anatomical images were processed with FreeSurfer to segment gray and white matter and to parcellate the cortex into 68 regions (34 per hemisphere) based on the Desikan-Killiany atlas ([https://](https://surfer.nmr.mgh.harvard.edu/fswiki/CorticalParcellation)

surfer.nmr.mgh.harvard.edu/fswiki/CorticalParcellation) [21, 23, 29]. These anatomical parcels served as seeds for subsequent MOSI-based parcellation. In line with previous pipelines [46, 77], nuisance variables—including 12 motion parameters, white matter, and CSF signals—were regressed out. A second-order polynomial was also fitted to model baseline drift. ALFF was calculated as the square root of signal power within the bandpass-filtered EPI data.

ALFF, Functional connectivity and MOSI analysis

ALFF reflects spontaneous neural activity by quantifying the amplitude of low-frequency fluctuations in the resting-state BOLD signal, computed as the square root of power within the band-pass filtered spectrum. Due to the small size and internal heterogeneity of subcortical nuclei, along with the absence of standardized partition in rsfMRI studies, no further parcellation was applied to these subcortical regions. Consequently, MOSI-based parcellation was restricted to the cortical areas. In other words, the neural node is defined as a voxel within subcortical nuclei, whereas in the FCX, a neural node corresponds to a MOSI-partitioned module (cluster). FC was measured via Fisher-transformed Pearson correlation coefficients, calculated between voxel-wise time series in subcortical areas and cluster-averaged time series in the FCX. Mean nodal strength was defined as the total FC centered on each subcortical voxel or frontal module.

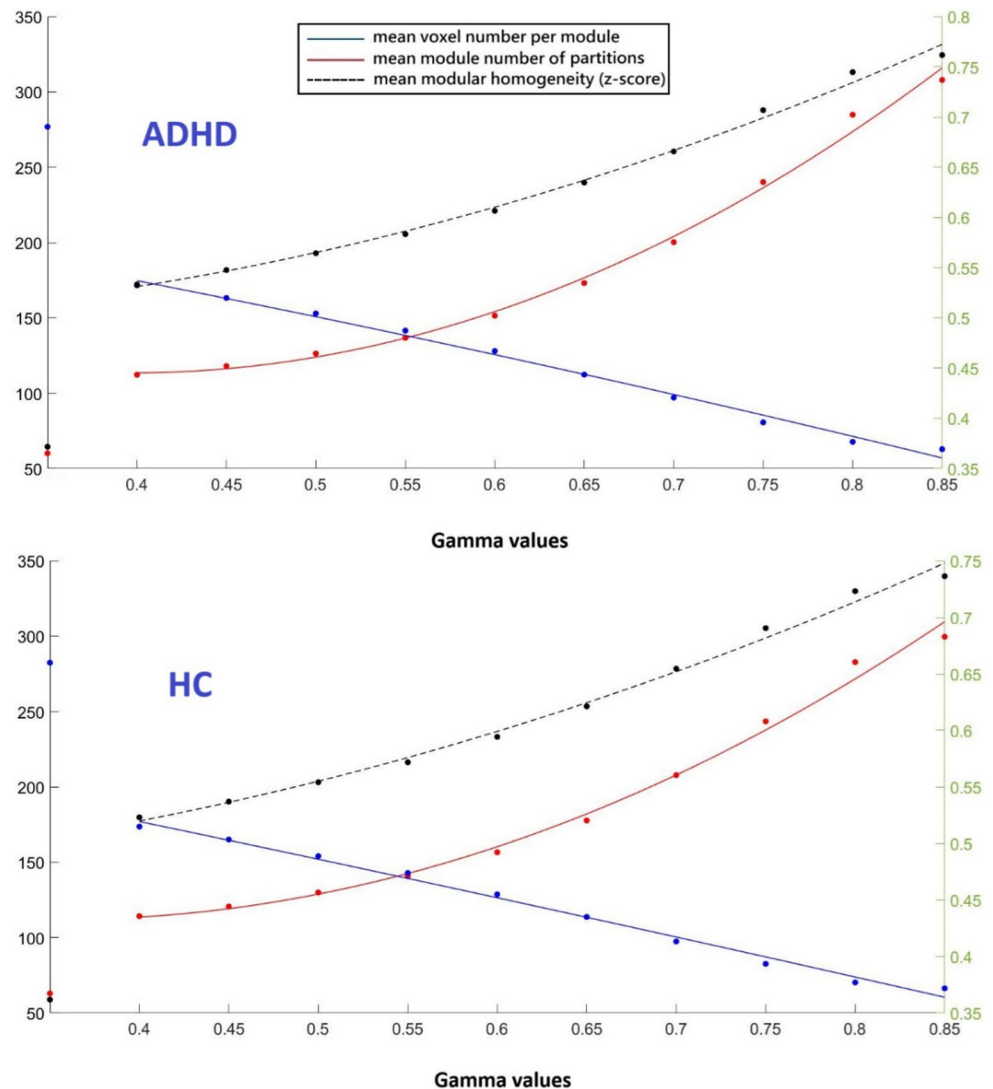
The FC-derived connectivity matrix served as the input for MOSI, a cortical parcellation framework combining modular decomposition and similarity-based aggregation [47]. The method iteratively partitions the cortex by first identifying local functional modules via community detection—implemented using the Louvain algorithm [7, 60]—and subsequently merging spatially contiguous modules

exhibiting high functional similarity. This procedure continues until the parcellation stabilizes. In summary, MOSI is governed by two principles: spatial adjacency and functional coherence, ensuring that neighboring voxels with similar time series are grouped together—an essential premise of functional parcellation. Voxels forming isolated modules of fewer than five were discarded to minimize the influence of spurious noise. The granularity of the final parcellation is adjustable via the resolution parameter gamma, which controls the number of resultant modules. Higher gamma values yield finer partitions. MOSI's performance was evaluated through intra-module homogeneity and benchmarked against standard atlas-based schemes (see **Results**). MOSI was adopted instead of a conventional atlas-based parcellation because it defines neural nodes according to intrinsic similarity in BOLD dynamics, grouping voxels with coherent temporal profiles into functional units. This data-driven strategy yields partitions with significantly higher intra-module homogeneity compared with atlas-informed

schemes (Fig. 2), indicating improved functional coherence. Importantly, MOSI generates subject-specific partitions, thereby accommodating individual variability in functional organization. This feature is particularly relevant for ADHD, a condition characterized by substantial heterogeneity in network architecture, where imposing a fixed anatomical partition may leave individual differences unaccounted for and obscure system-level core neuropathology.

While the full MOSI procedure was initially conducted across a broad gamma range (0.40 to 0.85), consistent with prior work involving whole-cortex partitioning (note: only the FCX was examined in this study) [42], further constraints were required for the formal analysis. Given that correlation analyses require a minimum of 30 data points for stable and interpretable estimates [8], the selection of modular resolution was accordingly limited. Empirically, a gamma value of 0.70 yielded an average of approximately 38 modules within the FCX for both ADHD and control groups. Therefore, only gamma values ≥ 0.70 (i.e., 0.70, 0.75, 0.80, 0.85)

Fig. 2 Scatter plots showing three metrics derived from the ADHD-200 dataset across 10 gamma values (X-axis), with second-order polynomial regression curves overlaid. Each plot contains 10 data points per metric, corresponding to the tested gamma values. The top panel illustrates results for the ADHD group, while the bottom panel shows those for the HC group. The points aligned vertically along the y-axis denote the initial parcellation using the Desikan-Killiany atlas. Red markers and curves represent the mean number of modules (left Y-axis), blue markers and curves indicate the average voxel count per module (left Y-axis), and black markers and curves denote the mean within-module z-score (right Y-axis), reflecting modular homogeneity



were included in the main analysis to ensure adequate statistical power for correlation-based measures.

Formal analysis I—correlation analyses between ALFF and nodal strength

Two types of correlation analyses were conducted to examine the association between ALFF and nodal strength. The first focused on fronto-to-subcortical connectivity, correlating nodal strength from frontal modules—defined by their functional connectivity with subcortical nuclei—with ALFF within subcortical regions, including Cau, NAc, Pal, Put, Tha, and the combined voxel set encompassing all five nuclei (F2S). To account for variability in module size across the FCX, a size-weighted averaging strategy was applied when computing representative (mean) nodal strength. The second analysis reversed the direction, assessing subcortico-to-frontal connectivity. Here, mean ALFF was calculated for each frontal module, and voxel-wise nodal strength of subcortical nuclei—quantifying their aggregate functional connectivity with frontal modules—was computed (S2F). As the subcortical unit of analysis was defined at the voxel level, no additional weighting was required. In summary, for the F2S metric, nodal strength was defined as the weighted sum of functional connectivity between all frontal modules and each individual subcortical voxel; conversely, for the S2F metric, it was defined as the average connectivity between all subcortical voxels and each individual frontal module.

Although correlation itself is non-directional, the association between nodal strength and regional power allows directional interpretation from a physiological standpoint. Nodal strength reflects the aggregate influence of distributed inputs from the rest of the network, whereas regional power indexes local intrinsic activity. It is therefore biologically more plausible that large-scale integrative input constrains local oscillatory amplitude, rather than local power diffusely determining the connectivity strength of all other nodes. Consider the case of a negative correlation. If regional (nodal) power were to exert a diffuse influence on the network in which the node is embedded, this would lead to a logical contradiction: the node with the smallest power would necessarily have the weakest functional connections with the rest of the nodes, which by definition have higher powers. However, given the negative relationship, that same node would be expected to exhibit the highest regional power. This self-refuting indicates that the direction cannot plausibly run from regional power to network connectivity. The same *reductio* applies under the positive correlation condition.

The directional interpretation proposed here is conceptually distinct from Granger causality and dynamic causal

modeling. These methods estimate temporal or model-based causal influences between neural nodes, but they do not permit inference about how large-scale networks interact at the aggregate level—for example, whether network A excites or inhibits network B. The directional influence inferred from the association between nodal strength and nodal power therefore addresses a dimension of network interaction not captured by conventional causal or effective connectivity approaches.

Formal analysis II—linear mixed-effects modeling of ALFF and nodal strength

The author employed a linear mixed-effects model (LME) to investigate how diagnostic group (*Group*: ADHD vs. HC), brain region (*Region*: frontal to subcortical nucleus vs. subcortical to frontal), and mean nodal strength (*d*) contribute to the prediction of mean ALFF (*a*), the dependent variable. Both ALFF and mean nodal strength were normalized using z-score transformation prior to inclusion in the model. The variable *Subject* indexed individual participant, each contributing repeated measurements across both regions. The model included fixed effects for *Group*, *Region*, *d*, and all interactions among them, including the three-way interaction (*Group* × *Region* × *d*). A random intercept was included for each *Subject* to account for within-subject dependencies due to repeated measures. The model was expressed as: $a = \beta_0 + \beta_1 d + \beta_2 \text{Group} + \beta_3 \text{Region} + \beta_4 (d \times \text{Group}) + \beta_5 (d \times \text{Region}) + \beta_6 (\text{Group} \times \text{Region}) + \beta_7 (d \times \text{Group} \times \text{Region}) + u_0[\text{Subject}] + \varepsilon$, where $u_0[\text{Subject}]$ represents the subject-specific random intercept, and ε is the residual error. This model allows each participant to have their own baseline level of ALFF, while estimating group-level and interaction effects assuming a common slope for nodal strength across subjects. The analysis was implemented using the `fitlme` function in MATLAB R2020a (The MathWorks, Natick, MA, USA), with the model specification: $a \sim \text{Group} * \text{Region} * d + (1 | \text{Subject})$.

An alternative, more complex model was considered, which included random slopes for the continuous predictor *b* at the subject level, specified in MATLAB as: $a \sim \text{Group} * \text{Region} * d + (1 + d | \text{Subject})$. This model allows individual subjects to have varying slopes with respect to *b*, capturing subject-specific differences in the effect of *b* on the outcome. However, model comparison based on Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), and log-likelihood favored the simpler model. The simpler model exhibited consistently lower AIC and BIC values and a higher log-likelihood, indicating better overall fit and parsimony (detailed results are presented in Part III of the Supplementary Materials). Given the characteristics of the data—spatially smoothed functional MRI

signals centered on small subcortical structures, where smoothing inherently attenuates local variability—the inclusion of random slopes did not yield meaningful model improvement and increased the risk of overparameterization. The more parsimonious random-intercept specification was therefore retained as the primary analytical framework. Although ADHD is clinically heterogeneous, model comparison indicates that the nodal strength–ALFF coupling is predominantly expressed as a shared architectural alteration. This pattern suggests that phenotypic heterogeneity is more likely to emerge downstream of this network shift rather than from substantial divergence in the coupling slope itself.

A Bonferroni-corrected significance threshold of $p < 0.01$ (i.e., 0.05/5 for the five subcortical nuclei) was applied. Primary inference was based on the minimum p -value across resolutions, given the possibility that effects may be resolution-dependent. For the LME analyses, results obtained under different gamma values were not statistically independent. Accordingly, a representative p -value was calculated using the geometric mean, serving as a descriptive stability index rather than a formal inferential statistic. Specifically, for four gamma values yielding p_1 , p_2 , p_3 , and p_4 , the representative p -value was calculated as $(p_1 \times p_2 \times p_3 \times p_4)^{(1/4)}$.

Results

Demographic characteristics were comparable between the combined type ADHD and HC groups ($n = 60$ each). There was no significant difference in age between groups (ADHD: 10.1 ± 1.4 years; HC: 10.1 ± 1.7 years; $t(118) = 0.0046$, $p = 0.9964$). Gender distribution also did not differ significantly: ADHD group had 42 males and 18 females, while the HC group had 33 males and 27 females. A chi-square test with Yates' correction yielded $\chi^2 = 2.28$, $p = 0.1314$.

Group comparisons of subcortical volumes between children with ADHD and HC revealed no statistically significant differences across the five examined nuclei (see Part I of the Supplementary Materials for details). Similarly, no significant between-group difference was observed in frontal lobe volume, with the ADHD group showing 6217.4 ± 543.9 voxels and the HC group 6421.8 ± 679.9 voxels ($p = 0.071$, $t = -1.82$). The trend toward reduced frontal volume in the ADHD group aligns with previous findings in the literature [55, 67]. The effectiveness of MOSI-based functional cortical parcellation is illustrated in Fig. 2.

Analysis I—correlation analyses between ALFF and nodal strength

This study is the first to examine the association between nodal strength and nodal power within the

fronto-subcortical network. While prior studies applying similar analytic approaches to cortical regions have reported a negative association—interpreted as reflecting a net inhibitory effect, whereby higher nodal strength corresponds to lower ALFF—the present findings in the fronto-striatal system reveal a distinct bimodal pattern. Specifically, F2S connections consistently exhibited a positive association with ALFF, whereas S2F connections showed a negative association, observed across both groups and robust across all gamma thresholds. This directional dissociation—characterized by uniformly positive F2S–ALFF and negative S2F–ALFF estimates across subcortical nuclei—is evident in both the correlation analyses (Tables 1 and 2) and the slope estimates derived from LME models (Tables 3 and 4 in the main text; Table S4 in the Supplementary Materials). Together, these findings suggest a dynamic interplay of excitatory and inhibitory influences underlying fronto-subcortical communication, consistent with the classical DeLong model of basal ganglia circuitry [2]. In this framework, cortical projections to the striatum are excitatory, whereas the net influence of the basal ganglia on the cortex is inhibitory. For example, the cortex provides excitatory input to the Put; the Put inhibits the external segment of the Pal, which in turn inhibits the internal segment of Pal or substantia nigra pars reticulata. These output nuclei exert inhibitory control over the ventral anterior and ventral lateral thalamic nuclei, which project excitatory signals back to the cortex. Because this pathway contains an odd number of inhibitory synapses, the overall effect of the indirect loop is net inhibitory at the cortical level. In the HC group, most correlations reached statistical significance, except for a positive trend in NAc under the F2S condition and negative trends in Cau and NAc under the S2F condition. In the ADHD group, a positive trend was observed in NAc under the F2S condition, with the remaining correlations showing statistical significance.

The strikingly opposite trends—indicative of frontal-to-striatal excitation and striatal-to-frontal inhibition—are shown in Fig. 3. For illustration, the voxels from the five subcortical nuclei were aggregated to emphasize the contrasting patterns. The x- and y-axes represent normalized ALFF and nodal strength, respectively, with ADHD and HC depicted in red and blue. The subplots in the left column contain more data points than those in the right column, as each voxel within the subcortical nuclei was treated as an individual analytic unit, whereas in the frontal lobe, the analytic units were defined based on MOSI-derived outputs. Interestingly, the association between frontal nodal ALFF and nodal strength in the Cau2F and NAc2F conditions reached statistical significance in the ADHD group but not in the HC group, suggesting a potential interaction effect in line with the hypothesis. The corresponding two-sample

Table 1 Correlation between subcortical ALFF and fronto-subcortical connectivity (F2S)

Gamma	ADHD	One-sample t-tests		HC	One-sample t-tests	
	mean (std)	t-scores	p-values	mean (std)	t-scores	p-values
Cau						
0.70	0.13 (0.26)	3.74	4.14E-04	0.15 (0.20)	5.85	2.31E-07
0.75	0.13 (0.26)	3.85	2.97E-04	0.15 (0.20)	5.93	1.70E-07
0.80	0.13 (0.26)	3.86	2.86E-04	0.15 (0.20)	5.94	1.61E-07
0.85	0.12 (0.26)	3.67	5.22E-04	0.16 (0.20)	6.09	9.26E-08
NAc						
0.70	0.09 (0.36)	2.02	4.82E-02	0.09 (0.32)	2.07	4.28E-02
0.75	0.09 (0.35)	2.05	4.53E-02	0.08 (0.31)	1.88	6.45E-02
0.80	0.09 (0.36)	1.86	6.81E-02	0.06 (0.32)	1.55	1.26E-01
0.85	0.09 (0.36)	1.93	5.83E-02	0.05 (0.32)	1.15	2.54E-01
Pal						
0.70	0.10 (0.23)	3.33	1.50E-03	0.13 (0.23)	4.29	6.63E-05
0.75	0.10 (0.23)	3.38	1.28E-03	0.13 (0.23)	4.45	3.85E-05
0.80	0.10 (0.22)	3.68	5.01E-04	0.13 (0.22)	4.52	2.99E-05
0.85	0.10 (0.23)	3.46	1.00E-03	0.13 (0.22)	4.47	3.65E-05
Put						
0.70	0.13 (0.20)	5.10	3.75E-06	0.11 (0.19)	4.68	1.74E-05
0.75	0.13 (0.20)	5.04	4.63E-06	0.12 (0.19)	4.98	5.88E-06
0.80	0.12 (0.19)	4.93	7.02E-06	0.11 (0.19)	4.50	3.29E-05
0.85	0.13 (0.19)	5.17	2.88E-06	0.11 (0.19)	4.73	1.45E-05
Tha						
0.70	0.09 (0.23)	3.20	2.21E-03	0.11 (0.20)	4.33	5.76E-05
0.75	0.10 (0.22)	3.29	1.70E-03	0.12 (0.20)	4.48	3.47E-05
0.80	0.10 (0.22)	3.37	1.32E-03	0.12 (0.19)	4.61	2.18E-05
0.85	0.09 (0.23)	3.12	2.80E-03	0.12 (0.20)	4.63	2.06E-05
Subcortical Nuclei						
0.70	0.11 (0.18)	4.40	4.53E-05	0.11 (0.15)	5.83	2.50E-07
0.75	0.11 (0.18)	4.54	2.85E-05	0.12 (0.14)	6.25	5.05E-08
0.80	0.11 (0.18)	4.55	2.69E-05	0.11 (0.14)	6.17	6.62E-08
0.85	0.10 (0.18)	4.38	4.92E-05	0.12 (0.15)	6.16	7.10E-08

$N=60$. Correlation coefficients were Fisher z-transformed. One-sample t-tests against zero were conducted, with p-values reported in scientific notation and thresholded at 0.01. **Subcortical Nuclei** indicates lumping all 5 nuclei together. All one-sample t-tests yielded positive t-values, whereas all two-sample t-tests were statistically non-significant

t-tests (not shown in Table 2) were as follows: For Cau2F at gamma values of 0.70, 0.75, 0.80, and 0.85, the t-scores (p-values) were -0.30 (0.766), -0.54 (0.592), -0.58 (0.561), and -1.00 (0.319), respectively; while For NAc2F at gamma values of 0.70, 0.75, 0.80, and 0.85, the t-scores (p-values) were -1.54 (0.126), -1.69 (0.094), -1.75 (0.082), and -1.70 (0.092), respectively. A potentially significant interaction effect was observed in the NAc, to be examined using LME models below.

Analysis II—LME analyses between ALFF and nodal strength

In the LME analysis, the geometric mean p-values for the F2S and S2F conditions across 4 gamma values of the Cau, NAc, Pal, Put, and Tha were (0.002, 0.231), (0.592, 0.002), (0.243, 0.043), (0.029, 0.004), and (0.012, 0.118), respectively (Table 3). An interaction effect in the

NAc approached statistical significance at gamma=0.80 and reached significance at gamma=0.85, respectively (Table 4). Notably, under a more complex—and potentially overly stringent—LME model incorporating random slopes, all main and interaction effects in subcortical regions were negative except for the significant interaction effect in NAc. These results are presented in Table 5; Fig. 4, where ADHD and HC are shown in red circles and blue triangles, respectively (geometric $p=0.009$; see Table S4 in the Supplementary Materials for additional details). There appear to be four distinct patterns in the main effects (ADHD vs. HC; refer to Tables 1 and 2): (1) less positive in F2S and less negative in S2F—Tha, Pal, and the combined subcortical nuclei; (2) less positive in F2S—Cau; (3) more negative in S2F—NAc; and (4) more positive in F2S and less negative in S2F—Put. The implications to the neuropathology of ADHD are elaborated in the **Discussion**.

Table 2 Correlation between frontal ALFF and fronto-subcortical connectivity (S2F)

Gamma	ADHD	One-sample t-tests		HC	One-sample t-tests	
	mean (std)	t-scores	p-values	mean (std)	t-scores	p-values
Cau						
0.70	-0.09 (0.24)	-2.77	7.49E-03	-0.07 (0.31)	-1.77	8.26E-02
0.75	-0.08 (0.21)	-2.83	6.41E-03	-0.05 (0.27)	-1.50	1.40E-01
0.80	-0.07 (0.19)	-2.85	5.94E-03	-0.05 (0.23)	-1.56	1.24E-01
0.85	-0.06 (0.18)	-2.47	1.64E-02	-0.02 (0.21)	-0.82	4.13E-01
NAc						
0.70	-0.12 (0.27)	-3.50	8.80E-04	-0.04 (0.29)	-1.12	2.66E-01
0.75	-0.11 (0.24)	-3.50	8.90E-04	-0.03 (0.25)	-0.96	3.39E-01
0.80	-0.10 (0.21)	-3.48	9.50E-04	-0.03 (0.22)	-0.89	3.79E-01
0.85	-0.07 (0.21)	-2.70	9.11E-03	-0.01 (0.20)	-0.34	7.32E-01
Pal						
0.70	-0.16 (0.21)	-5.98	1.37E-07	-0.22 (0.25)	-6.64	1.09E-08
0.75	-0.15 (0.19)	-6.04	1.12E-07	-0.18 (0.23)	-6.08	9.70E-08
0.80	-0.13 (0.18)	-5.66	4.77E-07	-0.17 (0.20)	-6.48	2.06E-08
0.85	-0.10 (0.16)	-4.85	9.50E-06	-0.14 (0.20)	-5.40	1.23E-06
Put						
0.70	-0.17 (0.22)	-5.95	1.56E-07	-0.26 (0.28)	-7.23	1.11E-09
0.75	-0.15 (0.19)	-6.27	4.65E-08	-0.21 (0.24)	-6.77	6.52E-09
0.80	-0.14 (0.17)	-6.11	8.48E-08	-0.19 (0.21)	-7.07	2.04E-09
0.85	-0.09 (0.17)	-3.91	2.43E-04	-0.15 (0.20)	-6.08	9.62E-08
Tha						
0.70	-0.13 (0.24)	-4.25	7.69E-05	-0.14 (0.29)	-3.87	2.71E-04
0.75	-0.12 (0.22)	-4.15	1.07E-04	-0.13 (0.26)	-4.04	1.59E-04
0.80	-0.10 (0.20)	-3.73	4.27E-04	-0.13 (0.22)	-4.58	2.47E-05
0.85	-0.07 (0.19)	-2.79	7.13E-03	-0.09 (0.20)	-3.61	6.43E-04
Subcortical Nuclei						
0.70	-0.13 (0.24)	-5.68	4.29E-07	-0.20 (0.28)	-5.53	7.74E-07
0.75	-0.12 (0.22)	-5.69	4.27E-07	-0.17 (0.26)	-5.13	3.34E-06
0.80	-0.10 (0.20)	-5.46	9.89E-07	-0.16 (0.22)	-5.65	4.93E-07
0.85	-0.07 (0.19)	-3.92	2.34E-04	-0.12 (0.20)	-4.62	2.12E-05

$N=60$. Correlation coefficients were Fisher z-transformed. One-sample t-tests were performed relative to zero, with p-values presented in scientific notation and thresholded at 0.01. **Subcortical Nuclei** indicates lumping all 5 nuclei together. All one-sample t-tests yielded negative t-values, whereas all two-sample t-tests were statistically non-significant

For completeness, between-group comparisons of ALFF and mean nodal strength were conducted for the five selected subcortical nuclei (either functionally connected to the frontal lobe or within subcortical regions) as well as within the frontal lobe. Except for a trend toward higher nodal strength at the NAc in the ADHD group within the subcortical network ($p=0.097$, $t=1.67$), all other comparisons yielded non-significant results. Detailed findings are presented in Parts II and III of the Supplementary Materials.

Discussion

This study aimed to empirically evaluate a neuropathological model of ADHD grounded in dialectic neuroscience [41]. The model contends that aberrant descending fronto-subcortical projections may constitute a core developmental vulnerability, impacting both ventral (predominant in

ADHD) and dorsal fronto-striatal pathways. Within the ventral circuitry, dysfunction in the autoregulatory FCX–VTA loop is posited as the primary locus of disruption in ADHD, with downstream propagation to the NAc further contributing to atypical reward processing and limbic dysregulation. The novel approach developed in this study enabled directional characterization of fronto-striatal interactions, revealing a consistent dissociation across subcortical targets and MOSI resolutions—excitatory in the F2S direction and inhibitory in the S2F direction, nicely concordant with the excitatory–inhibitory organization of the cortico-striato-thalamo-cortical loop in the DeLong model (as briefly outlined in the **Results**) [2]. A steeper positive slope in the F2S condition suggests that the frontal lobe may more effectively excite subcortical nuclei, likely via glutamatergic transmission [38], whereas a steeper negative slope in the S2F condition indicates that subcortical nuclei may impose stronger inhibitory influences on the FCX. These opposing slopes in

Table 3 Results of linear mixed-effects (LME) analysis without random slope terms: estimated group-wise mean slopes and group contrasts

Gamma		ADHD		HC		ADHD - HC		t-score	p-val
	Type	mean	SE	mean	SE	mean	SE		
Cau**	F2S	0.12	0.01	0.15	0.01	-0.03	0.01	-2.74	0.006
	S2F	-0.08	0.02	-0.07	0.02	-0.02	0.03	-0.56	0.577
0.75	F2S	0.12	0.01	0.15	0.01	-0.03	0.01	-2.72	0.007
	S2F	-0.08	0.02	-0.05	0.02	-0.02	0.02	-0.96	0.335
0.8	F2S	0.12	0.01	0.15	0.01	-0.03	0.01	-2.95	0.003
	S2F	-0.07	0.02	-0.04	0.02	-0.03	0.02	-1.23	0.219
0.85	F2S	0.12	0.01	0.15	0.01	-0.04	0.01	-3.68	0.0002
	S2F	-0.06	0.01	-0.02	0.01	-0.04	0.02	-1.83	0.067
NAc††									
0.7	F2S	0.09	0.02	0.09	0.02	-0.01	0.03	-0.21	0.833
	S2F	-0.10	0.02	-0.02	0.02	-0.08	0.03	-2.95	0.003
0.75	F2S	0.09	0.02	0.08	0.02	0.001	0.03	0.07	0.945
	S2F	-0.09	0.02	-0.02	0.02	-0.08	0.02	-3.17	0.002
0.8	F2S	0.08	0.02	0.07	0.02	0.01	0.03	0.38	0.701
	S2F	-0.09	0.02	-0.01	0.02	-0.07	0.02	-3.33	0.001
0.85	F2S	0.08	0.02	0.05	0.02	0.03	0.03	1.22	0.222
	S2F	-0.07	0.01	0.00	0.01	-0.06	0.02	-3.17	0.002
Pal†									
0.7	F2S	0.10	0.01	0.12	0.01	-0.02	0.02	-1.35	0.176
	S2F	-0.14	0.02	-0.20	0.02	0.06	0.03	2.19	0.028
0.75	F2S	0.10	0.01	0.12	0.01	-0.02	0.02	-1.43	0.152
	S2F	-0.13	0.02	-0.18	0.02	0.05	0.02	2.21	0.027
0.8	F2S	0.10	0.01	0.11	0.01	-0.01	0.02	-0.87	0.387
	S2F	-0.12	0.02	-0.16	0.02	0.04	0.02	1.79	0.073
0.85	F2S	0.10	0.01	0.11	0.01	-0.01	0.02	-0.96	0.338
	S2F	-0.09	0.01	-0.13	0.01	0.04	0.02	1.88	0.061
Put*††									
0.7	F2S	0.13	0.01	0.11	0.01	0.02	0.01	2.51	0.012
	S2F	-0.15	0.02	-0.23	0.02	0.08	0.03	2.94	0.003
0.75	F2S	0.13	0.01	0.11	0.01	0.01	0.01	1.51	0.131
	S2F	-0.14	0.02	-0.20	0.02	0.06	0.02	2.62	0.009
0.8	F2S	0.12	0.01	0.10	0.01	0.02	0.01	2.41	0.016
	S2F	-0.12	0.02	-0.18	0.02	0.05	0.02	2.47	0.014
0.85	F2S	0.13	0.01	0.11	0.01	0.02	0.01	2.20	0.028
	S2F	-0.08	0.01	-0.15	0.01	0.07	0.02	3.35	0.001
Tha***†									
0.7	F2S	0.09	0.01	0.11	0.01	-0.02	0.01	-2.28	0.023
	S2F	-0.11	0.02	-0.14	0.02	0.03	0.03	1.14	0.256
0.75	F2S	0.09	0.01	0.11	0.01	-0.02	0.01	-2.33	0.020
	S2F	-0.10	0.02	-0.13	0.02	0.04	0.02	1.43	0.154
0.8	F2S	0.09	0.01	0.11	0.01	-0.02	0.01	-2.06	0.040
	S2F	-0.08	0.02	-0.12	0.02	0.04	0.02	2.00	0.045
0.85	F2S	0.09	0.01	0.11	0.01	-0.03	0.01	-3.45	0.001
	S2F	-0.06	0.01	-0.10	0.01	0.03	0.02	1.60	0.110
Subc									
0.7	F2S	0.11	0.003	0.11	0.003	-0.00	0.005	-0.78	0.436
	S2F	-0.15	0.02	-0.19	0.02	0.04	0.03	1.43	0.152
0.75	F2S	0.11	0.003	0.11	0.003	-0.01	0.005	-1.15	0.251
	S2F	-0.13	0.02	-0.17	0.02	0.04	0.02	1.45	0.147
0.8	F2S	0.11	0.003	0.11	0.003	-0.00	0.005	-0.64	0.522
	S2F	-0.12	0.02	-0.15	0.02	0.04	0.02	1.59	0.112

Table 3 (continued)

Gamma		ADHD		HC		ADHD - HC			
0.85	F2S	0.10	0.003	0.11	0.003	-0.01	0.005	-1.81	0.070
	S2F	-0.09	0.01	-0.12	0.01	0.03	0.02	1.50	0.135

Two types of slopes are defined: F2S refers to the mean subcortical ALFF at a subcortical nucleus as a function of the mean nodal strength between the frontal lobe and that nucleus (i.e., frontal-to-subcortical), whereas S2F refers to the reverse direction. * and ** indicate $p < 0.05$ and $p < 0.01$ for F2S, respectively; † and †† indicate $p < 0.05$ and $p < 0.01$ for S2F, respectively

Abbreviations: Subc, combined subcortical structures; SE, standard error; p-val, p-value

Table 4 Results of linear mixed-effects (LME) analysis without random slope terms: Group x Direction interaction

Gamma					
Cau	mean	SE	t-score	p-val	dof
0.7	0.01	0.03	0.48	0.629	39,593
0.75	0.01	0.03	0.20	0.838	40,840
0.8	0.00	0.02	0.18	0.856	42,382
0.85	0.00	0.02	0.10	0.918	43,917
	geometric p value			0.802	
NAc					
0.7	-0.07	0.04	-2.03	0.043	11,709
0.75	-0.08	0.04	-2.26	0.024	12,956
0.8	-0.08	0.03	-2.49	0.013	14,498
0.85	-0.09	0.03	-2.94	0.003	16,033
	geometric p value			0.014	
Pal					
0.7	0.08	0.03	2.58	0.010	22,319
0.75	0.08	0.03	2.63	0.009	23,566
0.8	0.05	0.03	1.97	0.049	25,108
0.85	0.05	0.03	2.07	0.038	26,643
	geometric p value			0.020	
Put					
0.7	0.06	0.03	1.99	0.046	52,521
0.75	0.05	0.03	1.93	0.054	53,768
0.8	0.03	0.02	1.36	0.174	55,310
0.85	0.05	0.02	2.15	0.032	56,845
	geometric p value			0.061	
Tha					
0.7	0.05	0.03	1.72	0.086	69,841
0.75	0.05	0.03	2.07	0.039	71,088
0.8	0.06	0.02	2.57	0.010	72,630
0.85	0.06	0.02	2.73	0.006	74,165
	geometric p value			0.021	
Subc					
0.7	0.04	0.03	1.55	0.122	174,499
0.75	0.04	0.03	1.64	0.100	175,746
0.8	0.04	0.02	1.69	0.091	177,288
0.85	0.04	0.02	1.87	0.061	178,823
	geometric p value			0.091	

Group=ADHD vs. HC; Direction=F2S vs. S2F

Abbreviations: Subc, combined subcortical structures; SE, standard error; p-val, p-value; dof, degree of freedom

the F2S and S2F conditions may provide a valuable framework for examining the network balance between frontal and subcortical systems. The group comparison results were broadly consistent with the model's predictions. First, in

the F2S condition, correlations between nodal strength and power were lower in ADHD than HC across several subcortical structures, including the Cau, Pal, and Tha, as well as when all subcortical nuclei were considered collectively (Subc). Second, the NAc demonstrated a robust interaction effect, replicated across two independent LME models. Notably, the enhanced F2NAc slope may be partially offset by sub-optimally organized frontal-subcortical projections; however, it remained clearly observable in the group-by-direction interaction analyses (upper panels of Fig. 4). The observed trend of reduced frontal volume and increased NAc-centered FC aligns with prior reports [55, 56]. Subcortical volume differences were not statistically significant in the present sample. The persistence of functional coupling abnormalities in the absence of marked structural volume reduction supports the interpretation that the findings reflect developmental miswiring and network-level reconfiguration rather than structural atrophy per se.

Overall, group comparisons revealed parallel shifts in both F2S and S2F slopes within Pal, Tha, and Subc—specifically, reduced F2S positivity and attenuated S2F negativity—suggesting a preserved excitation–inhibition balance in these nuclei in ADHD. Notably, the Tha and Subc patterns further supports the view that, when considering the common relay station of striato-thalamo-cortical circuitry and the subcortical nuclei collectively, the overall excitation–inhibition balance remains intact. A similarly reduced F2S slope was also observed in Cau. The consistent reduction in F2S across Pal, Tha, Cau, and Subc lends support to the first prediction. However, this balance appears disrupted in the motor-related relay station Put, which exhibits increased F2Put and decreased Put2F in ADHD, consistent with previous research indicating that Put displayed abnormal activity 1 s before a tic [54]. This shift—marked by heightened excitation relative to inhibition—may lead to maladaptive activation of the motor system, primarily contributing to the high comorbidity with tic disorders [61, 75], although the precise neural mechanisms remain to be clarified.

However, in the ADHD group, the slope of NAc2F was significantly more negative than in HC, making it the only subcortical nucleus to show a significant interaction effect—thus supporting the second prediction. In addition to VTA-FCX, the NAc also plays a central role in the neuropathology of ADHD [41], becoming sensitized and

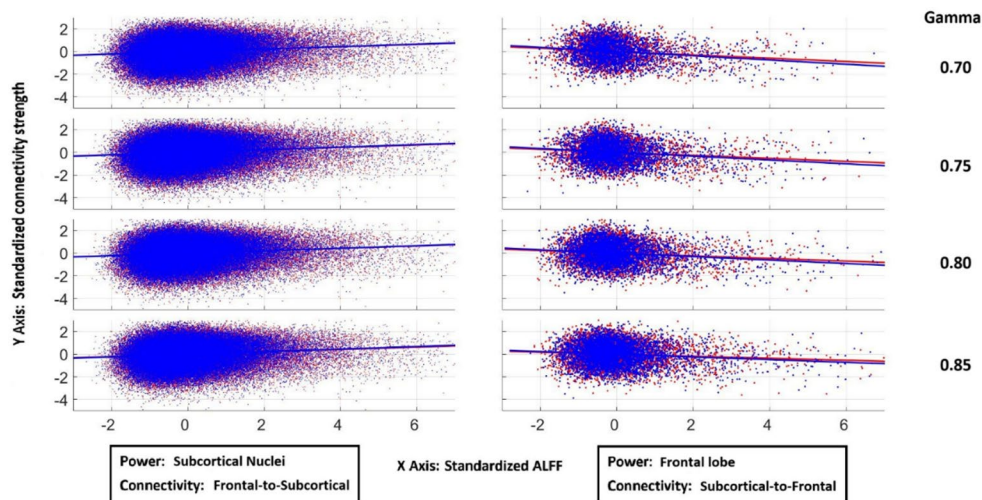


Fig. 3 Scatter plots with regression lines illustrating the relationships between regional power and functional connectivity. Rows correspond to four increasing gamma values (0.70 to 0.85). Left column: voxel-wise ALFF within subcortical nuclei plotted against mean frontal-to-subcortical nodal strength. Across gamma values of 0.70, 0.75, 0.80, and 0.85, the corresponding overall correlation coefficients for ADHD were 0.11, 0.11, 0.11, and 0.10, respectively, whereas those for HC were 0.11, 0.11, 0.11, and 0.11. All correlations were highly significant

(all $p < 10^{-10}$). Right column: mean ALFF within the frontal lobe plotted against mean subcortical-to-frontal nodal strength. Across gamma values of 0.70, 0.75, 0.80, and 0.85, the overall correlation coefficients for ADHD were -0.15 , -0.13 , -0.12 , and -0.09 , respectively, whereas those for HC were -0.19 , -0.17 , -0.15 , and -0.12 . All correlations were statistically significant (all $p < 10^{-10}$). The left and right columns show robust but opposing trends, as reflected in the opposite directions of the regression slopes. Blue indicates HC, and red indicates ADHD

disinhibited due to low tonic DA, which reduces presynaptic D2 receptor-mediated inhibition, and to hypofrontality, which weakens GABAergic regulation from the VTA [12, 34]. This low tonic DA state may, in turn, trigger compensatory enhancement of phasic DA signaling [35, 36]. Together, these mechanisms result in hyperactivity of the NAc, and consequently, the mesolimbic system. Through reciprocal suppressive interactions between the limbic system and the FCX [42, 50], hyperactivity in the NAc may ultimately exert stronger inhibitory influences on the FCX in ADHD—a pattern reflected in the analytic results. A similar, though non-significant, enhancement of S2F suppression in the caudate observed in the ADHD group may be driven by shared underlying hypo-dopaminergic states [41]. Hypoactivity in the FCX can reduce DA levels in the Cau [14, 69], and hypodopaminergicism is a key contributor to hypofrontality in ADHD. An elevated Cau2F nodal strength may indicate a shared dopaminergic deficiency between specific module(s) in the FCX and the Cau, which could further aggravate hypofrontality and manifest as increased Cau2F inhibition. In contrast, FCX modules less involved in caudate DA metabolism may exhibit weaker correlations and consequently show higher ALFF. Taken together, these two conditions may lead to a more negative association between Cau2F nodal strength and frontal nodal power. Aberrant F2S projections during development are unlikely to affect a single nucleus in isolation. Given the integrative organization of fronto-striatal circuitry, developmental perturbations in frontal output are expected to exert distributed influences

across multiple subcortical nuclei. Although the most pronounced alteration in ADHD lies in the VTA, other nuclei also demonstrate varying degrees of involvement, particularly the Cau. The contrasting F2S/S2F patterns in the Put/Pal may reflect compensatory adaptations arising from competitive dynamics between Cau-based goal-directed (action–outcome) systems and Put-based habitual stimulus–response systems [37].

The differential patterns observed in the Cau versus the Put/Pal likely reflect their distinct roles within cognitive and motor basal ganglia–thalamo–cortical loops. In HC, the slope mediating nodal strength versus nodal power of S2F at Cau (Cau2F) did not reach significance, contrasting with motor-related nuclei such as Put and Pal, which showed balanced F2S excitation and S2F inhibition. Consistent with the findings, fiber tracking research of the thalamus exhibits distinct patterns of reciprocal connectivity across subregions related to cognitive and motor basal ganglia loops. Specifically, the mediodorsal thalamic nucleus, primarily connected with Cau and prefrontal cognitive (and affective) circuits, shows substantial nonreciprocal corticothalamic projections from diverse frontal cortical areas. In contrast, the ventral anterior and ventrolateral thalamic nuclei, associated with Put and Pal within motor circuits (including the supplementary motor area, motor and premotor cortices), exhibit stronger reciprocal thalamocortical and corticothalamic connections. This differential organization aligns with the findings, as motor loops maintain tightly coupled, bidirectional thalamocortical communication, whereas

Gamma	ADHD			HC			ADHD - HC			Interaction			dof		
	Type	mean	SE	mean	SE		mean	SE	t-score	p-val	mean	SE		t-score	p-val
0.7	NAc														
	F2S	0.08	0.03	0.09	0.03	0.00	0.04	-0.07	0.942	-0.08	0.04	-2.26	0.024	11,709	
	S2F	-0.10	0.03	-0.02	0.03	-0.09	0.04	-2.01	0.045	-0.09	0.03	-2.47	0.014	12,956	
	F2S	0.08	0.03	0.08	0.03	0.00	0.04	0.11	0.912	-0.09	0.03	-2.47	0.014	12,956	
0.75	S2F	-0.10	0.03	-0.01	0.03	-0.08	0.04	-2.04	0.042	-0.09	0.03	-2.65	0.008	14,498	
	F2S	0.08	0.03	0.07	0.03	0.01	0.04	0.31	0.760	-0.09	0.03	-2.65	0.008	14,498	
	S2F	-0.09	0.03	-0.01	0.03	-0.08	0.04	-2.10	0.036	-0.10	0.03	-3.02	0.002	16,033	
	F2S	0.08	0.03	0.05	0.03	0.03	0.04	0.83	0.407	-0.10	0.03	-3.02	0.002	16,033	
0.85	S2F	-0.07	0.02	0.00	0.02	-0.07	0.03	-1.88	0.059	geometric p-val			0.009		

Although the correlations between ALFF and nodal strength are modest in magnitude (Tables 1 and 2), this should be interpreted in light of the analytic scale adopted in the present study. The frontal cortex (FCX) was modeled as a global structure, whereas distinct subcortical nuclei are known to project to partially segregated frontal territories. Substantial spatial heterogeneity within FCX is therefore expected, and aggregation across the entire region likely attenuates topographically specific effects. A more anatomically refined analysis that incorporates this projectional organization could plausibly strengthen observed associations. Nevertheless, the primary objective was to investigate ADHD from a developmental, systems-level perspective, given its marked heterogeneity. The FCX–VTA alteration is conceptualized within a broader fronto-subcortical framework rather than as an isolated VTA-specific abnormality, particularly as pathological influences may variably extend to basal ganglia structures. Accordingly, an unbiased whole-FCX approach was adopted to provide initial systems-level support for the proposed theoretical framework. Future work may enhance mechanistic specificity by selectively examining medial and orbital frontal subdivisions, which exhibit dense interactions with VTA and NAc.

It should be noted that VTA function was not directly measured in the present study. The inference regarding potential frontal–VTA abnormalities is based primarily on the broadly flatter F2S slopes observed in ADHD (Tha, Pal, Cau, and combined subcortical nuclei), which indicate reduced frontal output efficiency to the subcortical nuclei. With respect to structural connectivity, current fiber-tracking techniques are more reliable for large fiber bundles, such as the corticospinal tract, superior longitudinal fasciculus, and cingulum, whereas thinner projections mediating the FCX-to-VTA pathway remain technically difficult to delineate *in vivo*. Notably, projections from the FCX to the VTA follow comparatively longer and less compact trajectories than those to the basal ganglia, a characteristic that may confer greater susceptibility to developmental perturbations. Nevertheless, prior evidence of disrupted frontostriatal white matter integrity in ADHD provides structural plausibility

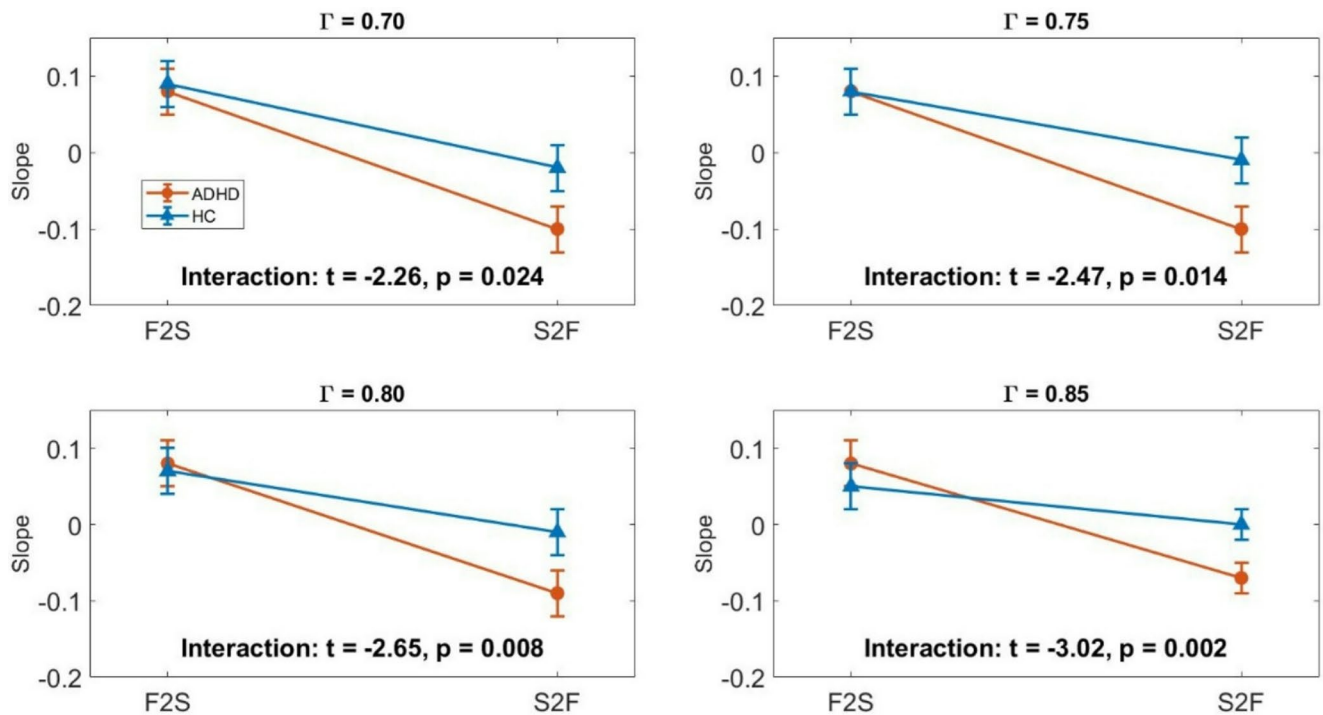


Fig. 4 Relationships between ALFF and nodal strength in the NAc and frontal lobe based on slopes derived from Linear Mixed Effects (LME) models at four gamma values. F2S: slopes of ALFF at NAc against mean functional connectivity between NAc and frontal lobe. S2F: slopes of mean ALFF at frontal lobe against mean functional connect-

tivity between NAc and frontal lobe. Data are shown for two groups, ADHD (red circles) and HC (blue triangles), with error bars representing standard errors. Interaction effects between group and condition are reported below each subplot

for the present findings [15], while direct confirmation of FCX–VTA connectivity awaits future investigation.

The present dataset is cross-sectional and consists primarily of children and early adolescents (mean age approximately 10 years), which constrains both developmental inference and generalizability to adult ADHD. As discussed above, the proposed model conceptualizes aberrant frontal–subcortical projections as gradually emerging alterations in circuit organization. Age-related differences in cortical maturation, striatal development, and symptom expression may therefore influence the directional interaction profiles captured by the nodal strength–ALFF (power) metrics. Extending this framework to adolescent and adult samples would help determine whether the observed patterns represent an early developmental configuration, a stable trait marker across the lifespan, or a stage-dependent manifestation that evolves with cortical maturation and compensatory processes. In addition, prospective follow-up of at-risk or subthreshold individuals could determine whether atypical nodal strength–power patterns precede and predict subsequent ADHD diagnosis. Longitudinal tracking from childhood into adulthood, as well as cross-sectional comparisons across age groups, would provide a more rigorous test of

the model’s developmental “miswiring” hypothesis and enhance its translational relevance.

Conclusion

This study empirically tested a neuropathology model of ADHD derived from dialectic neuroscience, which posits that aberrant descending fronto-subcortical projections—particularly those involving the FCX–VTA loop—constitute a core developmental vulnerability. Leveraging a novel directional framework, a consistent dissociation between F2S excitation and S2F inhibition across subcortical targets was identified, providing a foundation for examining directional network properties in ADHD. Group comparisons supported the model: diminished frontal drive (lower F2S correlations) was evident across multiple subcortical nuclei, and a robust interaction centered on the NAc aligned with prior evidence of mesolimbic dysregulation. More broadly, this work exemplifies the utility of dialectic neuroscience—a theory-driven, mechanistically anchored alternative to traditional psychological paradigms and data-driven approaches—as a promising direction for understanding psychiatric disorders at the systems level.

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Data availability Imaging data are from a publicly-released dataset, the ADHD-200 Consortium, sourced from the New York University Child Study Center (https://fcon_1000.projects.nitrc.org/indi/adhd200/).

Declarations

Human and animal rights This research analyzed the databank from a publicly released dataset. The author carried out no animal or human studies for this article.

Competing interests The author declares no competing interests.

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Toward the Core Neuropathology of Obsessive-Compulsive Disorder: An Analysis–Synthesis Framework Approach

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Abstract

Obsessive–compulsive disorder (OCD) is a prevalent and complex psychiatric condition, characterized by repetitive intrusive thoughts and compulsive behaviors performed to relieve the associated inner urge and tension. Beyond its core symptoms, OCD is associated with cognitive inflexibility, impaired saccade performance, and heightened error monitoring. Consistent with this broad spectrum of cognitive, affective, and sensorimotor alterations, prior research has reported hypofrontality, limbic hyperactivity, and abnormalities of the dorsal striatum. Following the methodological principles of dialectic neuroscience, a hybrid analysis–synthesis approach was adopted to formulate a candidate brain-based theory of OCD. A viable theory is expected to satisfy three key criteria: biological plausibility, comprehensiveness, and parsimony, resonating Bayesian framework. Existing empirical findings (analysis) are integrated into a model proposing an innate developmental vulnerability in neural organization—specifically, aberrant prefrontal–subcortical projections centered on the dorsal striatum—together with a design-level vulnerability in interactions between the caudate and limbic structures, including the amygdala, insula, and medial temporal lobe, which respectively mediate the major symptom dimensions of aggression/fear-of-harm, contamination, and symmetry/order. By incorporating subsequent network-level adaptations and empirically grounded neurophysiological mechanisms, the proposed model enhances explanatory breadth across a range of seemingly disparate or even contradictory observations. Notably, this framework offers a principled account of the dissociation between cognitive impairments and symptom severity in OCD. Multiple clinical and neurobiological features of OCD are reinterpreted in light of this underlying network dysfunction. In sum, the analysis–synthesis framework provides a concise yet powerful strategy for investigating the neural mechanisms of psychiatric disorders.

Key Points

- A brain-based theory of OCD is proposed, positing aberrant descending projections from the prefrontal cortex (PFC) to the dorsal striatum as a core developmental vulnerability underlying the disorder.
- Using a dialectical analysis–synthesis framework, the model reconciles diverse empirical findings into a parsimonious, biologically grounded account that coherently explains both clinical phenomenology and neuroimaging abnormalities in OCD.
- The theory foregrounds network-level dysregulation, whereby early developmental aberrations propagate downstream, reshaping interactions across fronto–striatal and limbic systems.
- Future empirical tests should target directional and interactive network properties, particularly at the level of the caudate and putamen, addressing a major unresolved gap in current OCD research.

Introduction

Psychiatric disorders are fundamentally distinct from psychological dysfunctions, although any of the former can manifest a wide range of the latter. Obsessive–compulsive disorder (OCD) and attention-deficit/hyperactivity disorder (ADHD), for example, may both exhibit impairments in attention, impulsivity, and executive control. While these difficulties may appear overlapping, their underlying subdomains may partly diverge—attentional bias in OCD versus distractibility in ADHD illustrates such divergence. Nevertheless, it is the clustered symptoms that provide the highest diagnostic value, which is why the current diagnostic standard (DSM-5) remains primarily grounded in symptomatology (American Psychiatric Association, 2013).

In medicine, symptoms and signs are distinct yet complementary: a symptom refers to the patient's subjective experience (e.g., dizziness or intrusive thoughts), whereas a sign denotes an objective finding detectable through clinical examination or measurement (such as heart rate variability or abnormal reflexes). In depression, for instance, a patient's complaint of lethargy constitutes a subjective symptom, yet clinicians can observe reduced facial expression and slowed movements as objective signs. Similarly, in anxiety disorders, palpitations represent a symptom, whereas an elevated heart rate measured via electrocardiogram provides an objective sign. Compared with psychological functions, which can often be delineated and quantified using brain science instruments and analytic methods—such as attention network analyses—it is worth asking whether symptomatology can be “localized” in a similar manner. Evidence suggests that this is feasible, though the underlying assumptions and rationale differ.

Consider nociception as an example. The symptom of pain—a subjective experience of a cutting wound on the thumb—is mediated by the nociceptive neural network but can be dissociated from the underlying physical injury. Here, the causal target organ is the finger. By analogy, psychiatric symptomatology can be understood primarily as a subjective interpretation of brain abnormalities, with peripheral manifestations (e.g., sympathetic overactivation in panic attacks) relevant in specific conditions. The brain is generally regarded as the principal target organ underlying most psychiatric symptoms. Neuropsychiatric disorders are not constrained to any particular psychological domain—for instance, neurodegenerative changes in Alzheimer's disease do not follow a predefined network of psychological functions. Accordingly, symptomatology provides a direct avenue to probe brain abnormalities beyond the limitations of single psychological dysfunctions. This framework supports placing symptomatology at a higher hierarchical level than psychological assessment in psychiatric practice, while recognizing the latter as an indispensable component of comprehensive evaluation.

Although conceptualizing symptomatology as a subjective interpretation of brain abnormalities may at first appear counterintuitive—given that the brain itself lacks dedicated sensory receptors—humans nonetheless experience emotions such as sadness or happiness, which emerge from the integrated dynamics of large-scale brain networks and interoceptive signals rather than from any specific “sad” or “happy” receptors (cf. nociceptors). Supporting this view, individuals can still *feel* emotions even in the absence of facial or autonomic feedback (Chwalisz et al., 1988; Keillor et al., 2002). This demonstrates that subjective interpretations of internal brain states can arise independently of peripheral sensory organs—effectively bypassing them—and underscores how psychiatric symptoms may originate directly from intrinsic neural aberrance rather than from external sensory input. Consistent with this notion, the symptom depression can be conceived as the subjective interpretation of a sustained large-scale network imbalance (Lee, 2025c; Lee & Xue, 2018a), rather than as a transient “sad” feeling generated by perturbing or activating a discrete psychological (emotion-related) network.

Building on the preceding conceptual groundwork, this research integrates symptomatology and neuroscientific insights within an analysis–synthesis framework to elucidate the core neural mechanisms underlying OCD. Notably, unlike the concept and ambition of “functional localization” in neuroimaging research—which assumes that specific brain regions or networks constitute the material foundations for executing neuropsychological functions—no brain region is presumed to have evolved solely to generate “symptoms.” Methodologically, it is therefore not feasible to “zoom in” as in cognitive neuroscience, where

a mental function such as working memory can be decomposed into components like the central executive and the buffer systems. In exploring the relationship between symptomatology and the brain, one must instead “zoom out,” inferring the potentially dysfunctional neural substrates from broad symptom categories rather than from fine-grained variations in their manifestations. This issue will be further elaborated in the section *Conjectured neural deviations related to OCD symptoms*. As reasoned above, most psychiatric symptoms can be regarded as rhetorical expressions of subjective interpretations of brain dysfunctions. The consistency of symptomatology, which forms the foundation of psychiatric diagnosis, strongly suggests that there also exists a material basis underlying psychiatric disorders—one that is distinct from the neural substrates supporting neuropsychological functions. However, the multiplicity and heterogeneity of symptom embodiment imply that the core neuropathology of OCD must be derived through additional inferential processes—constituting the central theme of this research, which applies the dialectic neuroscience framework to decipher OCD, in continuity with previous works that elucidated the neural bases of major depressive disorder (MDD), bipolar disorder, and ADHD (Lee, 2025a, 2025b, 2025c, 2025f; Lee & Xue, 2017, 2018a).

Following the structured format recommended by Lee (Lee, 2025d) and exemplified in prior work (Lee & Xue, 2017, 2018a), the present investigation begins with a focused literature review emphasizing evidence from brain science (**Introduction**) and proceeds through two principal stages. The first, **analysis**, provides a systematic outlines of neuroscientific findings and delineates the central features of OCD across multiple disciplinary domains (**Materials and Methods**). The second, **synthesis**, integrates these heterogeneous observations into a physiologically grounded and internally coherent mechanistic framework (**Results**). The resulting model is anchored in empirically supported network-level operations, constructed to remain parsimonious while accommodating the breadth of OCD-related phenomena. These defining attributes—biological plausibility, parsimony, and explanatory scope—correspond to the core elements of a Bayesian framework, ensuring that the model’s conclusions are both statistically principled and scientifically rigorous (Lee, 2025d). Although presented as a review, the manuscript adheres to the organizational structure of a standard research article, with dedicated sections for **the Introduction, Materials and Methods, Results, and Discussion**. Through the analysis–synthesis approach, the author proposes that developmental abnormalities in descending projections from the prefrontal cortex (PFC) to the dorsal striatum may represent a core neuropathology underlying the emergence of OCD. For abbreviations used in this thesis, please refer to Table 1.

Table 1 List of abbreviations

Abbreviation	Full Term
ACC	Anterior Cingulate Cortex
AIns	Anterior Insula
A–O	Action–Outcome
ADHD	Attention-Deficit/Hyperactivity Disorder
BLA	Basolateral Amygdala
CSTC	Cortico–Striato–Thalamo–Cortical
FC	Functional Connectivity
GPe	Globus Pallidus Externa
GPi	Globus Pallidus Interna
HD	Huntington’s Disease
MDD	Major Depressive Disorder
MTL	Medial Temporal Lobe
NAc	Nucleus Accumbens
OFC	Orbitofrontal Cortex
OCD	Obsessive–Compulsive Disorder
PFC	Prefrontal Cortex
SERT	Serotonin Transporter

S–R	Stimulus–Response
SNr	Substantia Nigra pars reticulata
SSRI	Selective Serotonin Reuptake Inhibitor
VTA	Ventral Tegmental Area

Clinical manifestation of OCD

OCD is a chronic and disabling condition, characterized by persistent obsessions and compulsions that cause marked distress, functional impairment, or consume substantial amounts of time. The 12-month prevalence of OCD in the United States is 1.2%, with similar rates internationally (1.1%–1.8%) (American Psychiatric Association, 2013). The mean age at onset is 19.5 years, and 25% of cases begin by age 14. OCD exhibits substantial psychiatric comorbidity, with the highest lifetime comorbidity rates observed for MDD (48%), followed by anxiety disorders (32%), ADHD (16%), and tic disorders (14%) (Sharma et al., 2021). Cross-sectional comorbidity with MDD is estimated to be 15.0% (Pinto et al., 2006) (note: values may vary across studies, although the ranking of the most common comorbidities is consistent).

Obsessions consist of recurrent and persistent thoughts, urges, or mental images that intrude into consciousness and are experienced as unwanted. Compulsions are repetitive behaviors or mental rituals performed in response to an obsession, sometimes carried out in a rule-like manner. Compared with other psychiatric conditions, OCD is outstandingly heterogeneous in terms of symptom profile. Although manifestations vary across patients, several symptom dimensions are commonly observed, including contamination-related obsessions with cleaning compulsions, symmetry obsessions with ordering, repeating, or counting behaviors, forbidden or taboo thoughts such as aggressive, sexual, or religious obsessions and their associated compulsions (e.g., mental rituals such as praying or repeating words), and harm-related obsessions often linked with checking behaviors aimed at preventing perceived danger. Among these, the three most frequently reported obsessions are contamination, aggression/fear of causing harm, and symmetry/order, typically accompanied by cleaning, checking, and counting/ordering compulsions, respectively (Mataix-Cols et al., 2005; Rasmussen & Eisen, 1992). The tic-related specifier for OCD is applied when an individual has a current or past history of a tic disorder. The main pharmacological treatment for OCD is selective serotonin reuptake inhibitors (SSRIs), with dosages generally two to three times higher than those typically used for other psychiatric conditions, such as depressive disorders (Bloch et al., 2010). Beyond the core diagnostic symptoms, individuals with OCD frequently exhibit additional neuropsychological and sensorimotor disturbances, highlighted below.

Among cognitive and sensorimotor paradigms, the most consistent findings in OCD concern deficits in flexibility and abnormalities in saccadic control (Chamberlain et al., 2021). Cognitively, OCD is characterized by impaired inhibitory control, exaggerated error monitoring, heightened doubt, and a propensity to default to rigid or habit-like behavioral strategies. Meta-analytic work demonstrates moderate effect-size deficits across multiple paradigms, including attentional set shifting (e.g., Wisconsin Card Sorting Test, Intra–Extra Dimensional set-shifting tasks), reversal learning, task switching, and motor-inhibition measures such as the Stroop, Trail-Making, and stop-signal tasks. Collectively, these findings establish cognitive inflexibility—particularly executive set-shifting—as a robust neurocognitive feature of OCD (review by (Gruner & Pittenger, 2017)). Alterations in sensorimotor control have also been reported, including prolonged saccadic latencies, reduced saccade accuracy, and markedly increased antisaccade-related errors (Jaafari et al., 2011). Other domains—such as reward processing (Figeet al., 2011; Marsh et al., 2015)—show substantial variability, with reports of both heightened and diminished neural responses; these domains are therefore not further elaborated in this thesis.

Affectively, patients commonly experience persistent anxiety, elevated threat appraisal, and a pervasive sense of incompleteness or internal disequilibrium. These affective states amplify intrusive thoughts and reinforce compulsive behaviors, thereby sustaining the canonical obsession–compulsion cycle. Functional impairment in academic and occupational contexts typically stems from symptom-driven disruptions—such as time-consuming rituals, perfectionistic checking, and the intrusive cognitive load imposed by obsessions—

rather than from generalized cognitive deficits. These symptom-related burdens delay task completion, undermine sustained engagement, and promote avoidance of high-demand responsibilities. Consequently, the accompanying academic and occupational difficulties largely reflect downstream effects of symptomatology rather than broad cognitive impairment.

Notably, the core phenomenology of OCD shows little correspondence with its documented neuropsychological or motor-control abnormalities—a dissociation that is uncommon among psychiatric disorders. In most conditions, deviations in cognition or behavior closely mirror the central psychopathology; for example, negative interpretive bias in depression reflects its primary affective distortion, whereas grandiose ideation in mania coheres with elevated mood and inflated self-appraisal. The absence of such alignment in OCD suggests that its symptomatic expressions and performance-level abnormalities arise from segregated neural networks that may nonetheless be influenced by a shared upstream driver. Consequently, attempts to account for obsessions or compulsions solely on the basis of these neuropsychological or oculomotor deviations are inadequate: reduced cognitive flexibility or elevated antisaccade error rates, for instance, does not inherently generate intrusive obsessions. Concordant with clinical observations, neuroimaging evidence shows that heightened error-related potentials and enhanced conflict detection (indexed by the stop-N2 in the stop-signal task) in OCD emerge independently of symptom burden (Lei et al., 2015; Riesel et al., 2011). Likewise, saccadic abnormalities show no association with overall severity in OCD (Jaafari et al., 2011).

Fronto-striatal structural and functional abnormalities

Structural imaging studies have shown that OCD is associated with volumetric alterations across multiple cortical and subcortical regions, including the PFC (dorsolateral PFC, inferior frontal cortex, medial PFC, and premotor cortex), dorsal anterior cingulate cortex (ACC), superior temporal cortex, posterior parietal cortex, caudate, putamen, and cerebellum (P. S. W. Boedhoe et al., 2017; Cheng et al., 2016; Jayarajan et al., 2015; Kuhn et al., 2013; Moon & Jeong, 2018; Pico-Perez et al., 2020; Szeszko et al., 2008; Tang et al., 2015; Togao et al., 2010). Neocortical areas generally exhibit reduced volume, in contrast to the dorsal striatum, which tends to show enlargement. Among these regions, the most consistently and relevantly implicated structures identified by meta-analyses are the PFC (or fronto-parietal network) and the striatum (Carlisi et al., 2017; Norman et al., 2016). Although reductions in dorsal ACC volume have been reported frequently (Jayarajan et al., 2015; Kuhn et al., 2013), this region—primarily involved in cognitive control and projecting to the caudate in concert with the dorsolateral PFC—remains functionally distinct from the rostral and subgenual ACC, which send dense projections to the ventral striatum, forming a limbic cortico-striatal pathway central to reward processing and other affective functions.

Various paradigms have been used to probe the cognitive networks underlying OCD. Studies consistently report reduced prefrontal activation during autonomous target detection (Rubia et al., 2011). Although the psychological conflict in OCD differs fundamentally from simple sensory–motor conflict resolution, basic paradigms such as the Simon and Flanker tasks have been applied to investigate OCD pathology. Reduced engagement of the PFC, dorsal ACC, and supplementary motor area during conflict processing has been observed (Fitzgerald et al., 2005; Marsh et al., 2014; Rubia et al., 2011), consistent with volumetric evidence of prefrontal structural alterations. With increasing task demands, individuals with OCD may exhibit elevated dorsal ACC activity (Ursu et al., 2003; Yucel et al., 2007), interpretable as compensatory effort to hypofrontality, reflecting the need to recruit additional neural resources. Enhanced dorsal ACC responses are also reported during error detection, independent of symptom severity (Lei et al., 2015; Maltby et al., 2005; Riesel et al., 2011; Ursu et al., 2003). Working memory, cognitive-switching and reversal learning tasks similarly reveal reduced dorsolateral PFC activation, together with decreased engagement across the fronto-parietal network, lateral orbitofrontal cortex (OFC), and caudate nucleus (Chamberlain et al., 2008; Gu et al., 2008; Moon & Jeong, 2018; Page et al., 2009; Remijnse et al., 2006). Interestingly, in contrast to the caudate, increased responses are often observed in the putamen (Remijnse et al., 2013), a finding confirmed in large-scale meta-analyses (Del Casale et al., 2016; Pico-Perez et al., 2020; Rasgon et al., 2017).

Deficient response inhibition has long been linked to the occurrence of compulsions; however, the observation that inhibitory lapses can alleviate rather than intensify inner tension challenges this oversimplified view. Behavioral performance on the stop-signal task does not reliably distinguish OCD patients from healthy controls, and shows no association with symptom severity (Fan et al., 2017). A recent meta-analysis reports a modest prolongation of stop-signal reaction times—approximately 23 msec on average—in OCD, though substantial heterogeneity is evident across studies (Mar et al., 2022). Nevertheless, inhibitory control remains a pertinent brain research focus in OCD. Attenuated neural responses to No-Go trials have been observed across prefrontal, parietal, and temporal regions, including the canonical inhibitory locus in the inferior frontal cortex and the caudate (Booth et al., 2003; Peterson et al., 2002; Roth et al., 2007). However, a recent meta-analysis found no consistent regional abnormalities associated with inhibitory control in OCD (Funch Uhre et al., 2022). Difficulty terminating inappropriate responses (i.e., the occurrence of compulsions) has also been linked to inefficient utilization of feedback signals, motivating the use of reward-based paradigms to probe OCD neuropathology. However, findings remain inconsistent, with studies reporting both increased and decreased medial PFC activity in response to feedback (Figue et al., 2011; Jung et al., 2011).

Consistent with the pattern observed across multiple cognitive paradigms, the Tower of London task—a higher-order planning measure—has similarly revealed reduced fronto-striatal engagement in OCD, primarily within the dorsolateral PFC and caudate nucleus (van den Heuvel et al., 2005). In line with this hypofrontality account, proton magnetic resonance spectroscopy studies have reported marked metabolic abnormalities in the dorsolateral PFC, including lowered N-acetylaspartate/creatine and choline/creatine ratios, together with an increased glutamate–glutamine/creatine ratio. This constellation suggests reduced neuronal integrity and diminished membrane turnover alongside a compensatory elevation in glutamatergic tone, reflecting an attempt to offset reduced cortical efficiency (Moon & Jeong, 2018). Overall, the evidence reinforces the hypofrontality hypothesis in OCD (both structural and functional), together with enlarged dorsal striatal volume (caudate and putamen).

Meta-analytic work consistently implicates several frontal regions in OCD, including the rostromedial PFC, inferior frontal gyrus, dorsal ACC, premotor cortex, and dorsolateral PFC (Carlisi et al., 2017; Norman et al., 2016; Pico-Perez et al., 2020). The caudate shows a distinct and task-dependent profile: although its volume is increased, its responsivity decreases during cognitive tasks yet increases during affective tasks (Pico-Perez et al., 2020; Rasgon et al., 2017). Thalamic responses generally parallel those of the caudate, showing reduced activity in cognitive contexts and heightened activity during affective processing (Rasgon et al., 2017). Importantly, these shifts arise from different subregions within each nucleus. Given that the caudate head—rather than its body or tail—is preferentially connected to medial, ventral, and dorsolateral PFC, the frontal pole, and the pre-supplementary motor area implicated in the neuropathology (Grahn et al., 2008), and considering evidence that the body and tail are more involved in visual stimulus–response (S–R) learning or working memory (Lawrence et al., 1998), the present thesis focuses on the caudate head. The opposite task-dependent response patterns in the caudate and thalamus may help reconcile earlier inconsistent findings. In contrast, the putamen demonstrates increased activity across both cognitive and affective paradigms, together with heightened engagement of premotor cortex, consistent with a cortico–striato–thalamo–cortical (CSTC) architecture centered on the putamen (Carlisi et al., 2017; Norman et al., 2016; Pico-Perez et al., 2020; Rasgon et al., 2017).

Two phenomena remain inadequately explained. First, within CSTC-related circuits, PFC volume reduction contrasts with dorsal striatal enlargement. Second, the dorsal striatum exhibits divergent functional responses during cognitive tasks: caudate activity is generally decreased, whereas putamen activity is consistently heightened.

Limbic structural and functional abnormalities

Structural imaging studies consistently demonstrate volumetric alterations in the rostral/subgenual ACC, OFC, amygdala, and hippocampus, generally trending toward reduced volume, despite some inconsistencies

across studies (P. S. Boedhoe et al., 2017; Carlisi et al., 2017; Fullana et al., 2014; Jayarajan et al., 2015; Kuhn et al., 2013; Kwon et al., 2003; Moon & Jeong, 2018; Szeszko et al., 1999; van den Heuvel et al., 2009). In contrast, meta-analytic evidence suggests that insular volume is often increased in OCD (Carlisi et al., 2017; Norman et al., 2016). Among these regions, the OFC has long been implicated in the expression of OCD symptoms (Montigny et al., 2013), and symptom severity frequently correlates negatively with OFC volume (Jayarajan et al., 2015; Venkatasubramanian et al., 2012).

Obsession has been hypothesized to arise from an overactive conflict or error signal, which continually alerts the patient that something is wrong despite contrary evidence (Pitman, 1987). Consequently, error detection has become a major focus in neuroimaging research on OCD, with consistent reports of hyperactivation in response to errors. Error processing engages broad cortical and subcortical networks, encompassing both cognitive and affective components such as frustration or self-blame. Beyond the dorsal ACC (summarized in the previous section), individuals with OCD show increased neural responses to errors in the rostral ACC and OFC (Fitzgerald et al., 2005; Maltby et al., 2005). The dorsal ACC, anatomically situated within the midcingulate cortex (Vogt et al., 2003), functions as an interface between prefrontal and limbic regions (Rolls, 2019), integrating cognitive control signals with affective and motivational input. In OCD, where hypofrontality is prominent, dorsal ACC hyperactivity during error detection is likely driven by excessive limbic input rather than intrinsic cognitive processes.

A consistent limbic finding in OCD arises from affective paradigms, which reliably demonstrate hyper-responsivity across regions including the insula, amygdala, and thalamus (Norman et al., 2016; Pico-Perez et al., 2020). Heightened activation is also observed in the caudate (contrasting its reduced engagement in cognitive contexts), putamen, and rostral ACC during emotion processing (Norman et al., 2016; Pico-Perez et al., 2020; Rasgon et al., 2017). Reduced deactivation of posterior cingulate cortex and precuneus—key nodes of the default-mode network—during non-affective tasks further supports this limbic hyperactivity profile (Rasgon et al., 2017). Consistent with this pattern, OCD participants show abnormal engagement of the left posterior hippocampus during spatial navigation, a response not observed in healthy controls (Marsh et al., 2015). Early visual areas, such as the inferior occipital gyrus, may also be influenced by limbic feedback; however, these findings are peripheral to the core pathology of OCD and lie beyond the scope of this thesis (Pico-Perez et al., 2020). Notably, the putamen exhibits both increased gray matter volume and heightened activation across cognitive and emotional tasks, a profile that diverges from other dorsal striatal structures and remains incompletely understood (Pico-Perez et al., 2020).

Impaired decision-making is another characteristic feature of OCD (Cavedini et al., 2006; Pinciotti et al., 2021). Clinically, patients display marked risk aversion, heightened intolerance of uncertainty, and excessive information gathering under ambiguous conditions. In line with limbic hyper-responsivity, individuals with OCD show increased amygdala activation during anticipation of risky outcomes in a competitive domino task (Admon et al., 2012). Moreover, subjective uncertainty in OCD is associated with widespread hyperactivation across the limbic system—including the amygdala, hippocampus, parahippocampal gyrus, insula, OFC, and ventromedial PFC—relative to controls (Stern et al., 2013), reflecting exaggerated emotional engagement during decision-making.

Conjectured neural substrates related to obsessions

Previous research has attempted to correlate specific symptoms of OCD to brain function or structure (Alvarenga et al., 2012; Hirose et al., 2017; Mataix-Cols et al., 2004; Okada et al., 2015; Pujol et al., 2004; Valente et al., 2005; van den Heuvel et al., 2009). Both reduced and enlarged gray-matter volumes have been reported across widespread cortical and subcortical regions in symptom generation, including temporal and parietal cortices, the medial frontal cortex, OFC, ACC, amygdala, and insula, as well as structures such as the caudate, putamen, thalamus, and portions of the cerebellum. Such diffuse abnormalities echo two important points: although classified as a single disorder, different symptom dimensions may arise from partially distinct neural substrates; and more broadly, symptoms may reflect epiphenomenal outputs of aberrant networks or cascading neural pathways, rather than disruptions of a particular normal neural function for which the brain

is designed—echoing the earlier point that symptoms do not arise from malfunctioning modules per se, as neural systems are evolved for functions, not for generating symptoms.

Taking a “zooming-out” approach—temporarily setting aside individual variability and making a categorical, first-pass approximation of symptom–brain correspondences—suggests the following: contamination-related distress may engage the anterior insula (AIns), a region implicated in visceral feelings of disgust (Bhikram et al., 2017); aggression and fear-of-harm concerns are likely mediated by the amygdala (Qu et al., 2024; Tonnaer et al., 2023; Zhu et al., 2024); and order–symmetry traits may involve medial temporal lobe (MTL) structures supporting spatial processing, including the hippocampus, entorhinal cortex, and parahippocampal place area (Moser et al., 2008; Schultz et al., 2012). Volumetric neuroimaging evidence provides preliminary support for this categorical mapping. Reduced insula volume has been linked to contamination/washing symptoms (Okada et al., 2015); aggression has been associated with decreased amygdala volume (Pujol et al., 2004); and symmetry/order traits have been related to MTL volume reductions, especially hippocampus (Reess et al., 2018; van den Heuvel et al., 2009). Nevertheless, reports on neural correlates of symptom dimensions show substantial variability. Beyond these three regions, additional PFC—particularly the OFC—and striatal structures such as the caudate and putamen are also frequently implicated (P. S. W. Boedhoe et al., 2017; Thorsen et al., 2018).

The results of functional imaging research appear to support these conjectures more consistently. Symptom-provocation studies show that individuals with contamination concerns exhibit heightened insular activation (Phillips et al., 2000; Shapira et al., 2003). Emotional-processing tasks that reliably engage the amygdala indicate that the aggression dimension is most closely aligned with amygdala responses (Via et al., 2014). The severity of aggressive symptoms was reflected in the altered FC between the caudate and the amygdala (Harrison et al., 2013). In tasks involving spatial memory processing, individuals with OCD show abnormal hippocampal engagement compared with healthy controls (Marsh et al., 2015). Notably, symptom-specific associated brain regions are unlikely to represent the core neuropathology of OCD. Instead, the core neuropathology should reside in neural aberrance that are common to patients regardless of their symptom profiles, situated outside the three symptom-related structures yet strongly shaped by their influence. In addition, the fact that obsessions are not invariably accompanied by compulsions strongly suggests that these phenomena are mediated by closely interacting yet segregated neural structures. Collectively, these findings indicate that limbic hyperactivity in OCD is a robust phenomenon, emerging across cognitive, affective, and decision-making contexts, and likely contributes to the disorder’s characteristic emotional and behavioral dysregulation and symptomatic manifestations.

Overall, widespread neural abnormalities have been reported in OCD, with conflicting connectivity patterns highlighted in a recent review (Perera et al., 2024). Among these, “triple network model” has been proposed to account for dysfunctions within and between the central executive, default-mode (limbic) (Lee & Xue, 2018b), and salience networks (Menon, 2011; Perera et al., 2024). Additionally, aberrations in CSTC pathways are frequently emphasized (Becker et al., 2023), and successful pharmacological treatment has been associated with widespread connectivity changes (Shin et al., 2014). However, a mean follow-up period of 5.1 years (range 1–11) revealed that 88% of children and adolescents with OCD were engaged in work or study (Micali et al., 2010). Similar to ADHD (Lee, 2025a), these broad neural abnormalities appear incongruent with the relatively benign clinical course, despite the acknowledged disability and challenges faced by patients. It has become clear that exploratory approaches, often reminiscent of phrenology and lacking rigorous *a priori* hypotheses, can be highly problematic, frequently yielding nearly “whole-brain” abnormalities associated with psychiatric disorders. Consequently, such widespread changes are unlikely to represent the core neuropathology and are better interpreted as secondary or associated alterations. The question then arises: how can the core neuropathology be identified amidst such heterogeneous and complex evidence? Centralized dialectics has been proposed to address these challenges inherent in complicated issues. Building on this framework, dialectic neuroscience has been developed to uncover the

core neuropathology of complex brain disorders, with canonical applications in psychiatric conditions (Lee, 2025a, 2025e; Lee & Xue, 2017, 2018a).

Materials and Methods

This section presents the analytic phase, structured into two components (**Materials**). The first offers a concise overview of key analytical insights derived from prior research and established knowledge, also providing a quick review list for readers. The second delineates the defining (neuro-)features of OCD that the subsequent synthesis seeks to integrate—conceptually representing the peripheral fragments of a jigsaw puzzle (see Figure 1 in (Lee, 2025d)). The **Methods** employ creative and non-linear reasoning to identify the central missing piece of the puzzle—an operating principle central to centralized dialectics—thereby allowing disparate findings to be assembled into a coherent whole. The product of this creative endeavor forms the content of Part I in the **Results** section. The validity of the proposed model will be assessed using Fisher’s combined probability meta-analytic test (Fisher, 1925). According to a heuristic scale of synthesis performance, integration of 1–2 observations is considered poor, 3–4 fair, 5–7 good, 8–10 very good, and over 10 excellent (Lee, 2025d). This manuscript presents a theoretical framework and does not involve human participants, animal subjects, or identifiable data; therefore, Institutional Review Board or research ethics committee approval was not required.

Part I: Analytic results

Fronto-striatal abnormalities in OCD

- (1) Reduced gray matter volume has been observed across multiple frontal regions, including the dorsolateral PFC, inferior frontal cortex, medial PFC, premotor cortex, and dorsal ACC.
- (2) The dorsal striatum—specifically the caudate and putamen—tends to show volumetric enlargement.
- (3) Across diverse cognitive paradigms, there is a robust pattern of reduced PFC responsivity, encompassing the rostromedial PFC, inferior frontal gyrus, dorsal ACC, premotor cortex, and dorsolateral PFC.
- (4) With increasing task demands, dorsal ACC activity tends to rise, and frontal engagement shows a pattern resembling that typically seen in healthy controls.
- (5) The caudate displays a task-dependent profile: its responsivity is reduced during cognitive tasks but elevated during affective tasks.
- (6) The putamen shows increased activity across both cognitive and affective paradigms.

Limbic abnormalities in OCD

- (7) Volumetric reductions in limbic and paralimbic structures—including the rostral/subgenual ACC, OFC, amygdala, and hippocampus—have been reported across studies.
- (8) Affective paradigms consistently reveal limbic hyper-responsivity across regions such as the insula, amygdala, and thalamus.
- (9) Consistent with this hyper-responsivity, limbic regions show increased activation during anticipation of risky outcomes or states of subjective uncertainty.
- (10) Tasks that depend on both cognitive and affective processes, such as reward learning, tend to yield mixed findings.

Neurophysiological understanding and some facts

- (11) A canonical neural circuit centered on the caudate is the CSTC loop, where the outputs of caudate reach the thalamus via the globus pallidus internal segment (GPi) and substantia nigra pars reticulata (SNr).
- (12) The dorsal striatum, particularly the caudate, receives strong inputs from the OFC and AIns, as well as from the ACC and the more dorsal and lateral regions of the PFC (Chikama et al., 1997; Robinson et al., 2012).

- (13) Both the amygdala and hippocampus send dense projections to the ventral striatum but only sparse projections to the dorsal striatum (Cho et al., 2013; Sesack & Grace, 2010; Voermans et al., 2004).
- (14) Despite (13), both the amygdala and hippocampus exert strong modulatory influences on caudate function through indirect pathways (Balleine et al., 2003; Corbit & Balleine, 2000; Corbit et al., 2002; Packard & Goodman, 2017).
- (15) Beyond the canonical CSTC loop (primarily via the mediodorsal nucleus of the thalamus), the GPi and SNr receive input from the caudate and project to intralaminar thalamic nuclei (Parent et al., 2001; Sidibé et al., 2002), which in turn can influence limbic and paralimbic systems.
- (16) The midline and intralaminar nuclei of the thalamus form a major part of the "limbic thalamus;" that is, thalamic structures anatomically and functionally linked with the limbic system (Vertes et al., 2022).
- (17) Saccade-related pathways involve CSTC circuits, with the caudate and frontal eye fields (including the supplementary eye field) serving as major relay nodes.
- (18) Huntington's disease (HD) in its early stage has long been regarded as a model of caudate pathology.
- (19) Symptom severity in OCD shows a consistent negative association with OFC volume, yet does not correlate with measures of cognitive inflexibility or response inhibition.
- (20) The fronto-parietal compartment and the limbic system interact via a reciprocal inhibitory mechanism, and disruptions in this dynamic have been implicated in MDD (Lee, 2025c; Lee & Tramontano, 2025).
- (21) The caudate mediates goal-directed, action–outcome (A–O)–based behavioral flexibility through its interactions with prefrontal and limbic circuits.
- (22) The putamen supports S–R habit formation via sensorimotor cortical inputs.
- (23) The caudate-based A–O system and the putamen-based S–R system compete for behavioral control; with overtraining, dominance shifts from A–O to S–R.
- (24) The net effect of serotonin on brain dynamics is predominantly inhibitory.
- (25) Within the striatum, serotonergic fiber density follows a ventro-dorsal gradient: lower in the dorsal striatum and higher, more uniform, in the ventral striatum, including the nucleus accumbens (NAc).

Part II: Cardinal (neuro-) features of OCD

The proposed brain theory of OCD is expected to account for a range of prominent features associated with the disorder, including:

- (1) Occurrence of obsessions;
- (2) Occurrence of compulsions, and the non-obligatory coupling between obsessions and subsequent compulsive behaviors;
- (3) Relief of tension from obsessions via compulsions;
- (4) Cognitive–behavioral inflexibility and impaired performance on saccade-related tasks;
- (5) Minimal association between core symptom manifestations and cognitive deficits or eye saccade abnormalities;
- (6) Prefrontal hypoactivity and limbic hyperactivity observed in neuroimaging;
- (8) Divergent neural responsivity in the caudate and putamen during cognitive tasks;
- (8) Volume reduction in the PFC and enlargement of the dorsal striatum;
- (9) Mechanisms of pharmaceutical interventions targeting core OCD symptoms;
- (10) Requirement of higher SSRI doses for effective treatment;
- (11) Comorbidity with ADHD and MDD.

Results

This section represents the synthetic phase of the study, complementing the analytic phase detailed in the **Materials and Methods**. It comprises two main parts. The first advances a candidate brain theory of OCD,

proposing that aberrant descending projections from the PFC to striatal structures—specifically the caudate and putamen—constitute the critical missing element in the current understanding of the disorder, with its biological plausibility established. The second part scrutinizes this model in depth by evaluating its explanatory scope and integrative strength. The first part is a product of creative thinking, whose validity can be assessed in terms of its neurobiological credibility and explanatory accountability.

Part I: Synthetic product—evidence for descending PFC–striatal projections and an open-ended limbic–striatal interaction as dual vulnerabilities in brain development and network regulation

Projections from the PFC to the basal ganglia originate primarily from layer 5 pyramidal neurons. These glutamatergic axons are slender, sparsely myelinated, and conduct substantially more slowly than heavily myelinated corticospinal fibers (Firmin et al., 2014; Innocenti et al., 2017; Lemon, 2019). In contrast, thalamocortical and corticothalamic projections benefit from robust developmental scaffolding. Transient embryonic structures, such as the subplate, and conserved molecular cues—including Netrin, Slit, Wnt, JNK, FGF, and Ephrin—ensure precise topographic targeting, typically terminating in cortical layer 4 (Cunningham et al., 2022; Hayano et al., 2014; Kostović & Judas, 2010; Poliak et al., 2015; Stoeckli, 2018). Guided by key developmental boundaries, such as the pallial–subpallial and diencephalon–telencephalon interfaces, these early-forming and structurally conserved circuits are relatively resilient to neurodevelopmental perturbations (Grant et al., 2012). Likewise, striatothalamic connections also emerge early in embryogenesis and benefit from conserved developmental guidance. For example, outputs from the dorsal striatum through the GPi and SNr reach thalamic relay nuclei—including the parafascicular and ventromedial nuclei—in a topographically organized fashion even during prenatal stages (Foster et al., 2021). Axon-guidance molecules such as Teneurin-3 (TENM3) play a crucial role in establishing dorsal-to-ventral mapping between thalamic nuclei and striatal domains, with *TENM3* mutant models exhibiting aberrant striatothalamic projection patterns and delayed motor learning (Tran et al., 2015). Moreover, the compartmental organization of the striatum (i.e., striosome vs matrix) and its segregation of projections to pallidal/nigral output nuclei impose structural constraints that refine thalamic terminal fields (Funk et al., 2023; Hunnicutt et al., 2016). These layered safeguards render the striatothalamic axis developmentally constrained, stable, and less prone to large-scale misrouting than later-arising corticofugal pathways.

By comparison, layer 5 corticofugal projections, including PFC-to-striatal fibers, must navigate complex embryonic territories without the benefit of transient scaffolds. Their development relies on prolonged molecular guidance across extended spatial domains, making them inherently more susceptible to miswiring. During early postnatal development, redundant collateral connections can transiently compensate for such mismatches (Ferino et al., 1987; Hui & Beier, 2022); see Figure 1 in (Lee, 2025a), but widespread synaptic pruning with age gradually reduces this compensatory benefits (Rakic et al., 1986; Stiles & Jernigan, 2010). Although pruning is largely adaptive, it can unmask pre-existing structural anomalies in inherently vulnerable circuits. It is important to note that feedback from the striatum to the cortex is largely indirect, relayed via the thalamus, highlighting an asymmetry in forward and backward projections within the CSTS system. Proper function of the CSTS network depends on coordinated connectivity between striatal neurons and their cortical targets. Mismatches within this auto-feedback loop can disrupt fronto-striatal function and structural organization, with pruning amplifying the consequences of developmental miswiring. Accordingly, unidirectional PFC-to-striatal projections constitute structurally and developmentally vulnerable pathways. Their relative fragility, compared to scaffolded striatothalamic and thalamocortical systems, provides a plausible circuit-level substrate for core deficits characteristic of OCD and related neurodevelopmental comorbidities, including ADHD (Lee, 2025a, 2025b).

In addition to direct PFC–striatal projections, caudate function is also shaped by inputs (direct and indirect) from limbic structures, including the AIns, OFC, amygdala, and hippocampus. While OFC and AIns projections establish direct cortico-to-striatal links, influences from the amygdala, and hippocampus often operate through indirect, polysynaptic routes. It is notable that the AIns, amygdala, and hippocampus lack closed reciprocal feedback circuits with the caudate, distinguishing them from canonical CSTC loops.

Specifically, the AIns project to the rostral and ventromedial portions of the caudate head, forming part of the limbic–associative corticostriatal pathway (Chikama et al., 1997). Through these connections, the AIns conveys interoceptive and visceral signals that inform A–O representations and support instrumental learning. However, this AIns–caudate pathway lacks a correspondent feedback connection to the AIns, rendering it an open-ended modulatory input that cannot self-regulate. Further, anatomical tracing studies indicate that the basolateral amygdala (BLA) has only sparse direct projections to the dorsal striatum, particularly the ventromedial part of the caudate head, whereas lesions of the BLA profoundly disrupt outcome-dependent instrumental learning (Balleine et al., 2003). Similarly, the hippocampus provides little or no direct projection to the caudate, yet hippocampal lesions also impair contingency-sensitive instrumental behavior (Corbit & Balleine, 2000; Corbit et al., 2002; Packard & Goodman, 2017). These apparent anatomy–function discrepancies can be explained by indirect pathways through which limbic structures modulate dorsal striatal function (see **Discussion: Dorsal striatum–centered neural circuitry** for elaboration).

When the frontal-to-caudate projections become misaligned, resulting in functional disorganization within the caudate, the limbic-to-caudate influences are prone to dysregulation, producing the characteristic symptom dimensions of OCD. The AIns, amygdala, and hippocampus may differentially contribute to obsessions with dirt/contamination, aggression/fear-of-harm, and symmetry, respectively, as inferred in the section *Conjectured neural substrates related to OCD symptoms* in the **Introduction**. Through the competitive interaction between the putamen and caudate, activation of motor plans within the former may attenuate aberrant neural activity in the latter—thus, compulsive behaviors transiently relieve the tension arising from obsessions. The combined weaknesses of the PFC-to-caudate and limbic–caudate interactions provide a compelling explanation for a distinctive feature of OCD—namely, that its core cognitive and oculomotor (eye saccade) deficits show no direct correspondence with the most diagnostically defining symptoms. This dissociation arises from two interrelated yet distinct structural vulnerabilities within the brain.

Although the NAc receives convergent inputs from the AIns, OFC, amygdala, and hippocampus—forming a framework for integrating limbic signals (Grace, 2000)—its primary influence is on reward processing, which is not a core feature of OCD symptomatology. In contrast, the caudate can modulate saccadic behavior, an effect not observed for the NAc. Thus, while both the NAc and caudate could be considered potential neural substrates based on their connectivity profiles, evaluation along additional functional dimensions allows the exclusion of the NAc as a core locus underlying OCD neuropathology. In fact, descending fronto-subcortical projections involving the ventral tegmental area (VTA), which produce subsequent abnormalities in the NAc, represent the core pathology of ADHD (Lee, 2025a, 2025b).

*Part II: Accountability evaluation of the descending PFC-subcortical model of OCD (note: the contents are in one-to-one correspondence with the core features summarized in the **Materials and Methods** section, Part II)*

Although behavioral accounts of OCD—such as negative reinforcement and maladaptive associative learning—offer rudimentary explanations for the maintenance of compulsive behaviors, they leave crucial questions unanswered: how do obsessions arise in the first place, and why does performing a compulsion provide immediate relief upon its initial execution? Such early efficacy cannot be sufficiently explained by reinforcement mechanisms alone. Critically, this initiating factor constitutes a core pathological driver that persists over time, exerting an ongoing influence on patients’ experiences and behaviors. Reinforcement-based learning may later shape how these behaviors manifest, but it does not replace the underlying pathology from which they originate.

- (1) The emergence of obsessions may stem from developmental vulnerabilities in descending PFC–subcortical projections, particularly those targeting the caudate. Subsequent dysregulation of limbic structures—including the amygdala, insula, and MTL—may underlie the three major categories of obsessions.

- (2) Following (1), vulnerabilities in descending PFC–subcortical projections involving the putamen may drive the emergence of compulsive behaviors. When aberrant descending PFC–subcortical projections predominantly impact the caudate rather than the putamen, obsessions may emerge with minimal accompanying compulsions.
- (3) Under insufficient PFC regulation, via the mechanism of competition between caudate-mediated A–O control and putamen-mediated S–R habitual responding, increased putamen activation can partially offset abnormal caudate activity.
- (4) Cognitive inflexibility and impaired saccade performance may reflect CSTC dysfunction, characterized by hypofrontality and aberrant caudate activity. Following (3), a reliance on habitual responding—implicated by enhanced putamen responsivity—may also contribute to the perseverative tendency in both cognitive tasks and clinical presentation.
- (5) With the caudate as an interface, the symptoms emerge from limbic-to-caudate perturbations (ventral to the caudate), whereas cognitive and saccadic deficits reflect fronto-striatal abnormalities (dorsal to the caudate). Consequently, symptom severity is dissociated from cognitive and sensorimotor deficits at both phenomenological and behavioral levels.
- (6) The occurrence of hypofrontality may directly result from developmental aberrance in the fronto-striatal pathway. Regarding limbic hyperactivity, caudate pathology itself may exert downstream influence on limbic structures, as supported by observations in early HD. The imbalance between fronto-parietal and limbic compartments may further amplify hypofrontality and limbic hyperactivity through a reciprocal suppression mechanism (Lee, 2025c; Lee & Tramontano, 2025).
- (7) The caudate receives inputs from the dorsolateral PFC (cognitive) and the OFC (limbic/affective). Hypofrontality and limbic hyperactivity may respectively account for the reduced and heightened responsivity to cognitive and affective challenges. The putamen has “learned” to override the caudate to relieve obsessive tension and thus becomes hyperactive across contexts, reflecting a consistent tendency to rely on habitual responding.
- (8) Developmental aberrance of descending PFC projections may contribute to reduced PFC volume during maturation. Chronic reductions in glutamatergic input to the dorsal striatum may account for its enlargement, in contrast to the hypodopaminergic VTA in ADHD, which may instead lead to reduced dorsal striatal volume.
- (9) The net effect of serotonin on large-scale neural activity is predominantly inhibitory (Anand et al., 2007; Brodie & Shore, 1957; Holthoff et al., 2004; Lee et al., 2011; Smith et al., 2011), potentially attenuating abnormal activity in both the limbic system and the caudate.
- (10) While serotonergic fibers are broadly distributed across the cerebral cortex and limbic structures, the dorsal striatum exhibits relatively lower fiber density, which necessitates higher SSRI doses to achieve therapeutic effects.
- (11) Differential topological patterns of developmental aberrance in fronto-striatal projections may contribute to ADHD and OCD, with the former primarily affecting the VTA and the latter the dorsal striatum (Lee, 2025a, 2025b). The limbic hyperactivity and frontality may contribute to vulnerability to clinical depression (Lee, 2025c; Lee & Xue, 2018a).

Using Fisher’s combined probability test, the synthetic model encompassing 11 cardinal features produced a highly significant result (chi-square = 65.7, $p < 10^{-7}$), under the assumption that each feature could be endorsed by chance at $p = 0.05$ based on prior empirical evidence. **Table 2** briefly summarizes the model’s explanatory power, with more detail elaborated in the **Discussion** section.

Table 2 Summary of the main features of ADHD explained by proposed network mechanisms

Queries/Phenomenon	Explanations
1. The occurrence of obsessions	Miswiring of PFC-to-caudate projections, along with their open-ended and indirect interactions with the limbic system, constitutes a developmental vulnerability
2. The occurrence of compulsions	Miswiring of PFC-to-putamen projections constitutes a developmental vulnerability
3. Relief of tension from obsessions via compulsions	Putamen S–R system attenuate abnormal caudate activity via competitive interactions
4. Cognitive and sensorimotor impairments	Deviant caudate-centered CSTC pathway, enhanced putamen-mediated habitual response, and hypofrontality
5. Little relevance between core symptoms and cognitive and sensorimotor abnormalities	With the caudate as an interface, ventral and dorsal circuits respectively give rise to obsessions and cognitive–sensorimotor impairments
6. Prefrontal hypoactivity and limbic hyperactivity	Impaired PFC development and caudate-mediated limbic dysregulation
7. Divergent neural responsivity in caudate and putamen	Inefficient fronto-striatal projections to the caudate and heightened putamen habitual responding
8. Volume reduction in the PFC and increase in striatum	Developmental aberrance in the PFC and reduced glutamatergic input to the dorsal striatum
9. Therapeutic effects of SSRIs	Predominantly inhibitory influence on the limbic system and dorsal striatum
10. Higher SSRI dosage is needed	Lower serotonergic fiber destiny in the dorsal striatum
11. The comorbidity with ADHD and major depression	Miswiring PFC to subcortical projection involving VTA or dorsal striatum, and compartment-level large network imbalance

Discussion

This manuscript follows the framework of “dialectic neuroscience”, previously applied to MDD, bipolar disorder, and ADHD (Lee, 2025a; Lee & Xue, 2017, 2018c). This approach ensures scientific rigor by satisfying three criteria—parsimony (two categories of vulnerability: development- and design-level), rationality (Part I of the **Results**), and accountability (Part II of the **Results**)—which can be formalized within a Bayesian framework (Lee, 2025d). Although this thesis cites a broad range of studies, it is not intended as a traditional review article, as its goal is not to scrutinize a single topic. Rather, it aims to channel creative thinking into scientific inquiry, integrating disparate pieces of evidence—peripheral elements of a larger puzzle—to reveal the core, central missing element, here the neuropathology of OCD (see Figure 1 in (Lee, 2025d)). Unlike traditional hypothesis-driven work, the rigor of this article rests on probabilistic validation. Accordingly, the analysis–synthesis structure constitutes a distinct form of research article, neither review nor narrow hypothesis paper, designed to generate new insights into complex neuroscientific problems. Within this framework, the manuscript proposes that OCD may stem from aberrant descending PFC–striatal projections and their developmental pruning, coupled with a structural vulnerability in caudate–limbic interactions. The discussion first outlines the physiological functions of the dorsal striatum, then examines the explanatory breadth of the proposed brain theory of OCD, and finally highlights the central theoretical features of dialectic neuroscience.

Dorsal striatum–centered neural circuitry

The dorsal striatum, comprising the caudate and putamen, is not a homogeneous structure but is organized into two major compartments: striosomes (patches) and matrix. Striosomes are enriched in μ -opioid receptors and exhibit low acetylcholinesterase activity. They are most prominent in the rostral (head) portion of the caudate, near the dorsal aspect adjacent to the putamen, and also appear along the borders of the ventral putamen and the NAc shell (Eblen & Graybiel, 1995; Gerfen, 1984; Graybiel, 2000). In the caudate, striosomes preferentially receive limbic-related information, largely conveyed indirectly via limbic cortices such as the OFC, ACC, and ventromedial PFC and through ventral-striatal relays, with only sparse direct input from the amygdala. Functionally, these caudate striosomes contribute to the processing of emotion, motivation, and value signals. By contrast, the matrix is broadly distributed throughout the caudate, receives inputs from sensorimotor and association cortices, and supports action selection, motor control, and cognitive processing. This compartmental organization allows the striatum to integrate internal limbic information with external sensorimotor and cognitive inputs, providing a structural basis for the caudate’s role in goal-directed behavior. In the putamen, striosomes receive relatively sparse associative and premotor inputs and project preferentially to dopamine-containing neurons in the substantia nigra pars compacta, whereas the matrix receives dense sensorimotor cortical input and forms the principal output pathway to the pallidum that mediates motor control and habit formation.

Building on this compartmental organization of the dorsal striatum, the corticostriatal architecture further differentiates the functional roles of the caudate and putamen through their participation in distinct CSTC loops. The CSTC system comprises several partially segregated yet functionally integrated circuits that converge within the dorsal striatum. Among these, three major prefrontal loops primarily target the caudate nucleus, each corresponding to specific cognitive or motor domains (Alexander et al., 1986; Grahm et al., 2008). The oculomotor loop, originating from the frontal eye field and supplementary eye field, projects to the dorsal caudate head and mediates saccadic control and visual attention. The cognitive, or dorsolateral prefrontal, loop arises from the dorsolateral PFC (BA 9/46) and terminates in the central caudate head and body, supporting executive operations such as working memory and planning. The orbitofrontal loop, derived from the lateral OFC, converges on the ventromedial caudate head and subserves value-based decision making, rule shifting, and affective evaluation. In contrast, the putamen receives predominant input from motor-related cortices—including the primary motor cortex, premotor cortex, and supplementary motor area—giving rise to the sensorimotor loop that governs the initiation, sequencing, and refinement of motor actions. Notably, in the canonical CSTC pathway originating from the caudate, the principal thalamic relay is

the mediodorsal nucleus. Beyond this mediodorsal-mediated CSTC loop, the GPi and SNr, which receive input from the caudate, also project to the intralaminar thalamic nuclei, most prominently the centromedian–parafascicular complex. These intralaminar nuclei lie outside the canonical CSTC architecture and connect with limbic and paralimbic regions, thereby allowing basal ganglia output to modulate affective and associative processing beyond closed CSTC loops (Parent et al., 2001; Sidibé et al., 2002). Such downstream projections provide a neurobiological substrate through which caudate pathology can influence limbic and paralimbic structures.

Paralleling the segregated CSTC pathways, the dorsal striatum also shows a clear functional dissociation. Convergent animal and neuroimaging evidence indicates that the putamen supports S–R habit formation via sensorimotor cortical inputs, whereas the caudate mediates goal-directed A–O control through interactions with prefrontal and limbic circuits (Grahn et al., 2008). Experimentally, the two systems dissociate under outcome devaluation or contingency degradation paradigms (Balleine et al., 2003; Lichtenberg et al., 2017; Pickens et al., 2003). More specifically, the caudate contributes to instrumental learning by selecting appropriate action plans, activating relevant action schemas, and integrating outcome evaluations to guide flexible behaviors. Consistent with this role, lesions or inactivation of the caudate abolish sensitivity to outcome devaluation and contingency changes, thereby impairing goal-directed control. In contrast, disrupting putamen function does not eliminate goal-directed responding and may even increase sensitivity to outcome devaluation—an effect consistent with weakening habitual S–R dominance and thereby unmasking A–O mechanisms (Balleine et al., 2003).

This functional dissociation within the dorsal striatum represents only one facet of a more complex organization. In practice, caudate-based A–O learning and putamen-based S–R habits interact in highly dynamic ways. A–O associations initially encoded in the caudate can, with overtraining, transition into putamen-mediated habitual control. When both systems are concurrently engaged, they do not contribute additively—instead, they compete for behavioral control to avoid interference (Brovelli et al., 2011; Kono et al., 2023; Turner et al., 2022; Vandaele et al., 2019). This competition is thought to arise from several mechanisms, including conflict resolution by prefrontal circuits, lateral inhibitory interactions between striatal territories, and state-dependent recruitment of inhibitory interneuron populations (Burke et al., 2017; Fino et al., 2018).

As summarized in *Part I* of the **Results**, open-ended limbic–striatal interactions at the caudate are influenced by the AIns, amygdala, and hippocampus. The AIns project directly to the caudate without a corresponding feedback pathway, unlike other CSTS loops, whereas the amygdala and hippocampus interact with the caudate primarily via indirect routes, lacking both direct feedforward and feedback connections. The anatomical organization is consistent with functional connectivity (FC) evidence showing that the caudate exhibits moderately significant FC with the AIns but not with the amygdala or hippocampus (Cacciola et al., 2017; Robinson et al., 2012). Nevertheless, all three structures exert strong modulatory influences on caudate function and instrumental learning, conveying information about internal state, affective value, and contextual cues, respectively. These functional influences, observed despite limited direct connectivity, provide critical modulatory signals for action selection and contextual integration, but also introduce potential vulnerabilities in network balance. There are several indirect routes through which these limbic and paralimbic structures exert their modulatory influence. First, the BLA and hippocampus project extensively to the OFC, medial PFC, and related limbic regions, which in turn provide robust inputs to the caudate head. This pathway allows sensory-specific outcome information and contextual/episodic representations to enter goal-directed circuitry. Second, both the BLA and hippocampus send projections to the ventral striatum, which can influence the dorsal striatum through spiraling striato-nigro-striatal loops (Haber et al., 2000), enabling motivational, value-related, and contextual signals to propagate from ventral to dorsal territories. Through these limbic-to-prefrontal-to-caudate routes and ventral-to-dorsal striatal loops, the amygdala and hippocampus shape goal-directed action selection and A–O representations despite their minimal direct connectivity with the caudate. In parallel, feedback from the caudate may reach these limbic/paralimbic structures indirectly via the OFC and intralaminar nuclei.

The neural consequence of deviant descending frontal-subcortical projections during development (Synthetic Results 6 and 8)

The compromise of the fronto-striatal pathway itself may produce hypofrontality and reduced caudate responsivity, findings that have been consistently replicated across cognitive paradigms and supported by independent meta-analyses (P. S. Boedhoe et al., 2017; Carlisi et al., 2017; Del Casale et al., 2016; Norman et al., 2016; Rasgon et al., 2017). However, the pathological impact may accumulate within and extend beyond this circuit. The central nervous system is highly specialized yet deeply interconnected: focal perturbations seldom remain confined but tend to propagate through distributed networks, generating cascading structural and functional consequences. For example, focal brain lesions such as infarcts can induce remote structural and functional changes (Duering et al., 2015). This principle underscores an important distinction: psychological research commonly examines specific functional domains that map onto modular brain systems, whereas psychiatric disorders often transcend modular boundaries, producing cross-domain abnormalities that reflect broader neural system dysfunction. In this context, deviant descending frontal–subcortical projections may drive progressive alterations across multiple neural networks.

One consistent structural pattern in OCD, relative to controls, is reduced frontal cortical volume—including the OFC—together with enlargement of the striatum and pallidum (Norman et al., 2016). Pruning of aberrant frontal-to-striatal projections may contribute to cortical thinning, whereas diminished glutamatergic drive from the PFC to the dorsal striatum could promote striatal and pallidal enlargement, potentially through reduced glutamatergic exposure (Christian et al., 2011; Martin & Wellman, 2011). Similar mechanisms may also account for the insular or AIns volume increases occasionally reported in OCD (Carlisi et al., 2017; Klugah-Brown et al., 2023; Nishida et al., 2011; Tang et al., 2015). Note that the insula receives heterogeneous afferents—including thalamic, limbic, sensory, and multimodal association inputs—so altered PFC projections constitute only one element within a broader anatomical architecture (Carlisi et al., 2017; Klugah-Brown et al., 2023). Compensatory neural responses may also emerge to counter reduced fronto-striatal efficiency, recruiting additional resources to sustain performance under increasing task demands (Ursu et al., 2003; Yucel et al., 2007). Consistent with both fMRI and structural findings, compensatory frontal hyperactivation may elevate local glutamatergic transmission, contributing further to PFC volumetric loss (Marsh et al., 2014; Moon & Jeong, 2018).

A central question for the proposed model is whether caudate aberrancy can influence limbic and paralimbic structures in ways that contribute to the genesis of obsession symptoms. HD provides a model of progressive caudate pathology for testing this question. HD is an autosomal dominant neurodegenerative disorder marked by motor, cognitive, and affective disturbances, with neuronal loss beginning in the striosomal compartment of the caudate head and progressing dorsoventrally (Douaud et al., 2006; Grahn et al., 2008). In a route-recognition paradigm studied in HD, caudate dysfunction was associated with heightened hippocampal responses (Voermans et al., 2004). Converging evidence from HD cohorts shows structural and functional abnormalities in limbic and salience-processing regions: reduced amygdala volume (greater in symptomatic than presymptomatic carriers) (Ahveninen et al., 2018; Douaud et al., 2006), impairments in disgust processing in both symptomatic patients and asymptomatic gene carriers (Gray et al., 1997), and parallel reductions in insular cortex integrity implicated in interoception and salience (Douaud et al., 2006; Stoebner et al., 2023). Collectively, these observations indicate that progressive caudate pathology can exert downstream effects on the hippocampus, amygdala, and insula, providing face validity for the hypothesis that caudate dysfunction may drive limbic hyperactivity relevant to obsession formation. Although it remains unclear through which precise pathways caudate pathology impacts the limbic system, the predominantly GABAergic nature of basal ganglia outputs offers a plausible mechanistic link. Reduced inhibitory influence on downstream targets would be expected to weaken regulatory control over limbic structures, thereby contributing to the limbic hyperactivity consistently observed in OCD, elaborated below.

Degeneration or hypofunction of the caudate is expected to disinhibit downstream basal ganglia output via a sequence of GABAergic connections along the indirect pathway, involving projections from the caudate

to the globus pallidus externa (GPe), from the GPe to the GPi and SNr, and subsequently from the GPi/SNr to the thalamus, ultimately resulting in enhanced thalamic activity (Alexander & Crutcher, 1990). Importantly, projections from the GPi and SNr to thalamic nuclei are not strictly constrained by canonical CSTC topography but instead exhibit a relatively loose, functionally organized arrangement (Haber & Calzavara, 2009). Within this framework, intralaminar thalamic nuclei—most notably the centromedian–parafascicular complex—play a pivotal role in transmitting basal ganglia output to limbic and paralimbic structures, including the amygdala, medial temporal lobe, and insula (Dillingham et al., 2015; Kumar et al., 2023; Vertes et al., 2022; Zhang & Bertram, 2002). Consequently, caudate dysfunction can propagate through these non-canonical thalamic pathways to induce abnormally heightened activity in limbic and paralimbic regions, providing a mechanistic explanation for the widespread limbic hyperactivity observed in HD and related basal ganglia disorders. The relatively loose mapping from the GPi/SNr to the thalamus ensures that this influence is distributed rather than strictly focal, accounting for the complex and partially overlapping patterns of limbic dysregulation. Heightened thalamic activity during affective processing in OCD lends support to the above inference (Rasgon et al., 2017).

Notably, a reciprocal suppression relationship exists between the fronto-parietal and limbic compartments (Lee, 2025c; Lee & Xue, 2018a). In OCD, intrinsic hypofrontality combined with limbic hyperactivity may amplify large-scale network imbalance through this mutual inhibitory mechanism: the limbic system exerts a disproportionately stronger suppression influence on the fronto-parietal compartment, while the counter-regulatory inhibition from the fronto-parietal system onto the limbic region becomes attenuated. Without adequate downregulation and top-down coordination from the PFC, aberrant limbic inputs to the caudate may persist and undergo Hebbian strengthening, further stabilizing limbic hyperactivity and reinforcing the imbalance between limbic and fronto-parietal compartments.

Limbic hyperactivity may contribute to volume reductions across multiple regions—such as the ACC—potentially via calcium-overload–related toxicity (Alberdi et al., 2005). These limbic reductions become more pronounced when directly comparing adults with pediatric OCD (Figure 1a and 1b in (P. S. Boedhoe et al., 2017)), with the adult pattern reflecting longer illness duration. As the disorder progresses, subcortical limbic structures—including the amygdala, hippocampus, and thalamus—tend to show progressive atrophy, whereas striatal and pallidal volumes increase (P. S. Boedhoe et al., 2017; Pico-Perez et al., 2020). Findings in pediatric or first-onset patients, however, are markedly heterogeneous, ranging from enlarged hippocampal volumes to reduced dorsal striatal volumes, underscoring substantial developmental variability in early-onset OCD (Christian et al., 2008; Valente et al., 2005). The characteristic adult profile—reduced limbic/paralimbic volumes alongside enlarged striatal and pallidal structures—emerges most clearly when contrasted with pediatric OCD and is consistent with progressive neurobiological change over time. Supporting this temporal effect, insular volume appear to diminish in older or more chronic samples (Radua & Mataix-Cols, 2009; Yildiz et al., 2020), in line with the possibility that prolonged hyperactivity eventually leads to atrophy. Overall, chronic hyperactivity may drive the reduction of subcortical limbic and paralimbic volumes (Christian et al., 2011; Martin & Wellman, 2011), whereas diminished glutamatergic input from the PFC likely contributes to striatal and pallidal enlargement. Concordant with the proposed model, multiple studies have also reported corresponding reductions in adjacent white-matter pathways alongside regional gray-matter loss (Koprivova et al., 2009; Lazaro et al., 2014; Moon & Jeong, 2018). In contrast, ADHD typically shows reduced caudate volume, a pattern most plausibly linked to hypodopaminergism (Lee, 2025a).

Mixed neuroimaging findings in OCD may, in part, reflect opposing trends in regional volume and responsivity. Limbic structures often show reduced volume yet heightened responsivity, whereas the caudate can exhibit the reverse pattern—enlarged volume accompanied by reduced responsivity to cognitive tasks. For example, beyond the established contribution of the inferior frontal cortex, subcortical nodes such as the caudate nucleus also participate in inhibitory control via cortico-striatal loops (Booth et al., 2003; Peterson et al., 2002). Recent meta-analytic evidence, however, does not indicate a reliable reduction in caudate responsivity during inhibitory control (Funch Uhre et al., 2022). Limbic regions likewise add to these inconsistencies in prior analyses, such as neural response to reward feedback signals (Figeet et al., 2011; Jung

et al., 2011). Another major source of these mixed results may lie in circuit-level heterogeneity: the caudate is embedded in both cognitive CSTC circuits (via the dorsolateral PFC) and affective CSTC circuits (via the OFC). These two cortical inputs show opposite activity patterns in OCD—reduced dorsolateral PFC engagement but increased OFC/affective engagement. Studies that pool cognitive and affective paradigms therefore tend to produce null or inconsistent caudate findings, whereas analyses that separate these conditions reveal opposite context-dependent response patterns (Rasgon et al., 2017). This circuit dissociation provides a parsimonious explanation for the apparent inconsistencies in the broader neuroimaging literature.

Both OCD and ADHD exhibit alterations in large-scale brain network connectivity, reflecting disrupted integration between functional systems (Cortese et al., 2016; Gursel et al., 2018). The frontal lobes, as top-down control hubs, orchestrate coordination among networks such as the frontoparietal, salience, and default-mode systems. In ADHD, dysfunction of frontal regions likely underlies widespread hypoconnectivity across these networks and reduced anticorrelation between the default-mode and task-positive networks. Similarly, in OCD, frontal lobe abnormalities may contribute to consistent between-network hypoconnectivity, even if within-network connectivity varies. Thus, frontal dysfunction provides a unifying mechanism linking large-scale connectivity disturbances observed in both disorders. The cascade of abnormalities observed in OCD can be mapped naturally onto the framework of the triple-network model (Perera et al., 2024): Aberrant frontal–striatal projections initiate hypofrontality and consequent disruption of executive control networks. In parallel, caudate dysfunction, together with reciprocal fronto–limbic interactions, amplifies limbic hyperactivity and thereby contributes to the dysregulation of the default-mode network (Lee & Xue, 2018b). Additionally, altered caudate–insula interactions account for the aberrant functioning of the salience network. Together, these network-level perturbations—spanning executive, default-mode, and salience systems—provide a coherent circuit-based explanation for the imbalance across three large-scale networks. Notably, the framework proposed in this thesis provides a mechanistic account of OCD, elucidating both the underlying neural disturbances and the processes through which they emerge and develop. In contrast, the triple-network model offers a descriptive mapping of network-level abnormalities without specifying the causal or developmental mechanisms that give rise to these alterations. While influential in guiding neuroimaging research, its explanatory power remains limited compared with a mechanistically grounded approach.

Network mechanisms for the symptom of obsessions (Synthetic Results 1 and 5)

Around the globe, OCD exhibits a broadly similar symptom structure, encompassing themes such as contamination, symmetry, hoarding, taboo thoughts, and fear of harm. Nonetheless, meaningful variation in symptom expression exists across populations, and sociocultural contexts can shape the specific content of obsessions and compulsions. In an analogous fashion, just as overarching constructs such as hypofrontality and limbic hyperactivity are employed to provide a high-level neurobiological landscape while temporarily bracketing finer distinctions, the present account adopts a comparable zoom-out perspective on obsessional symptoms. This approach aims to establish their broad pathological foci, while temporarily suspending consideration of more context-dependent nuances.

From this perspective, obsessions related to contamination, fear of harm, and symmetry can be provisionally mapped onto dysregulated activity within the AIns, amygdala, and MTL, respectively. This conjecture has received preliminary support from neuroimaging studies examining symptom-specific neural correlates in OCD, using both volumetric approaches (Okada et al., 2015; Pujol et al., 2004; Reess et al., 2018; van den Heuvel et al., 2009) and functional paradigms (Phillips et al., 2000; Shapira et al., 2003; Via et al., 2014). Crucially, however, these limbic abnormalities are not posited as primary pathological loci. Rather, they are conceptualized as downstream consequences of caudate pathology, which perturbs limbic processing through disrupted caudate–limbic interactions. This interpretation is supported by convergent evidence indicating that caudate dysfunction can induce secondary alterations across multiple limbic structures (Ahveninen et al., 2018; Douaud et al., 2006; Stoebner et al., 2023; Voermans et al., 2004), a pattern observed in early HD, a prototypical caudate-based disorder. More broadly, the dysregulation

between the caudate and limbic system exposes a fundamental vulnerability in the brain's architectural design. In contrast to the tightly organized closed-loop structure of CSTC circuitry, caudate–limbic interactions lack an equivalent regulatory loop. This loose and asymmetric connectivity renders the system intrinsically susceptible to instability, allowing limbic perturbations to be amplified rather than effectively constrained. Such a design-level vulnerability provides a neurobiological explanation for why heterogeneous obsessional contents can arise from a shared underlying neuropathological substrate.

As outlined above, limbic inputs exert a substantial influence on instrumental learning, yet the caudate—though central to CSTC circuitry—provides relatively limited direct feedback for gating or suppressing those symptom-pertinent limbic signals. When the PFC is intact, top-down control can effectively modulate limbic drive; however, a developmental vulnerability of PFC–striatal projections undermines this regulatory capacity. Consequently, structural and functional weaknesses at the caudate–limbic interface emerge alongside PFC–striatal aberrance, leading to sustained and insufficiently regulated limbic influence on the caudate. In summary, these developmental and design-level vulnerabilities form a unified pathological architecture: developmental fragility of the PFC–striatal pathway manifests as impaired cognitive and FPC-to-limbic control, whereas design flaw within the caudate–limbic configuration gives rise to limbic dysregulation and the emergence of obsessional symptoms. Within the present framework, limbic circuitry contributes to the thematic expression of obsessions rather than serving as the primary source of the disorder. By explicitly separating symptom-related neural correlates from core pathophysiology, this model avoids phrenological interpretations and reconciles heterogeneous symptom–circuit associations without conflating them with the disorder's primary neural origin.

Since the amygdala and MTL lack direct projections to the caudate, their influence is most plausibly routed through the OFC, which serves as a major hub for limbic integration. Although the AIns does project to the caudate, its paralimbic signals are also likely integrated within the OFC before being conveyed to the striatum, consistent with established accounts of limbic network interactions (Mega et al., 1997). Symptom-oriented neuroimaging studies have accordingly implicated the OFC across multiple obsessive dimensions in OCD: OFC volume and activity correlate with the intensity of contamination, aggression, sexual/religious, and hoarding symptoms (Alvarenga et al., 2012; Mataix-Cols et al., 2004), while OFC volume also shows a negative association with overall symptom magnitude (Jayarajan et al., 2015; Venkatasubramanian et al., 2012). Although associations between symptom severity and caudate volume or activation have also been reported, such findings remain compatible with the present neural model of OCD (Mataix-Cols et al., 2004; van den Heuvel et al., 2009). On this basis, symptom provocation is expected to commonly engage the OFC, a prediction supported by meta-analytic evidence from symptom-evoked fMRI studies (Rotge et al., 2008). Notably, these meta-analyses do not reveal a dominant effect within any single symptom-specific limbic region, likely because distinct obsessive dimensions recruit partially dissociable limbic inputs that become “diluted” in pooled analyses. Even cingulo-opercular involvement in OCD, often linked to prototypical disgust-triggered symptoms, has been controversial (Becker et al., 2023; de Vries et al., 2019). Instead, the most robust and consistent activations are observed in the OFC and ACC, which function as key interfaces mediating interactions between limbic structures and the caudate—particularly the caudate head. Fractional anisotropy in OFC–striatal fibers has been reported to be higher in OCD than in healthy controls (Nakamae et al., 2014), supporting the view that structural alterations within this pathway are implicated in symptom expression. Taken together, incorporating the OFC yields a more coherent account of prior symptom-related neuroimaging findings and helps reconcile their apparent heterogeneity. By contrast, attempts to explain obsessive symptoms primarily in terms of error-monitoring mechanisms derived from cognitive neuroscience are insufficient, both at the phenomenological level and with respect to the available empirical evidence.

From the perspective of instrumental learning, limbic inputs in this context are maladaptive because they lack action-initiated associations. As a result, such inputs perturb the fundamental functional logic of the caudate—namely, the principle that actions lead to outcomes. What becomes salient under these conditions is therefore not an action-to-outcome ($A \rightarrow O$) association, but rather an outcome-without-action representation, or conversely, an urge that proceeds from outcome to action ($O \rightarrow A$). These abnormal limbic

inputs to the caudate arise from susceptibility at three structural levels. First, impaired frontal coordination and regulation prevent effective modulation of limbic inputs at the level of the caudate. Second, although limbic–caudate interactions are intrinsically strong, they lack dedicated regulatory circuitry and are ordinarily mediated through instrumental A–O learning mechanisms; evolution has not equipped this system to handle outcome signals in the absence of action. Third, abnormal limbic inputs originated from caudate dysfunction are further amplified by limbic hyperactivity secondary to hypofrontality. Distinct limbic signals may converge on different caudate subregions, while higher-order cognition mediated by the PFC–striatal network imbues these signals with cognitive context. Accordingly, amygdala-derived signals in OCD are not expressed as simple reflexive fear or aggression, but rather as contextually elaborated representations shaped by the OFC and PFC–caudate and ultimately manifested, through the subject’s interpretive experience, as fear-of-harm–related symptoms.

The neural mechanisms by which symmetry alleviates tension arising from less ordered spatial arrangements are not fully understood, though emerging neuroscience evidence offers preliminary insights. From the standpoint of neural dynamics, both symmetry and orderly regularity (e.g., repetition, predictable spatial organization) exert a stabilizing influence on sensory processing. Across animal electrophysiology and human neuroimaging, structured patterns reliably evoke more synchronized and less variable neural responses than irregular or random configurations. In macaque inferior temporal cortex, symmetric and regularly repeating stimuli generate more distinctive and consistent single-unit responses because neurons tend to prefer identical parts across positions (Pramod & Arun, 2018). Human fMRI studies similarly show enhanced activation in extrastriate regions when observers view symmetric or regularly ordered dot patterns compared to random stimuli (Sasaki et al., 2005). EEG/ERP evidence converges on this principle: the sustained posterior negativity (SPN) increases not only with symmetry but also with other forms of regularity, reflecting a robust extrastriate response to predictable structure (Jacobsen et al., 2018). Because structured patterns reduce perceptual uncertainty and generate more predictable population activity, they may suppress “untuned” limbic noise—for example, unmodulated input from MTL sources—and thereby stabilize information entering downstream systems such as the caudate.

In addition to MTL, parietal cortex is also crucial for spatial processing and sends projections to the dorsal striatum (Giarrocco & Averbeck, 2023; Selemon & Goldman-Rakic, 1988), so a parietal-to-striatal contribution to symmetry/order symptoms in OCD cannot be fully ruled out. Developmentally, however, parietal corticostriatal projections mature earlier and stabilize more rapidly than their prefrontal counterparts (Gerván et al., 2017). This dissociation makes parietal outputs less likely to constitute a major locus of developmental weakness. Clinically, striatal dysfunction secondary to parietal lesions is correspondingly uncommon. For these reasons, the present work does not center on parietal cortex. Although parietal abnormalities in OCD have been reported (P. S. W. Boedhoe et al., 2017; Okada et al., 2015), these findings are more plausibly secondary or compensatory to prefrontal dysfunction, given the strong reciprocal interactions between frontal and parietal regions.

Network mechanisms for the symptoms of compulsion (Synthetic Results 2, 3 and 7)

Supported by animal and neuroimaging evidence, the putamen serves as the substrate for S–R habit formation, reflecting the incremental strengthening of simple S–R associations in which actions are triggered directly by external cues without reference to outcomes, through inputs from sensorimotor neocortex. By contrast, the caudate supports behavioral flexibility, providing cognitive control via prefrontal and limbic circuits involved in A–O relational and spatial information processing (Devan et al., 2011; Grahm et al., 2008). A competitive relationship exists between A–O and S–R control: extensive training may shift behavioral control from A–O to S–R responding, whereas S–R associations can be attenuated when A–O representations are re-engaged to accommodate novel contexts or contingencies. This competition between caudate-based A–O control and putamen-based S–R control is generally attributed to learning-dependent biases and output-level gating within parallel CSTC loops, rather than direct mutual inhibition between the two striatal regions (Graybiel, 2008; Redgrave et al., 1999). Notably, medial PFC projections spanning the dorsal striatum have

been shown to be critical for suppressing previously acquired associations (Rhodes & Killcross, 2004), suggesting a potential top-down influence in modulating the competition between these striatal control systems.

Building on this conceptualization—where compulsive behavior arises from a competitive interplay between the caudate and putamen, with the putamen tempering caudate-driven obsession—both behavioral and neurobiological predictions follow. Behaviorally, this interaction should manifest in paradigms examining A–O learning and habit transfer. If OCD depends on putamen-mediated compulsions to relieve obsession-related urges and anxiety, this reliance is expected to appear as an exaggerated habitual response when A–O contingencies change. In a canonical A–O learning and habit-transfer paradigm, participants first learn two action–outcome associations, each linking a specific action to a rewarding outcome. Both actions are subsequently overtrained to bias behavior toward habitual responding, and an outcome-devaluation test then assesses whether participants reduce responding specifically to the action whose outcome has been devalued. Although OCD patients acquire A–O contingencies normally, they often fail to adjust behavior after devaluation, showing excessive reliance on habitual control (“slips-of-action”) compared with goal-directed evaluation (Gillan et al., 2011). Thus, the behavioral signature commonly interpreted as exaggerated habit bias can instead be understood as a maladaptive compensatory response, in which the system attempts to counteract dysregulated caudate signals via putamen-driven output.

In addition, the imbalance between the putamen and caudate should also be reflected in their neural activity patterns. As summarized previously, reduced caudate responsivity has been documented across a broad range of cognitive tasks, a finding supported by meta-analytic evidence (Del Casale et al., 2016; Rasgon et al., 2017) and consistent with the model of impaired fronto-striatal projections. In affective paradigms, however, caudate subregions diverge: the head shows increased activation, whereas the body shows reduced activation (based on 54 task-fMRI studies and over 1,000 participants) (Rasgon et al., 2017). Heightened caudate-head activity in affective contexts accords with the proposed model in which the caudate receives aberrant limbic inputs via OFC. By contrast, the putamen tends to exhibit increased activation during cognitive tasks (Pico-Perez et al., 2020), particularly when alternating stimulus congruence across trials disproportionately engages habitual responses in OCD. Under such conditions, individuals with OCD show elevated putamen activation, consistent with increased recruitment of S–R habits. This heightened engagement is accompanied by stronger FC between the putamen and other fronto-striatal regions (Marsh et al., 2014). In affective paradigms, putamen hyperactivation emerged as a robust and dependable finding, as demonstrated in the large-scale meta-analysis (Pico-Perez et al., 2020; Rasgon et al., 2017), fully in line with the theoretical prediction. Taken together, these behavioral and neural patterns converge with the proposed neuropathological framework: putamen-mediated habitual compulsions, though maladaptive, counterbalance dysregulated caudate signaling driven by limbic inputs, thereby mitigating obsession-related urges or anxiety through competitive mechanisms. These caudate–putamen interactions, grounded in symptom-related neural dynamics and instrumental–habit learning mechanisms, are reflected across both behavioral regulation and neural responsivity.

The competition between S–R and A–O control is not haphazard, but determined by context. The linkage between compulsive behaviors and their corresponding obsessive content is mediated by action schemas jointly represented in the caudate and putamen. Accordingly, putamen-driven motor output cannot recruit arbitrary action patterns to counteract caudate-related obsessive urges; rather, it preferentially engages action plans that are contextually congruent with the obsessive theme. This constraint provides a neural basis for the strong content-specific concordance between obsessions and compulsions—for example, contamination-related obsessions preferentially recruiting washing-related motor programs. As previously noted, descending PFC–subcortical projections constitute a developmental liability whose functional impact varies across individuals. It is therefore reasonable to infer that disruptions in PFC–striatal projections may concurrently affect both the caudate and the putamen. When frontal control over the dorsal striatum is weakened, the competition between the caudate and putamen proceeds without effective PFC engagement. Under conditions in which aberrant descending PFC–subcortical influences predominantly affect the caudate

while the putamen remains under effective PFC regulation, obsessive phenomena may emerge with minimal or absent accompanying compulsive behaviors. When compulsions effectively relieve the tension or aversive state induced by obsessions, this linkage is strengthened through negative reinforcement, whereby the removal of an aversive internal state increases the likelihood of compulsive behavior. Importantly, behavioral theory can account for the persistence of compulsive actions, but it cannot fully explain why these behaviors alleviate the associated discomfort and tension. This limitation highlights the insufficiency of a purely behavioral perspective for understanding OCD; by contrast, the present neurobiological account provides a mechanistically coherent explanation for this phenomenon.

In summary, because direct mutual inhibition between the caudate and putamen is absent, the putamen can only modulate—rather than fully suppress—aberrant caudate activity. Stereotyped and habit-like actions mediated by the putamen act through a competitive mechanism to temporally and partially alleviate excessive caudate drive arising from limbic inputs, reducing obsession-related urge or anxiety without fully abolishing it. The caudate–putamen interplay also explains why compulsions can relieve obsessional distress even though patients recognize that no genuine causal relationship exists between them.

Neural mechanisms underlying neuropsychological and sensorimotor impairment (Synthetic Results 4)

Converging evidence indicates that individuals with OCD show mild to moderate impairments in cognitive flexibility and saccade-related tasks, particularly set-shifting and antisaccade paradigms (Chamberlain et al., 2021; Gruner & Pittenger, 2017; Jaafari et al., 2011). Hypofrontality provides a plausible account for many of these behavioral abnormalities, affecting working memory (e.g., n-back), cognitive switching, conflict processing (e.g., Stroop and flanker tasks), response inhibition (e.g., Go/No-Go and stop-signal tasks), and reversal learning. In addition, limbic hyperactivity has been consistently observed in OCD, manifesting across affective paradigms, heightened subjective uncertainty, and exaggerated performance and error monitoring (Lei et al., 2015; Riesel et al., 2011; Stern et al., 2013).

Although PFC dysfunction can lead to a broad range of cognitive impairments, certain indices help differentiate deficits arising from PFC versus dorsal striatal dysfunction. Among these, learned irrelevance (or latent inhibition) is especially informative (Owen et al., 1993). Specifically, patients with frontal-lobe excisions exhibited intact performance when required to orient attention toward previously irrelevant information, whereas early-stage, unmedicated Parkinson's disease patients were impaired both in disengaging from prior task sets and in shifting attention to previously irrelevant dimensions (Grahn et al., 2008; Owen et al., 1993). Similarly, individuals with OCD show prolonged unlearning of previously irrelevant information, reflecting enhanced latent inhibition (Swerdlow et al., 1999). This pattern suggests that OCD-related cognitive inflexibility has a notable subcortical component, particularly involving the dorsal striatum. Despite ongoing debate, deficient response inhibition has been implicated in OCD. Impairment in response inhibition is often associated with impulsivity, as observed in ADHD, whereas OCD—both clinical and subclinical populations—is typically characterized by behavioral and cognitive rigidity (Ramakrishnan et al., 2022). Approximately 25% of OCD patients present with comorbid OC personality disorder (Pozza et al., 2021), and more than 50% exhibit OC personality traits (Pinto et al., 2015). Hyperactivity in the putamen, resulting from aberrant descending projections from the PFC to the dorsal striatum, as well as inherent competition with the caudate, may underlie habitual behavioral tendency and provide a potential neuroscientific explanation for these seemingly divergent behavioral profiles. The 23-ms prolongation in reaction time observed in the stop-signal task may reflect the additional effort required to overcome habitual response patterns (Funch Uhre et al., 2022; Mar et al., 2022), consistent with the observation that neuroimaging studies have not revealed a convergent deficit in classical inhibitory centers in OCD (Funch Uhre et al., 2022).

The antisaccade task requires participants to suppress a reflexive saccade toward a visual target and instead generate a voluntary saccade to the mirror opposite location, whereas the prosaccade task involves a visually-guided saccade to the target. Meta-analytic evidence indicates that both tasks consistently engage a distributed fronto–subcortical–parietal network, including the frontal and supplementary eye fields, striatum (notably the caudate), thalamus, and intraparietal cortex (Jamadar et al., 2013). Antisaccades recruit

additional prefrontal regions, such as the dorsolateral and ventrolateral PFC, reflecting greater cognitive control demands, whereas prosaccades predominantly rely on the basic visuo-motor network. The caudate contributes to the execution of both prosaccades and antisaccades via the cortico-striato-tectal pathway, whereas the suppression of reflexive saccades relies primarily on direct dorsolateral PFC projections to the superior colliculus (Condy et al., 2004). The core of this pathological model lies in the PFC and caudate, central nodes of the oculomotor CSTC circuit, providing a coherent explanation for the observed saccadic abnormalities. Importantly, the superior colliculus receives direct inputs from both frontal and parietal eye fields (see review (Shipp, 2004)), forming a long descending pathway that is relatively more susceptible to developmental aberrations, as postulated in OCD, which may further compromise saccade performance. Developmental abnormalities in descending PFC projections that impair the regulation of subcortical oculomotor circuits in OCD may also underlie similar saccadic deficits across other psychiatric conditions (transdiagnostic), such as ADHD, autism, and schizophrenia (Toghi et al., 2025).

From a symptomatology perspective, prior attempts to account for OCD within a purely cognitive-neuroscience framework remain insufficient. For example, an earlier review titled *Cognitive neuroscience of obsessive-compulsive disorder* summarized prior work as follows (not reflecting the author's own position and with no intent of personal criticism): "...obsessions are caused by an overactive conflict or error signal continually telling the patient that something is wrong despite evidence to the contrary." The central limitation of this view is its inability to explain the stereotyped structure and origins of obsessions. Likewise, the proposal that "...compulsions are behaviors that attempt to reduce this heightened conflict signal or to correct perceived errors," and that "...studies of response inhibition examining the suppression of motor output in OCD are directly relevant for repetitive motor compulsions," fails to address the fundamental question of where compulsions originate and why these behaviors can "correct" a perceived error or relieve inner tension—rather than trigger frustration—when response inhibition fails. These basic clinical features hence remain unaccounted for in conventional cognitive-neuroscience models. In line with the preceding arguments, neuroimaging studies show that neural activity related to error detection and conflict resolution does not correlate with symptom severity or expression (Lei et al., 2015; Maltby et al., 2005; Riesel et al., 2011; Ursu et al., 2003). Similarly, saccadic abnormalities are not associated with overall clinical burden (Jaafari et al., 2011). Taking the caudate as an interface, the proposed model from dialectic neuroscience may clarify a core issue in previous interpretations: prior studies often misattributed network impairments "dorsal" to the caudate (cognitive deficits) to account for network dysfunctions "ventral" to the caudate (limbic origin, OCD symptoms). For further elaboration, see the section *Defining characteristics of dialectic neuroscience*.

Although increased putamen activity and volume are commonly reported findings in OCD, they have received relatively little attention. Considering the balance between the caudate and putamen, examining these structures together within the context of inadequate PFC regulation may provide a more comprehensive network-level explanation for cognitive and behavioral inflexibility in OCD.

Potential mechanisms of pharmaceutical treatments (Synthetic Results 9 and 10)

The first-line treatment for OCD is SSRI, with the required dosage typically two to three times higher than that used in depressive disorders (Bloch et al., 2010). Although the distributions, functions, and neurochemical interactions of the various serotonin-receptor subtypes are complex (Hoyer et al., 1986; Varnäs et al., 2004), two basic trends emerge. Firstly, serotonergic fibers are widely distributed in the cerebral cortex and limbic-system structures, where they form abundant axonal terminals or varicosities (Charnay & Léger, 2010). Within the striatum, however, there is a ventro-dorsal gradient: the dorsal striatal region exhibits relatively lower serotonergic fiber density, whereas the ventral striatum, including the NAc, contains a denser and more homogeneous distribution of varicosities. This pattern has been consistently observed in non-human primates using immunohistochemistry and confirmed in human post-mortem studies employing stereology-based quantification (Hörtnagl et al., 2020; Lavoie & Parent, 1990). Such a gradient may reflect functional differences, with ventral striatum being more involved in reward and emotional processing, whereas dorsal striatum is predominantly associated with cognition, motor and habitual circuits. In addition,

the density of the serotonin transporter (SERT) in the striatum is higher than in the neocortex and most limbic structures, excepting the amygdala; see Figure 4 in (Beliveau et al., 2017).

Secondly, the overall influence of serotonin on large-scale neural activity is predominantly inhibitory. Neural inhibition following acute SSRI administration spans a wide range of cortical and subcortical regions (Anand et al., 2007; Holthoff et al., 2004; Smith et al., 2011). This observation aligns with Brodie and Shore's proposal that serotonin and norepinephrine may exert inhibitory and excitatory modulation, respectively, on central nervous system activity (Brodie & Shore, 1957). Consistently, the author's earlier work demonstrated a global trend in which carriers with low transcriptional efficiency of the SERT exhibited reduced regional neural power, independent of frequency band (Lee et al., 2011). A recent large-scale study (HC vs. OCD: 1,760 vs. 1,905) complements this viewpoint, showing that long-term SSRI exposure may lead to widespread cortical thinning across the brain (P. S. W. Boedhoe et al., 2017). SSRI administration may dampen abnormal activities in the caudate (and putamen) as well as in the inputs from limbic structures, which are relevant to the core symptoms of OCD.

From treatment perspective, another key question in OCD is why SSRI doses need to be so high. In comparison with MDD, restoration of the compartment-level imbalance between fronto-parietal and limbic systems in MDD is innately facilitated by fronto-parietal activity through reciprocal suppression mechanisms (Lee, 2025c; Lee & Xue, 2018a). This, together with the understanding of serotonergic fiber density and SERT distribution in the striatum, provides three physiological explanations for the higher SSRI doses required in OCD: (1) Serotonergic fiber density in the dorsal caudate-putamen is relatively low, reducing baseline serotonergic modulation of striatal circuits (Hörtnagl et al., 2020; Lavoie & Parent, 1990). (2) SERT density is relatively high in the striatum, potentially necessitating higher doses of SSRIs to achieve sufficient synaptic serotonin levels. (3) There is no effective mechanism for maintaining network balance between the caudate-putamen and limbic structures. This interaction is further constrained by aberrant descending projections from the PFC to the striatum, which limit the intrinsic capacity of the PFC-dorsal striatal system to exert compensatory regulation over limbic activity and may thereby contribute to the need for higher SSRI dosages.

In addition to SSRIs, atypical antipsychotics—especially risperidone—are frequently used as augmentation treatment for OCD (McDougale et al., 1995). Its primary mechanisms are D2 receptor blockade and 5-HT_{2A} receptor antagonism. The pharmacological actions of risperidone align well with the present theoretical framework, but are difficult to reconcile with the tripartite model, as detailed below. D2 blockade engages the basal-ganglia indirect pathway described in the DeLong model, modifying striatal processing in a manner that can attenuate abnormal neural activities related to OCD symptoms within the caudate-putamen circuitry. Moreover, 5-HT_{2A} receptors exert excitatory effects on cortical and striatal neurons (Aghajanian & Marek, 2000); thus, their antagonism enhances the net inhibitory influence of the serotonergic system and synergizes with SSRI-induced elevations in extracellular serotonin. Through these dual mechanisms—modulation of striatal circuit dysfunction and reinforcement of serotonin-mediated inhibitory control—risperidone can improve symptoms in SSRI partial responders. According to DSM-5 criteria, compulsive behaviors typically occur in response to obsessions (American Psychiatric Association, 2013), which is consistent with both clinical observations and mechanistic considerations. Reflecting this relationship, pharmacological treatments generally improve both obsessions and compulsions rather than targeting compulsions alone. In particular, antipsychotic augmentation has been shown to produce significant improvements in both symptom domains (Dold et al., 2013; Thamby & Jaisooriya, 2019), aligning with the theoretical framework proposed in this study, whereby treatment primarily modulates neural activity in the caudate—or both the caudate and putamen—to indirectly normalize circuits underlying core OCD symptoms.

Notably, the proposed model posits dorsal structural and ventral functional abnormalities, with the dorsal striatum serving as the critical interface. In line with this view, symptom improvement following pharmacological treatment is typically not accompanied by parallel gains in executive performance, indicating that the cognitive deficits are not simply secondary to symptom severity (Kim et al., 2020; Nielen & Den Boer, 2003) but instead reflect underlying structural and network changes, such as reduced cortical

volume or CSTC abnormalities (Carlisi et al., 2017; Norman et al., 2016). This dissociation parallels the well-documented disconnect between symptomatology and cognitive or saccadic deficits in OCD, and stands in sharp contrast to other psychiatric disorders—such as depression or ADHD—in which antidepressants or central stimulants typically “normalize” symptoms and cognitive performance in tandem.

A few studies have suggested that successful treatment can increase OFC volume in OCD patients (Huyser et al., 2013), similar to how effective treatments in MDD or ADHD have been shown to partially normalize disorder-related neural aberrations. These findings align with the proposed pathological framework of OCD, in which symptoms are expressed through dysregulated communication along the OFC–caudate pathway.

Comorbidity with other neuropsychiatric disorders and additional model-accounted phenomena (Synthetic Result 11)

Descending projections from the PFC to subcortical structures, followed by extensive synaptic pruning, represent a developmental vulnerability and may be viewed as a cost associated with late embryonic and postnatal frontal expansion. Disturbances in different topographical patterns of these projections are therefore expected to yield distinct functional consequences and, ultimately, divergent psychiatric phenotypes. Aberrant projections to the VTA are implicated in ADHD (Lee, 2025a, 2025b), whereas abnormalities in descending fibers targeting the dorsal striatum are associated with OCD. Interestingly, because the trajectory to the VTA is substantially longer than that to the dorsal striatum, the prevalence of ADHD (approximately 6–7% in children and adolescents) exceeds that of OCD (less than 2%). When both the VTA and the dorsal striatum are involved, OCD and ADHD may co-occur (Masi et al., 2006; Miyauchi et al., 2023), a combination associated with more severe symptomatology and a more treatment-refractory clinical course (Mersin Kilic et al., 2020; Miyauchi et al., 2023). Compared with ADHD, OCD typically shows a slower therapeutic response to pharmacological treatment. Whereas ADHD is primarily characterized by dysregulation of neurotransmitter systems, particularly dopamine, which allows for relatively rapid medication effects, OCD appears to be more strongly associated with structural and circuit-level alterations. Consequently, effective treatment of OCD may rely more heavily on mechanisms of neural plasticity, requiring longer-term intervention to induce clinically relevant changes in dysfunctional neural networks.

It is implausible to assume that aberrant descending projections from the PFC selectively affect the caudate without any involvement of the putamen; rather, differences are more likely to reflect the degree of engagement across dorsal striatal subregions. In some individuals with OCD, obsessions are prominent in the absence of marked compulsions, a pattern that may reflect predominant caudate involvement with relatively preserved putamen function. By contrast, isolated dysfunction of the putamen has been hypothesized to contribute primarily to tic generation. Consistent with this view, up to 30% of individuals with OCD have a lifetime tic disorder (American Psychiatric Association, 2013), a prevalence higher than that observed in ADHD, where approximately 20% meet criteria for comorbid tic disorders (Rothenberger & Heinrich, 2022; Wanderer et al., 2021). This discrepancy may indicate greater involvement of motor-related dorsal striatal structures—particularly the putamen—in OCD relative to ADHD. In contrast, a caudate-centered pathology in HD is associated with a high prevalence of OC symptoms (Anderson et al., 2010). Nevertheless, these manifestations are not fully equivalent to classical OCD, as HD often presents a mixture of OC and perseverative behaviors that are difficult to disentangle clinically (Zadegan et al., 2024).

Through reciprocal suppression mechanisms between fronto-parietal and limbic compartments (Lee & Xue, 2018a), hypofrontality may exert less inhibitory control over the limbic system, resulting in limbic hyperactivity. Conversely, limbic hyperactivity can suppress frontal function, leading to hypofrontality. This hybrid pattern of hypofrontality and limbic hyperactivity is frequently observed across psychiatric disorders, though it may arise from distinct neural mechanisms. For example, stress-induced hypofrontality may underlie primary MDD (Lee, 2025c); hyperactive VTA–NAc circuits may drive limbic hyperactivity via mesolimbic pathway in bipolar depression (Lee & Xue, 2017); enhanced phasic dopaminergic transmission and NAc activity may account for limbic hyperactivity in ADHD; and stroke can produce hypofrontality

contributing to post-stroke depression. In OCD, hypofrontality and dysregulated limbic activity co-occur alongside an inefficient fronto-striatal network, as summarized in the previous sections. Limbic hyperactivity may, in itself, account for the high comorbidity of anxiety disorders observed in OCD (Etkin & Wager, 2007).

Several clinical and neurobiological findings can be tentatively integrated within the proposed framework, which in turn adds further support to its plausibility. Acquired OCD following various forms of brain injury has been shown to implicate the frontal cortex, the basal ganglia, and the pathways linking them (Coetzer, 2004). This pattern can be readily accommodated by the present account: disruption of PFC–dorsal striatal pathways permits untuned limbic inputs to drive obsessive phenomena, which in turn elicit compulsive behaviors through competitive interactions between the caudate and putamen. Consistent with the proposed model, evidence from neurosurgical interventions implicates the OFC–caudate pathway in the manifestation of OCD symptoms. Gamma ventral capsulotomy targets the ventral anterior limb of the internal capsule—a major conduit for OFC projections to the ventral striatum and caudate—thereby directly intersecting this circuit and is associated with symptom improvement in treatment-resistant OCD (Cecconi et al., 2008). Similarly, deep brain stimulation of the ventral capsule has been applied in treatment-resistant OCD, with its anatomical locus closely corresponding to the pathway through which OFC-driven signals are thought to give rise to symptoms (Williams et al., 2016).

Among formally classified OCD-related conditions, body dysmorphic disorder shows the highest comorbidity with OCD (Say Öcal et al., 2019), with a disproportionate emphasis on symmetry- and order-related obsessions (Frías et al., 2015). Face and body image processing depend on the fusiform face area and the extrastriate/fusiform body areas (Taylor et al., 2007), which are anatomically adjacent to—and strongly interconnected with—the MTL, a region implicated in order- and symmetry-related obsessive phenomena. Aberrant processing or heightened sensitivity within these visual body-processing regions may therefore propagate via MTL pathways to the OFC and subsequently to the caudate. In the context of insufficient PFC regulation, as implicated in both OCD and body dysmorphic disorder, such signals may be further amplified, providing a plausible neural account for their high comorbidity and shared emphasis on symmetry/order obsessions. Alterations in the rostral ACC may contribute to reward-related abnormalities observed in OCD and related conditions, such as trichotillomania (Marsh et al., 2015), given that the rostral and subgenual ACC provide substantial inputs to the ventral striatum (White et al., 2013).

Defining characteristics of dialectic neuroscience: a rigorous integrative framework for complex brain science problems

The theoretical foundation of dialectic neuroscience is grounded in *centralized dialectics* (Lee, 2025d), a novel dialectical approach designed to introduce creative and nonlinear reasoning into problem solving in a systematic and reliable manner. Unlike conventional Hegelian thesis–antithesis dialectics, which emphasize antagonistic opposition, centralized dialectics seeks to resolve complex problems by identifying parsimonious underlying mechanism(s). Conceptually, this approach can be understood as locating the central missing piece(s) of a jigsaw puzzle that renders the entire structure intelligible. In the present thesis, this central missing piece is articulated in Part I of the **Results** section: hybrid of fronto-striatal miswiring combined with a deficient caudate–limbic feedback loop constitutes the core neuropathology of OCD, wherein aberrant limbic inputs to the caudate—originating from the amygdala–OFC, insula or insula–OFC, and MTL–OFC—respectively give rise to the core symptom dimensions of aggression/harm, contamination, and symmetry. Within the proposed theoretical framework of OCD, it is unsurprising that fronto-parietal (including dorsal ACC) and OFC abnormalities emerge across symptom dimensions and are negatively linked to overall severity (P. S. Boedhoe et al., 2017; Carlisi et al., 2017; Gilbert et al., 2008; Jayarajan et al., 2015; Montigny et al., 2013; Norman et al., 2016; Tang et al., 2015; Venkatasubramanian et al., 2012).

The confidence in the outputs of dialectic neuroscience rests on its accountability, which can be approximated using Fisher’s combined probability meta-analytic test: the more disorder-specific empirical features the framework can explain, the more reliable it becomes. Crucially, this accountability enables the framework to integrate and make sense of peripheral pieces—empirical findings that may initially appear

unrelated or even mutually incompatible—thereby addressing the very complexity that arises from the fragmented and heterogeneous nature of the data or viewpoints. In stark contrast, traditional cognitive neuroscience approaches typically rely on *a priori* assumptions and probe-specific tasks to examine isolated cognitive components. While such approaches remain valuable, they largely provide these peripheral pieces without offering a principled mechanism to reconcile them into a coherent explanatory framework.

Methodologically, dialectic neuroscience adopts phenomenological *epoché* or bracketing (Husserl, 2012), whereby conventional cognitive neuroscience interpretations and hypotheses are temporarily suspended, leaving the experimental design and empirical results as the primary building blocks for subsequent reconstruction. Through an effort guided by creative and nonlinear thinking, this approach can tackle complex problems and uncover their underlying mechanism(s). Notably, the biological plausibility, accountability, and parsimony of the reconstructed framework can be formally incorporated within a Bayesian posterior probability structure (Lee, 2025d), ensuring its scientific rigor. Consequently, the application of centralized dialectics—in this case, dialectic neuroscience—embodies both integrative and rigorous features: the former is largely absent in most empirical approaches, and the latter is often lacking in hypothesis papers. Building on this foundation, psychiatric brain research can finally achieve a new level of solid, hypothesis-driven investigation.

Cognitive neuroscientists employ a variety of paradigms to investigate brain functions. Yet it is widely recognized that psychological functions are emergent phenomena at the level of cognition and behavior, which are far removed from the material dynamics of neural circuits. Neuropsychiatric disorders, however, require a fundamentally different perspective: the underlying abnormalities reside at the material, lower level of the central nervous system, and no single brain region can be assumed to have evolved solely to produce “symptoms.” Consequently, most neuropsychiatric disorders cannot be adequately conceptualized as purely psychological in nature. Despite substantial contributions from cognitive neuroscience, the considerable hierarchical gap between psychology (upper level) and brain disorders (lower level) has rarely been addressed adequately, either methodologically or theoretically. Dialectic neuroscience offers a solution, helping to establish the identity of psychiatric brain research. Rather than relying on prior “psychological” interpretations, it leverages creative and nonlinear thinking to integrate existing brain science knowledge and findings—particularly aberrant neural network manifestations—into a rigorous theoretical formulation, thereby providing an alternative route to identify the core neuropathology of brain disorders, as exemplified in OCD.

Beyond its deliberate focus on the brain at the materialistically lower level of the hierarchy, dialectic neuroscience adopts a strategy fundamentally different from the zoom-in approach characteristic of cognitive neuroscience, which emphasizes isolated subcomponents or subprocesses of theoretical models. In contrast, dialectic neuroscience operates through a zoom-out perspective. Its conceptual pillars—such as hypofrontality coupled with limbic hyperactivity in OCD, the generally inhibitory effects of SSRIs, the atrophic consequences of chronic glutamatergic exposure, and the assignment of major limbic regions to the three dominant obsessive domains—are all formulated at a zoom-out level while temporarily withholding attention to variations. Crucially, this zoom-out strategy tolerates heterogeneity and discrepancies, because its primary objective is to identify the core neuropathology before delineating finer-grained details. Without such a perspective, inquiry risks remaining confined to peripheral phenomena, endlessly circulating among local details without establishing solid conceptual ground. Once the core neuropathology is defined, prior findings and established knowledge can be coherently re-situated within a unified framework—whether they are derived from cognitive tasks, affective paradigms, or clinical profiles. At this stage, a zoom-in approach becomes both meaningful and productive, allowing more nuanced questions to be addressed, such as subtypes, disease-specific impairment in cognition, variability in clinical manifestations, and plastic or compensatory changes. This process mirrors the use of a microscope: starting with a broad overview to locate the target, followed by a focused examination of specific details; this order cannot be reversed. In the absence of an anchored core pathology, empirical findings tend to remain scattered and weakly connected, or can only be organized at a largely descriptive level—as exemplified by the “triple network model,” which

summarizes a wide array of large-scale brain networks affected in OCD, leading to interpretations that appear at odds with the disorder's relatively benign clinical course.

Although earlier studies have reported correlations between symptom dimensions and regional brain volume or function (Mataix-Cols et al., 2004; Thorsen et al., 2018), many of these findings have not been consistently replicated in subsequent meta-analyses. From a symptomatological perspective, as noted earlier, psychiatric symptoms arise from subjective interpretations of central and/or peripheral neural aberrance, and their underlying neuropathology need not be spatially isomorphic. Crucially, it is implausible to assume that any brain region—shaped by long-term evolution—is specialized solely to generate a specific psychiatric symptom. Nevertheless, the assumption that psychiatric neuropathology can be elucidated through the logic of functional localization continues to implicitly permeate psychiatric brain research. This highlights a key strength of dialectic neuroscience: its capacity to accommodate variability without forfeiting mechanistic coherence. Accordingly, certain questions in psychiatric research may demand alternative methodological strategies. For example, if obsessive contamination-related symptoms arise from convergent inputs to the caudate from one or multiple nodes within the broader insula–amygdala–OFC network, then meta-analysis from studies of stringent thresholds may unsurprisingly fail to pinpoint a single locus generating that specific symptom. Taking a different strategy, for example by loosening the threshold and performing a conjunction across studies, may help reveal the broader network involved in symptom generation.

Dialectic neuroscience proceeds as a progressive and iterative process. It first aims to identify a core neuropathology that possesses a meaningful degree of explanatory power and face validity—for example, the proposal that the primary pathology of OCD lies in aberrant directional projections from the frontal cortex to the dorsal striatum. If this core claim is subsequently supported by empirical evidence (see **Conclusions and Predictions**), the theory can be further refined—for instance, with respect to its dorsal and ventral components, where the caudate serves as an interface, or to gender difference that has not been addressed in this thesis—thereby entering the next cycle of analysis and synthesis (see Fig. 2 in (Lee, 2025d)). Scientific investigation of psychiatric disorders is therefore not a one-step endeavor, but an ongoing process of iterative refinement. Notably, the symptom-related inferences outlined above are grounded in a broad body of neuroscience and brain-science knowledge and serve to integrate the core features of OCD within a coherent framework. This approach is fundamentally distinct from conventional hypothesis-driven papers, which typically address isolated phenomena without providing such integrative synthesis.

With the availability of rigorous hypothesis- or theory-driven approaches, the increasing and continued reliance of psychiatric brain research on blind engineering strategies becomes a concerning direction. Engineering methods can realize their full value only when embedded within a rigorous theoretical framework. For example, machine-learning–based classification may help delineate disorder-specific patterns of hypofrontality and limbic hyperactivity across MDD, bipolar disorder, ADHD, and OCD. Such data-driven insights can, in turn, feed back into existing models and proposed pathologies, providing material for further theoretical refinement. This iterative integration of theory-guided inquiry and targeted engineering may represent a more productive and principled trajectory for future psychiatric brain research. Without first zooming out to establish a clear direction and a solid hypothesis, exploratory efforts often amount to little more than beating around the bush, leaving researchers with no option but to hand over high-dimensional, messy results to blind engineering methods. This dynamic has, in large part, constituted the central bottleneck faced by functional neuroimaging research in psychiatry over recent decades.

For readers unfamiliar with the framework, why is it called “dialectics”? Four key aspects are highlighted: (1) complexity (peripheral pieces of a jigsaw puzzle) versus simplicity (the central missing piece); (2) analysis versus integration/synthesis; (3) filling in the central missing piece allows peripheral pieces to make sense in relation to one another; and (4) accountability occupies a central role in the process. The contrasting nature of the first two aspects reflects a Hegelian sense, whereas the latter two align with the original meaning of dialogue. During the dialectical process, the original interpretations of laboratory findings are bracketed (*epoché*), allowing creative thinking to reinterpret and integrate prior studies, and to flexibly develop new guiding insights.

Conclusions and Prediction

OCD had traditionally been classified as an anxiety disorder; however, recent research suggests that anxiety may not be the primary emotional process underlying OCD symptoms, as substantial phenomenological differences exist between OCD and other anxiety or fear-based disorders (Bartz & Hollander, 2006). Accordingly, DSM-5 reclassified OCD from the anxiety disorders section to a distinct category—Obsessive-Compulsive and Related Disorders. Based on the present thesis, primary OCD is better conceptualized as a developmental disorder. OCD and ADHD may share common neuropathological substrates rooted in aberrant fronto-to-subcortical projections, with differential involvement of the dorsal striatum and VTA, respectively (Lee, 2025a, 2025b). This framework accounts for their distinct symptomatic profiles, neuropsychological impairment, and their notably high comorbidity. The onset of these conditions during childhood or adolescence likely reflects the manifestation of latent circuit pathology following fronto–subcortical pruning. Collectively, these findings suggest that OCD and ADHD represent developmental manifestations of fronto–subcortical miswiring, differentiated by their distinct topological patterns of circuit involvement, whereas late-onset phenotypes with similar symptom profiles are more plausibly understood as acquired neurological conditions arising from analogous neuropathological processes. Although framing OCD as a developmental disorder is not the prevailing view, the condition frequently co-occurs with developmental disorders, and the observed hypogyrification within the frontal and parietal cortices lend support to this perspective (Rus et al., 2017).

From the standpoint of the proposed account and contemporary brain science, a central limitation of earlier cognitive-neuroscience interpretations lies in misattributing fronto-striatal inflexibility to processes that more likely arise from indirect limbic–striatal perturbation. Antisaccade abnormalities, impaired response inhibition, and cognitive inflexibility—although frequently reported—cannot explain the core symptomatology of OCD. Obsessions and compulsions are disorder-specific, whereas these cognitive abnormalities are not. Accordingly, psychological paradigms alone are insufficient to identify the core pathology of OCD; instead, they function as probes that provide valuable, complementary clues to underlying neuropathology. An important point: effective synthesis depends on thorough analyses, and previous contributions from cognitive neuroscience and neuropsychology are highly appreciated, even though their inherent limitations in addressing complex issues prevent them from providing a sound guiding theory. Consequently, the model developed within dialectic neuroscience that integrates clinical, neuropsychological and neural features, is grounded in established evidence, and provides a coherent synthesis of existing findings. Rooted in centralized dialectics and informed by Bayesian inference, this framework affords stronger theoretical confidence and a more comprehensive account of OCD across multiple dimensions. In summary, centralized dialectics provides a principled framework for tackling complex issues. Dialectic neuroscience applies this approach to brain science questions to integrate diverse findings, distinguish core from peripheral abnormalities, and yield a coherent understanding of neural systems, thereby highlighting its utility for elucidating fundamental mechanisms, including those underlying psychiatric disorders such as OCD.

Although fronto–striatal abnormalities have been implicated in OCD, existing accounts remain largely descriptive and non-directional, offering limited mechanistic integration. Within the framework of dialectic neuroscience, the present work advances a different proposal: OCD arises from aberrant descending PFC–subcortical projections and their subsequent neural cascades. Importantly, the model clarifies why prior structural and functional approaches have yielded limited or inconsistent results. As for structural connectivity, current fiber-tracking methods—such as tract-based spatial statistics—are most reliable for large, coherent white-matter bundles, including the corticospinal tract, superior longitudinal fasciculus, and cingulum (Silk et al., 2013). In contrast, the much thinner, less well-myelinated, and more diffuse pathways linking the PFC to the striatum pose substantial technical challenges and remain difficult to resolve using existing diffusion-based techniques. Moreover, because the proposed pathology is intrinsically directional, conventional unidirectional FC analyses are ill-suited to capture its core abnormality. Analogous to prior work in ADHD (Lee, 2025d), three predictions follow from the model: (1) descending influence from the PFC to

subcortical nuclei is selectively attenuated in OCD; (2) a robust interaction effect is expected between group (OCD versus neurotypical controls) and directionality, contrasting prefrontal-to-caudate with caudate-to-prefrontal influences, as assessed using directional neural metrics. In brief, attenuation of frontal-to-caudate influence reduces caudate engagement, which in turn weakens caudate-to-prefrontal modulation, giving rise to a direction-dependent interaction; and (3) given that there is an anatomical bridge between the caudate and the AIns, and that contamination represents the most prevalent obsessive symptom dimension, the model predicts altered connectivity strength between the caudate head and the AIns as a candidate limbic network feature. Although the role of the OFC has been emphasized in the model, empirical verification of its involvement is constrained by methodological limitations, as the OFC is particularly vulnerable to susceptibility-related artifacts in fMRI. Other limbic structures, such as the amygdala and hippocampus, may also show related connectivity alterations with the OFC depending on the specific symptom profile.

Through the framework of dialectic neuroscience, psychiatric brain research can move beyond studies lacking core-pathology hypotheses, leave behind blind engineering approaches, and embark on a new era of truly core-pathology-driven investigation.

Author contributions

This article is authored by a single individual. All relevant CRediT roles—Conceptualization, Formal analysis, Methodology, Project administration, Writing – original draft, and Writing – review and editing—were solely carried out by the author.

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Directional Weakening of Frontal–Caudate Coupling in Obsessive-Compulsive Disorder

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Running Title: Frontal–to-subcortical miswiring in Obsessive-Compulsive Disorder

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Abstract

Background: This study empirically evaluates a theoretical model of obsessive-compulsive disorder (OCD) positing that aberrant frontal-to-striatal projections—particularly involving the caudate and putamen, with downstream effects on the limbic system—constitute a core neurobiological vulnerability. The model predicts attenuated directional influences between the frontal cortex and dorsal striatum, giving rise to group-by-direction interaction effects.

Methods: Structural and resting-state functional MRI data from 61 individuals with OCD and 61 healthy controls were analyzed. The cerebral cortex was parcellated using Modular Analysis and Similarity Measurements (MOSI), and mean amplitude of low-frequency fluctuations (ALFF) as well as mean time series were extracted from each frontal node. Subcortical structures, including the caudate and putamen, were treated at the voxel level as individual neural nodes. Relationships between nodal power (ALFF) and nodal strength were quantified to derive directional metrics, defined as frontal-to-subcortical (F2S) and subcortical-to-frontal (S2F) correlations. Group differences and interactions between direction and diagnostic group were examined. Functional connectivity (FC) between the caudate head and anterior insula was also investigated to explore aberrant caudate–limbic interactions.

Results: A consistent bimodal pattern was observed, with positive F2S and negative S2F associations across both caudate and putamen, reflecting a directional excitation–inhibition balance. Individuals with OCD exhibited attenuated F2S excitation and reduced S2F inhibition, accompanied by significant group-by-direction interactions in both subcortical nuclei, in line with theoretical predictions. Additionally, FC between the caudate head and anterior insula was significantly decreased in the OCD group.

Conclusions: The proposed developmental model of OCD was empirically supported.

Introduction

Obsessive-compulsive disorder (OCD) is a long-lasting and debilitating psychiatric condition, defined by intrusive thoughts and repetitive behaviors that lead to significant distress, impair daily functioning, or occupy a considerable portion of time. Epidemiological data indicate a 12-month prevalence of approximately 1.2% in the United States, with comparable figures reported across other countries, ranging from 1.1% to 1.8% (American Psychiatric Association, 2013). Obsessions are recurrent, intrusive thoughts, urges, or images experienced as unwanted, while compulsions are repetitive behaviors or mental rituals performed in response. OCD is highly heterogeneous, but common symptom dimensions include contamination with cleaning, symmetry with ordering or counting, forbidden/taboo thoughts with mental rituals, and harm-related obsessions with checking behaviors. The most frequent presentations involve contamination, aggression/fear of harm, and symmetry/order, typically accompanied by cleaning, checking, and counting/ordering compulsions, respectively (Mataix-Cols et al., 2005; Rasmussen & Eisen, 1992). In addition to characteristic symptoms, OCD is frequently accompanied by a range of neuropsychological abnormalities, including deficits in cognitive flexibility and impairments in saccadic control (Chamberlain et al., 2021). Persistent negative affect is also a core feature, characterized by chronic anxiety, heightened threat perception, and a pervasive sense of incompleteness or internal tension. These emotional disturbances amplify intrusive thoughts and drive compulsive behaviors, reinforcing the cyclical interplay of obsessions and compulsions. Furthermore, affective dysregulation may compromise emotional flexibility, increasing stress sensitivity and reducing the capacity to regulate distress.

Consistent with its heterogeneous clinical and neuropsychological presentation, OCD is associated with widespread neural abnormalities involving the fronto-temporo-parietal cortex—particularly the frontal cortex (FCX)—as well as the basal ganglia (Carlisi et al., 2017; Norman et al., 2016; Pico-Perez et al., 2020), and limbic structures (Norman et al., 2016; Pico-Perez et al., 2020). “Triple network model” has been proposed to account for dysfunctions within and between the central executive, default-mode (limbic), and salience networks (Menon, 2011; Perera et al., 2024). A notable feature of OCD is the weak correspondence between its clinical symptoms and documented neuropsychological or motor-control abnormalities, a pattern that contrasts with

most psychiatric disorders (e.g., negative cognitive bias aligning with depressed mood; severe depression may present with pseudodementia). In OCD, deficits in cognitive flexibility or oculomotor control do not directly account for obsessions or compulsions. Neuroimaging evidence shows that enhanced error monitoring and conflict detection occur independently of symptom severity (Lei et al., 2015; Riesel et al., 2011), while saccadic abnormalities similarly exhibit no clear association with overall clinical burden (Jaafari et al., 2011). Together, these findings suggest that symptom expression and neuropsychological impairments arise from partially dissociable neural systems, potentially driven by a shared upstream mechanism.

While complexity is intrinsic to nearly all psychiatric conditions, dialectic neuroscience—an approach grounded in centralized dialectics—offers a framework for developing integrative theories of psychopathology (Lee, 2025c). This approach has been applied to major depressive disorder, bipolar disorder, and autism spectrum disorder (Lee & Xue, 2017, 2018), with theoretical models subsequently supported by empirical findings (Lee, 2025b, 2025d, 2026b). In OCD, a candidate theory has recently emerged, positing descending PFC–striatal projections and open-ended limbic–striatal interactions as dual vulnerabilities in brain development and network regulation (Lee, 2026c), providing a unifying framework to reconcile diverse and seemingly conflicting findings (Lee, 2025a). The former may contribute to cognitive and sensorimotor impairments, while the latter may relate to limbic abnormalities and obsessive symptoms. Compulsive behaviors have been proposed to arise from a competition between innate action–outcome (A–O) processes, mediated by the caudate (Cau), and stimulus–response (S–R) processes, mediated by the putamen (Put) (Grahn et al., 2008), with the latter potentially mitigating obsessive urges. The present study aims to empirically evaluate this theoretical account.

Resting-state functional magnetic resonance imaging (rsfMRI) data from previous studies were utilized to test the proposed hypotheses (Jung et al., 2017), for which causal inference is central. Although correlation is inherently unidirectional, recent work indicates that certain causal interpretations may still be inferred in cross-modal contexts (Lee & Tramontano, 2025). This approach has previously been applied in major depressive disorder to evaluate the hypothesis of compartment-level mutual suppression (Lee, 2025b), and in attention-deficit/hyperactivity disorder (ADHD) to assess cortical–striatal miswiring (Lee, 2026a). Specifically, nodal

strength—defined as the total functional connectivity (FC) of a node—appears to influence nodal power (i.e., ALFF), but not vice versa. Following the methodology of prior ADHD research (Lee, 2026a), two directional metrics were employed to characterize interactions within the frontal–subcortical network, capturing fronto-to-striatal (F2S) and striatal-to-frontal (S2F) relationships based on canonical fronto-striato-thalamo-cortical loops (Alexander & Crutcher, 1990; Grahn et al., 2008). The F2S index captures the association between frontal nodal strength and subcortical ALFF, whereas S2F reflects the reverse relationship. Observed positive F2S and negative S2F values indicate a dynamic interplay of excitatory and inhibitory influences within fronto-subcortical circuits, consistent with the classical DeLong model of cortico-striato-thalamo-cortical (CSTC) circuitry (Alexander et al., 1986), where cortical projections to the Cau and Put are excitatory and the net effect of the basal ganglia on cortex is inhibitory.

Subcortical nuclei, including the Cau and Put, were incorporated in accordance with the proposed OCD model. Functional parcellation of the cortex will be performed using MOSI (Modular Analysis and Similarity Measurements) (Lee & Tramontano, 2021). The core neuropathology of OCD was hypothesized to manifest through a two-way interaction, reflecting differences in correlations between F2S and S2F across OCD and healthy control (HC) groups (OCD vs. HC $\times$ FCX-to-Cau/Put vs. Cau/Put-to-FCX). FC between the Cau head and anterior insula was used as a surrogate measure to investigate aberrant Cau–limbic interactions in OCD.

Materials and Methods

MRI datasets and preprocessing

Data from 122 participants (61 with OCD) were obtained from the dataset provided by Department of Psychiatry, Seoul National University College of Medicine (Jung et al., 2017), with written informed consent provided by all individuals. The functional and structural MRI (sMRI) images of the entire brain were recorded using 3.0 Tesla Trio MRI scanner (fMRI: TR=3.5s, TE=30ms, Flip Angle=90°, voxel size=1.9x1.9x3.5mm³, 35 slices, 118 volumes; sMRI: TR=1.67s, TE=1.89ms, Flip Angle=9°, voxel size=1.0x0.98x0.98mm³, 208 slices).

Resting-state fMRI data were preprocessed using AFNI (Cox, 1996). The pipeline comprised despiking,

correction for slice acquisition timing, motion correction, alignment to each subject's T1-weighted anatomical image, spatial smoothing with a 6 mm FWHM Gaussian kernel, and temporal bandpass filtering (0.01–0.1 Hz). The filtering step was implemented using the 1dBport function, which isolates frequency components through sinusoidal basis regressors. To allow for signal equilibration, the initial four volumes were removed. Structural T1 images were processed with FreeSurfer to perform tissue segmentation (gray and white matter) and to parcellate the cortex into 68 regions (34 per hemisphere) according to the Desikan–Killiany atlas (Dale et al., 1999; Desikan et al., 2006; Fischl et al., 1999). These regions were subsequently used as seed units for MOSI-driven parcellation. Consistent with established preprocessing strategies (Lee et al., 2014; Xue et al., 2014), nuisance regression included 12 motion parameters as well as signals from white matter and cerebrospinal fluid. In addition, a second-order polynomial term was included to account for low-frequency baseline drift. ALFF was then computed as the square root of the power spectrum within the bandpass-filtered EPI time series.

Functional connectivity and MOSI analysis

FC was quantified using Fisher-transformed (r-to-z) Pearson correlation coefficients, computed between voxel-wise time series in subcortical regions and the cortex, as well as cluster-averaged time series within the FCX, which was parcellated using MOSI (details below). The resulting FC matrices served as input for MOSI, a cortical parcellation method that integrates modular decomposition with similarity-based aggregation (Lee & Tramontano, 2021). MOSI operates through an iterative process: it first detects local functional modules using community detection via the Louvain algorithm (Blondel et al., 2008; Reichardt & Bornholdt, 2006), then merges spatially contiguous modules that exhibit high functional similarity. This cycle repeats until the parcellation reaches stability. The framework is guided by two main principles—spatial proximity and functional coherence—ensuring that neighboring voxels with similar activity patterns are grouped into the same module, a core requirement for meaningful functional parcellation. To reduce noise, modules containing fewer than five voxels were excluded. The resolution of the final parcellation is controlled by the gamma parameter: higher gamma values produce more finely subdivided modules. MOSI's effectiveness was evaluated by intra-module

homogeneity and compared to conventional atlas-based parcellations (see **Results**). Nodal strength was calculated as the total FC associated with each subcortical voxel or MOSI-derived frontal module.

Due to the small size and internal heterogeneity of subcortical nuclei, along with the absence of standardized partition in rsfMRI studies, no further parcellation was applied to these subcortical regions. Consequently, MOSI-based parcellation was restricted to the cortical areas. In other words, the neural node is defined as a voxel within subcortical nuclei, whereas in the FCX, a neural node corresponds to a MOSI-partitioned module (cluster).

Although the MOSI framework was originally implemented over a wide gamma interval (0.30–0.85), in line with previous whole-cortex parcellation work (Lee, 2025b), additional restrictions were necessary for analyses specifically targeting the FCX. Because reliable correlation estimation requires at least 30 observations (Bonett & Wright, 2000), the range of acceptable modular resolutions had to be constrained. Empirical evaluation indicated that a gamma level of 0.70 produced, on average, more than 30 modules within the FCX in both OCD and control groups. Accordingly, to maintain sufficient statistical reliability in correlation-based analyses, the primary interpretation is restricted to gamma values ≥ 0.70 (0.70, 0.75, 0.80, 0.85), whereas results spanning all 12 gamma levels are provided in the Tables for completeness.

Formal analysis I—correlation analyses between ALFF and nodal strength

Three distinct correlation analyses were performed to evaluate the relationship between ALFF and nodal strength. ALFF quantifies spontaneous neural activity by measuring the amplitude of low-frequency fluctuations in the resting-state BOLD signal. It is calculated as the square root of the signal's power within the band-pass filtered frequency range. The first analysis targeted fronto-to-subcortical interactions by correlating nodal strength derived from frontal modules with ALFF measured in subcortical regions, specifically the Cau and Put (F2S). To control for differences in module size within the FCX, a size-weighted averaging approach was used to obtain representative nodal strength values. The second analysis examined the reverse direction, focusing on subcortico-to-frontal connectivity. In this case, ALFF values were averaged within each frontal module, while

nodal strength was calculated at the voxel level within the subcortical nuclei (S2F). In the second analysis, the subcortical unit of analysis was defined at the voxel level; therefore, no additional weighting was applied, and the mean was calculated by simple averaging. Together, these two analyses characterize the interaction between the FCX and the dorsal striatum. The third analysis employed the same analytic approach in cortical regions—including frontal, temporal, parietal, and limbic areas—as previously described (Lee, 2025b), to evaluate whether the cortical inhibitory patterns are altered in OCD.

Formal analysis II— Interaction analysis of group by direction effects

A standard interaction analysis was conducted based on the results of Formal analysis I to evaluate group-by-direction effects. The factors included group (OCD vs. HC) and direction (F2S vs. S2F), with analyses performed separately for the Cau and Put. This approach allowed for direct assessment of whether the directional coupling between frontal cortex and dorsal striatum differed between groups. Because results obtained across different gamma values reflect varying topological resolutions rather than fully independent observations, statistical inferences were not based on a single threshold. Instead, findings were reported at both $p < 0.05$ and $p < 0.01$ to provide a more comprehensive characterization of the robustness of the interaction effects across resolutions.

In an additional exploratory analysis, the Cau head was defined as the most anterior 50% of the structure (Tremols et al., 2008), and the anterior insula as the most anterior 35% of the insula (Long et al., 2022). Fisher-transformed FC strength between these regions was compared between the OCD and HC groups.

Results

The demographic profiles of the combined OCD and HC groups ($n = 61$ per group) were similar, based on the dataset from (Jung et al., 2017). Group comparisons indicated no significant age differences (OCD: 26.1 ± 7.2 years; HC: 25.6 ± 6.5 years; $t(120) = 0.40$, $p = 0.722$). Likewise, the proportion of males and females did not differ meaningfully between groups, with 36 males and 25 females in the OCD group and 41 males and 20 females in the HC group. A chi-square test applying Yates' continuity correction confirmed this ($\chi^2(1) = 0.563$, $p = 0.452$).

Group comparisons of subcortical volumes between children with OCD and HC showed no significant differences in either nucleus examined (Cau: $p = 0.677$; Put: $p = 0.984$). Frontal lobe volume similarly did not differ between groups ($p = 0.733$). The successful application of MOSI-based functional cortical parcellation is demonstrated in Figure 1.

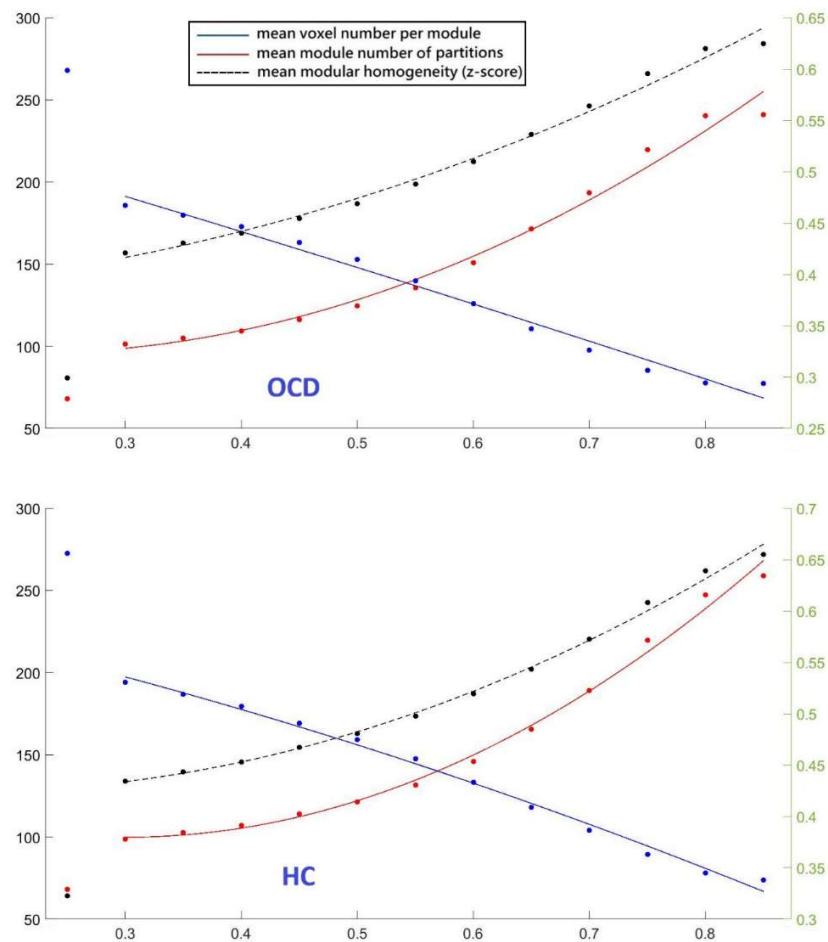


Figure 1. Scatter plots showing three metrics derived from the OCD dataset across 12 gamma values (X-axis), with second-order polynomial regression curves overlaid. Each plot contains 12 data points per metric, corresponding to the tested gamma values. The top panel illustrates results for the OCD group, while the bottom panel shows those for the HC group. The points aligned vertically near the y-axis denote the initial parcellation using the Desikan-Killiany atlas. Red markers and curves represent the mean number of modules (left Y-axis), blue markers and curves indicate the average voxel count per module (left Y-axis), and black markers and curves denote the mean within-module Fisher-transformed z-score (right Y-axis), reflecting modular homogeneity.

Analysis I—correlation analyses between ALFF and nodal strength

This study applied the analytic approach previously used in ADHD research to examine nodal strength and nodal power within the fronto-subcortical network (Lee, 2026a). The current results replicate the previously reported bimodal pattern in the fronto-striatal system. Specifically, F2S connections (mean nodal strength; similar descriptions apply below) consistently displayed a positive relationship with ALFF, whereas S2F connections were negatively associated. These directional associations were observed in both groups and remained robust across all gamma thresholds. This dissociation—manifested as uniformly positive F2S–ALFF and negative S2F–ALFF across subcortical nuclei—is clearly reflected in the correlation analyses (Tables 1 and 2) and aligns with established physiological models of CTSC circuitry (Alexander et al., 1986). Overall, these findings point to a dynamic balance of excitatory and inhibitory influences shaping fronto-subcortical communication.

Comparison of directional neural metrics between OCD and HC revealed consistent patterns in both the Cau and the Put: OCD participants showed reduced F2S excitation and S2F inhibition, in line with predictions of weakened fronto-striatal interactions and interaction effects. Although the Cau and Put exhibited similar overall trends, the group difference in S2F was more pronounced in the Cau, whereas the reduction in F2S was larger in the Put.

The relationship between nodal strength and nodal power was first examined in the cortex (Lee & Tramontano, 2025), where a robust negative association was interpreted as reflecting net neural inhibition and was subsequently applied to characterize the core neuropathology of major depressive disorder (Lee, 2025b). The same analytical approach was applied in the present study, revealing that cortical inhibition in OCD was weaker than in the HC group (i.e., less negative; see Table 3).

Table 1. Correlation between subcortical ALFF and fronto-subcortical connectivity (F2S)

	OCD	HC	two-sample t-tests		OCD	HC	two-sample t-tests		
Gamma	mean (std)	mean (std)	t	p-val	mean (std)	mean (std)	t	p-val	
Cau					Put				
0.30	0.12 (0.18)	0.19 (0.19)	-1.63	0.107	0.00 (0.16)	0.12 (0.19)	-3.02	0.003	**
0.35	0.12 (0.18)	0.19 (0.18)	-1.66	0.101	0.00 (0.16)	0.12 (0.19)	-3.03	0.003	**
0.40	0.12 (0.18)	0.19 (0.18)	-1.67	0.098	0.00 (0.16)	0.11 (0.19)	-2.96	0.004	**
0.45	0.12 (0.18)	0.19 (0.18)	-1.58	0.118	0.00 (0.16)	0.11 (0.19)	-2.96	0.004	**
0.50	0.12 (0.18)	0.19 (0.18)	-1.63	0.106	0.00 (0.16)	0.11 (0.19)	-2.84	0.006	**

0.55	0.12 (0.19)	0.19 (0.18)	-1.72	0.090	0.01 (0.16)	0.11 (0.19)	-2.85	0.006	**
0.60	0.13 (0.18)	0.19 (0.18)	-1.53	0.131	0.01 (0.16)	0.11 (0.19)	-2.82	0.006	**
0.65	0.13 (0.18)	0.19 (0.19)	-1.55	0.126	0.01 (0.16)	0.11 (0.19)	-2.72	0.008	**
0.70	0.13 (0.18)	0.19 (0.19)	-1.59	0.115	0.01 (0.16)	0.11 (0.19)	-2.61	0.011	*
0.75	0.13 (0.18)	0.19 (0.18)	-1.62	0.109	0.02 (0.16)	0.11 (0.20)	-2.59	0.011	*
0.80	0.14 (0.18)	0.19 (0.18)	-1.32	0.190	0.02 (0.16)	0.12 (0.18)	-2.86	0.005	**
0.85	0.14 (0.18)	0.19 (0.18)	-1.28	0.204	0.01 (0.16)	0.13 (0.20)	-3.13	0.002	**

Sample sizes were N = 61 per group (df = 120). Correlation coefficients were Fisher-transformed. Independent two-sample t-tests were performed for all comparisons, with all t-values being negative.

Abbreviations: std, standard deviation; t, t-score; p-val, p-value.

Table 2. Correlation between frontal ALFF and fronto-subcortical connectivity (S2F)

Gamma	OCD	HC	two-sample t-tests			OCD	HC	two-sample t-tests	
	mean (std)	mean (std)	t	p-val		mean (std)	mean (std)	t	p-val
Cau					Put				
0.30	-0.21 (0.39)	-0.38 (0.34)	2.19	0.031	*	-0.44 (0.36)	-0.52 (0.38)	0.94	0.348
0.35	-0.20 (0.40)	-0.38 (0.33)	2.23	0.028	*	-0.43 (0.36)	-0.52 (0.39)	1.13	0.263
0.40	-0.20 (0.39)	-0.38 (0.33)	2.31	0.023	*	-0.41 (0.35)	-0.52 (0.38)	1.39	0.169
0.45	-0.20 (0.38)	-0.37 (0.34)	2.20	0.030	*	-0.40 (0.34)	-0.50 (0.38)	1.18	0.240
0.50	-0.19 (0.37)	-0.35 (0.32)	2.10	0.039	*	-0.39 (0.33)	-0.46 (0.37)	0.87	0.387
0.55	-0.19 (0.36)	-0.35 (0.33)	2.16	0.033	*	-0.37 (0.32)	-0.45 (0.36)	0.96	0.338
0.60	-0.17 (0.33)	-0.34 (0.35)	2.42	0.018	*	-0.34 (0.31)	-0.43 (0.37)	1.16	0.251
0.65	-0.15 (0.29)	-0.32 (0.31)	2.56	0.012	*	-0.32 (0.29)	-0.37 (0.35)	0.79	0.432
0.70	-0.14 (0.28)	-0.32 (0.30)	2.81	0.006	**	-0.29 (0.26)	-0.37 (0.34)	1.16	0.250
0.75	-0.13 (0.26)	-0.24 (0.31)	1.72	0.090		-0.28 (0.25)	-0.28 (0.35)	0.01	0.993
0.80	-0.10 (0.23)	-0.23 (0.25)	2.59	0.011	*	-0.24 (0.22)	-0.27 (0.29)	0.59	0.556
0.85	-0.11 (0.22)	-0.21 (0.23)	2.09	0.040	*	-0.23 (0.20)	-0.21 (0.27)	-0.39	0.696

Sample sizes were N = 61 per group (df = 120). Correlation coefficients were Fisher-transformed. Independent two-sample t-tests were performed for all comparisons, with all t-values being positive except for one negative value.

Abbreviations: std, standard deviation; t, t-score; p-val, p-value.

Table 3 Correlation between ALFF and nodal strength in the cortex

Gamma	OCD	HC	t	p-val	
0.30	-0.46 (0.15)	-0.57 (0.16)	3.16	0.002	**
0.35	-0.46 (0.16)	-0.56 (0.16)	2.98	0.004	**
0.40	-0.46 (0.15)	-0.55 (0.16)	2.81	0.006	**
0.45	-0.45 (0.14)	-0.54 (0.16)	2.77	0.007	**
0.50	-0.45 (0.13)	-0.52 (0.14)	2.39	0.019	*
0.55	-0.44 (0.13)	-0.51 (0.15)	2.35	0.021	*
0.60	-0.43 (0.14)	-0.50 (0.13)	2.56	0.012	*
0.65	-0.41 (0.12)	-0.49 (0.13)	3.09	0.003	**
0.70	-0.39 (0.13)	-0.46 (0.12)	2.64	0.010	*
0.75	-0.38 (0.13)	-0.45 (0.12)	2.88	0.005	**
0.80	-0.36 (0.12)	-0.44 (0.12)	3.04	0.003	**
0.85	-0.35 (0.11)	-0.43 (0.12)	3.14	0.002	**

* and ** indicate p-val < 0.05 and p-val < 0.01, respectively. All t-scores are positive.

Abbreviations: std, standard deviation; t, t-score; p-val, p-value.

Analysis II—Interaction analysis of group by direction effects

Directional neural metrics, derived from Fisher-transformed correlation coefficients between nodal strength and nodal degree, were entered into an interaction analysis with group (OCD vs. HC) and direction (F2S vs. S2F) as factors. The results were consistent with theoretical predictions and exhibited similar patterns in both the Cau and Put, as presented in Table 4 and Figures 2 and 3.

The exploratory analysis revealed reduced FC between the Cau head and anterior insula in the OCD group ($t = -2.04$, $p = 0.044$), with mean Fisher-transformed correlation coefficients of 0.15 (SD = 0.16) for OCD and 0.22 (SD = 0.16) for HC, respectively. Although previous studies have defined the anterior insula as approximately one-third of the entire insula, connectivity with the dorsal anterior insula appears more pronounced. Guided by this observation, an additional analysis restricted the region of interest to the dorsal anterior insula (approximately 18% of the insula) (Long et al., 2022), resulting in a stronger and more significant effect ($t = -2.44$, $p = 0.017$). Mean Fisher-transformed FC was 0.16 (SD = 0.15) in the OCD group and 0.19 (SD = 0.14) in the HC group.

Table 4. Interaction analysis of group (OCD vs. HC) by directional neural metrics (F2S vs. S2F)

Gamma	mean (std)	t	p-val		mean (std)	t	p-val	
Cau					Put			
0.30	-0.24 (0.09)	-2.58	0.011	*	-0.19 (0.09)	-2.21	0.030	*
0.35	-0.24 (0.09)	-2.62	0.010	*	-0.21 (0.09)	-2.42	0.018	*
0.40	-0.25 (0.09)	-2.70	0.008	**	-0.22 (0.08)	-2.67	0.009	**
0.45	-0.23 (0.09)	-2.58	0.012	*	-0.20 (0.08)	-2.50	0.014	*
0.50	-0.22 (0.09)	-2.49	0.015	*	-0.17 (0.08)	-2.16	0.034	*
0.55	-0.23 (0.09)	-2.59	0.011	*	-0.18 (0.08)	-2.26	0.026	*
0.60	-0.24 (0.09)	-2.69	0.009	**	-0.19 (0.08)	-2.48	0.015	*
0.65	-0.23 (0.08)	-2.77	0.007	**	-0.16 (0.08)	-2.11	0.038	*
0.70	-0.24 (0.08)	-3.08	0.003	**	-0.18 (0.07)	-2.46	0.016	*
0.75	-0.17 (0.08)	-2.23	0.028	*	-0.10 (0.07)	-1.41	0.163	
0.80	-0.19 (0.07)	-2.72	0.008	**	-0.14 (0.06)	-2.25	0.027	*
0.85	-0.15 (0.07)	-2.34	0.022	*	-0.10 (0.06)	-1.69	0.095	

* and ** indicate $p\text{-val} < 0.05$ and $p\text{-val} < 0.01$, respectively. All t-scores are negative.

Abbreviations: std, standard deviation; t, t-score; p-val, p-value.

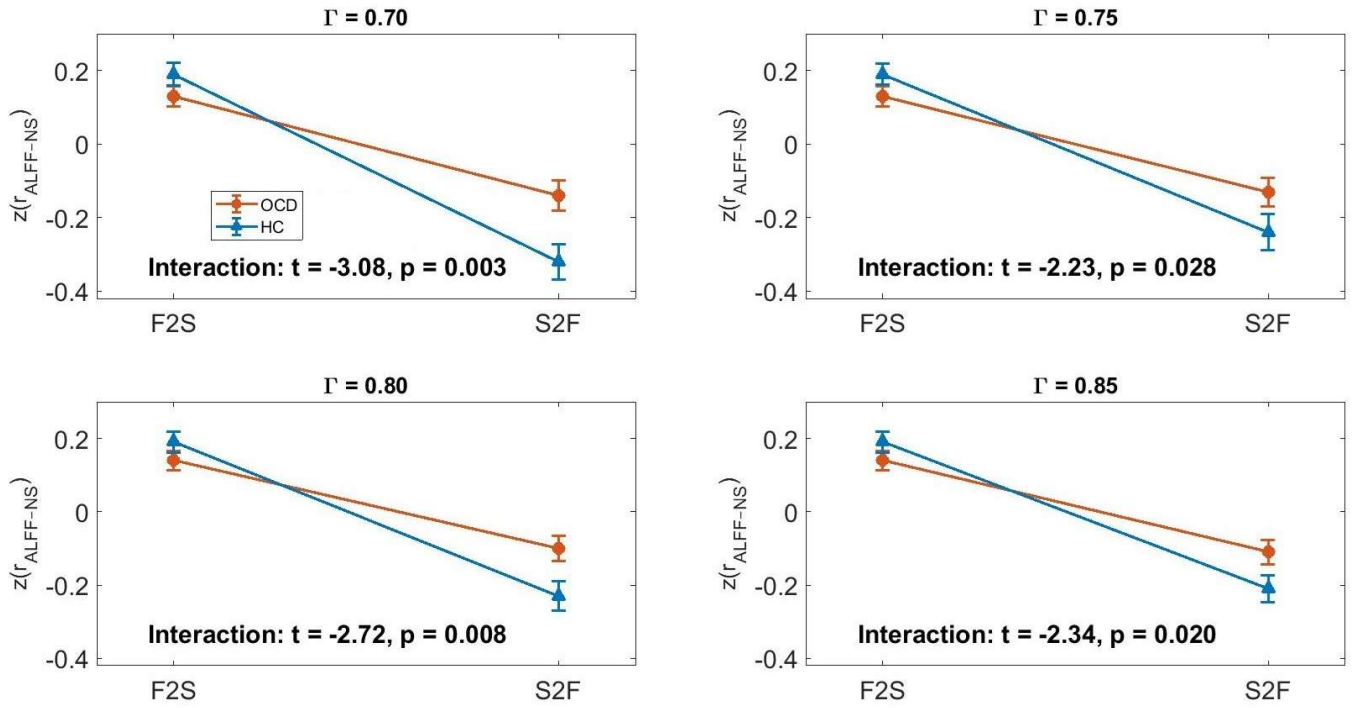


Figure 2. Relationships between ALFF and nodal strength in Cau and frontal lobe based on Fisher-transformed correlation coefficients at four Gamma values. F2S: correlation of ALFF in Cau and mean functional connectivity between Cau and frontal lobe. S2F: correlation of mean ALFF in frontal lobe and mean functional connectivity between Cau and frontal lobe. Data are shown for two groups, OCD (circles) and HC (triangles), with error bars representing standard errors. Interaction effects between group and condition are reported below each subplot.

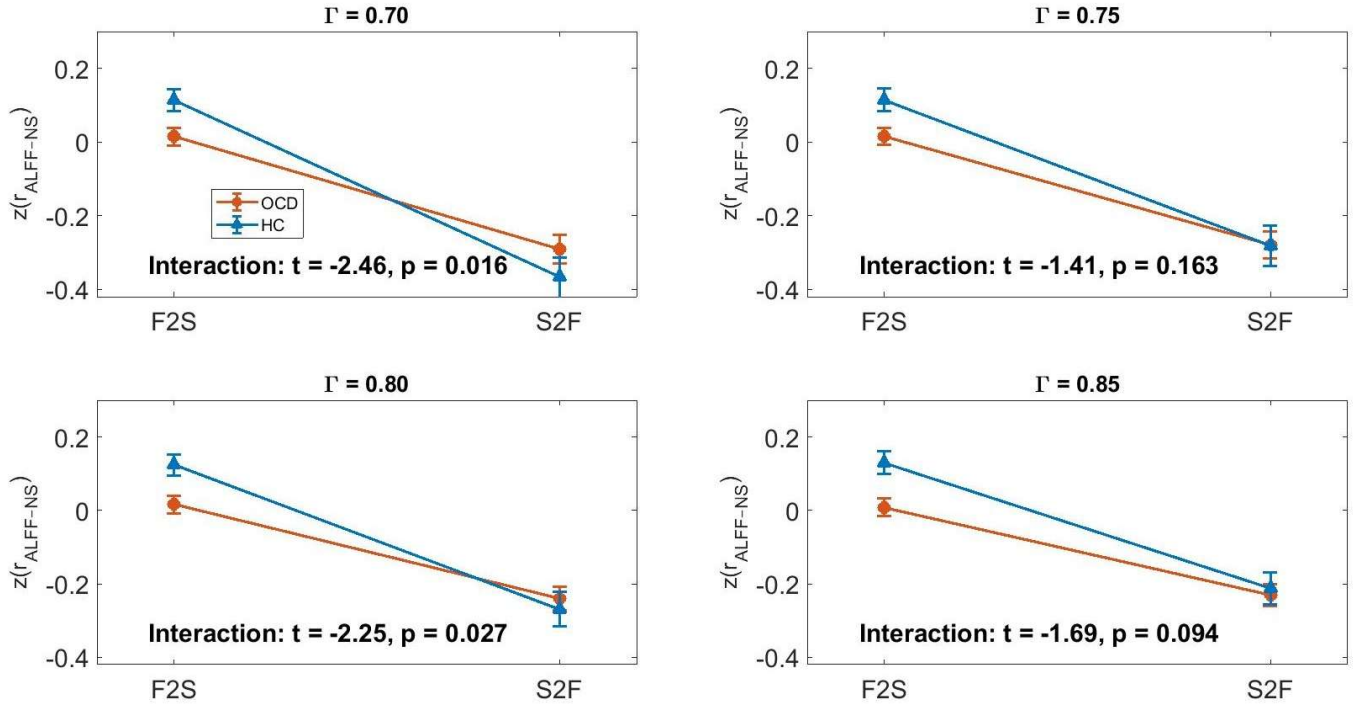


Figure 3. Relationships between ALFF and nodal strength in Put and frontal lobe based on Fisher-transformed correlation coefficients at four Gamma values. F2S: correlation of ALFF in Put and mean functional connectivity between Put and frontal lobe. S2F: correlation of mean ALFF in frontal lobe and mean functional connectivity between Put and frontal lobe. Data are shown for two groups, OCD (circles) and HC (triangles), with error bars representing standard errors. Interaction effects between group and condition are reported below each subplot.

Discussion

This study aimed to empirically evaluate a neuropathological model of OCD grounded in dialectic neuroscience (Lee, 2025a). The model proposes that aberrant descending fronto-striatal projections represent a core developmental vulnerability, affecting both dorsal fronto-striatal and ventral limbic pathways (Lee, 2026c). Within the dorsal circuitry, dysfunction in the autoregulatory FCX–Cau/Put loop is hypothesized to constitute the primary locus of disruption in OCD, with downstream effects propagating to the limbic system and contributing to obsessive symptoms. Compulsive behaviors are conceptualized as arising from competitive interactions between the Cau and Put, with the Put potentially mitigating aberrant neural activity in the Cau. Consistent with theoretical predictions, the proposed developmental vulnerability was reflected in the directional F2S and S2F

neural metrics, with both excitatory and inhibitory effects attenuated in OCD, as evidenced in the interaction analysis. To examine limbic abnormalities and given concerns regarding fMRI signal susceptibility in the orbitofrontal cortex, FC between the Cau head and anterior insula was assessed, revealing disrupted connectivity in OCD. Collectively, these empirical findings provide robust support for the predictions of the neuropathological model derived from dialectic neuroscience.

In the interaction analyses, two out of the twelve p-values exceeded 0.05, reflecting a relative attenuation of the Put-to-FCX inhibitory effect. Importantly, this observation is not inconsistent with the theoretical framework. Prior evidence indicates that in OCD, the Put exhibits heightened reactivity across both cognitive and affective domains (Carlisi et al., 2017; Norman et al., 2016; Pico-Perez et al., 2020; Rasgon et al., 2017). Considering that compulsive behaviors are hypothesized to emerge from a competitive interplay between Cau-mediated A–O processes and Put-mediated stimulus–response S–R processes, elevated Put activity plausibly strengthens its inhibitory feedback to the FCX (Lee, 2026c). Mechanistically, this enhanced inhibitory influence may reduce the observable interaction effect in the Put, whereas the Cau demonstrates a more pronounced directional interaction in the same analyses.

This study replicated the author’s recent work by employing directional neural metrics to characterize fronto-striatal interactions (Lee, 2026a), revealing a consistent dissociation across subcortical regions and MOSI resolutions: excitatory in the F2S direction and inhibitory in the S2F direction. The steeper positive slope in F2S suggests that frontal regions exert stronger excitatory influence on subcortical targets, likely via glutamatergic pathways (Groenewegen & Trimble, 2007), whereas the pronounced negative slope in S2F indicates inhibitory feedback from subcortical structures to the frontal cortex. The physiological validity of these directional metrics is supported by the well-established DeLong CSTC loop (Alexander et al., 1986). Importantly, they provide a basis for inferring network-level causal interactions, revealing how large-scale circuits regulate one another. In contrast to Granger causality or dynamic causal modeling, which estimate temporal or model-based influences between individual nodes, the relationship between nodal strength and nodal power captures aggregate excitatory or inhibitory tendencies across networks, offering a perspective on interaction not accessible through conventional

connectivity and causal analyses.

In the cortex, the negative relationship between nodal strength and nodal power remained robust (Lee & Tramontano, 2025). However, this relationship was consistently weaker in OCD than in HC across all gamma values, indicating reduced cortical inhibition in the OCD group. Two interpretations may account for this finding. First, following the principle of Occam's razor, the effect may arise from pathology within the CSTC circuit. Given the central role of the FCX in large-scale brain organization, dysfunction within CSTC could propagate and influence interactions across other cortical regions. Second, the effect may reflect developmental abnormalities in white matter wiring that are not restricted to CSTC, but instead manifest more broadly in cortico-cortical interactions. At present, the first interpretation is favored. Cortical development follows a posterior-to-anterior trajectory, with the frontal lobe maturing relatively late. In addition, cortical organization is hierarchical, with higher-order association regions exerting integrative and regulatory control over lower-level sensory and behavioral systems. Consequently, dysfunction in the frontal lobe may disrupt interactions and reduce computational efficiency across distributed cortical networks, as stronger inhibitory balance is typically associated with more efficient and economical neural processing.

These findings further underscore the importance of theory-driven research. In the absence of a guiding framework, purely exploratory studies are unlikely to produce cumulative insights; fragmented empirical observations often remain isolated, either relegated to data-driven modeling approaches such as machine learning without advancing mechanistic understanding, or superficially described under the term of "triple network", which encompasses much of the cortex—a breadth of neural involvement that stands in stark contrast to the relatively benign clinical course typically seen in OCD. By contrast, dialectic neuroscience—grounded in centralized dialectics—provides a structured framework to integrate disparate findings, distinguish core from peripheral abnormalities, and generate coherent models of psychiatric pathology. Crucially, a well-formulated theory allows the derivation of falsifiable predictions, moving research beyond descriptive characterization toward hypothesis-driven investigation. Together, these considerations highlight the necessity of such an approach for uncovering the fundamental mechanisms underlying disorders like OCD.

Conclusion

This study supports a neuropathological model of OCD grounded in dialectic neuroscience, in which aberrant descending fronto-striatal projections represent a core developmental vulnerability affecting both dorsal cognitive–motor and ventral limbic pathways. Compulsive behaviors appear to emerge from competitive interactions between Cau-mediated A–O processing and Put-mediated S–R processes, with the latter mitigating abnormal activity in the former. Directional neural metrics revealed attenuated excitatory and inhibitory effects in OCD, consistent with the model's predictions. Disrupted Cau–insula FC provides preliminary evidence that dorsal striatal dysfunction may propagate to the limbic system. Reduced cortical inhibition suggests frontal cortex abnormalities can affect distributed networks, diminishing computational efficiency. Collectively, these findings underscore the value of theory-driven research: by integrating diverse empirical observations, a coherent framework emerges that enables falsifiable predictions, advances mechanistic understanding, and moves beyond purely descriptive or data-driven approaches in elucidating the core neural underpinnings of OCD.

Authors Contributions

TW Lee is the sole contributor: Conceptualization, Methodology, Formal analysis, Investigation, Visualization, Writing – original draft, Writing – review & editing.

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Statements and Declarations

No conflicts of interest to declare.

Compliance with ethical standards

This research analyzed the databank from a publicly released dataset. The author carried out no animal or human studies for this article.

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Figure Legends

Figure 1. Scatter plots showing three metrics derived from the OCD dataset across 12 gamma values (X-axis), with second-order polynomial regression curves overlaid. Each plot contains 12 data points per metric, corresponding to the tested gamma values. The top panel illustrates results for the OCD group, while the bottom panel shows those for the HC group. The points aligned vertically near the y-axis denote the initial parcellation using the Desikan-Killiany atlas. Red markers and curves represent the mean number of modules (left Y-axis), blue markers and curves indicate the average voxel count per module (left Y-axis), and black markers and curves denote the mean within-module Fisher-transformed z-score (right Y-axis), reflecting modular homogeneity.

Figure 2. Relationships between ALFF and nodal strength in Cau and frontal lobe based on Fisher-transformed correlation coefficients at four Gamma values. F2S: correlation of ALFF in Cau and mean functional connectivity between Cau and frontal lobe. S2F: correlation of mean ALFF in frontal lobe and mean functional connectivity between Cau and frontal lobe. Data are shown for two groups, OCD (circles) and HC (triangles), with error bars representing standard errors. Interaction effects between group and condition are reported below each subplot.

Figure 3. Relationships between ALFF and nodal strength in Put and frontal lobe based on Fisher-transformed correlation coefficients at four Gamma values. F2S: correlation of ALFF in Put and mean functional connectivity between Put and frontal lobe. S2F: correlation of mean ALFF in frontal lobe and mean functional connectivity between Put and frontal lobe. Data are shown for two groups, OCD (circles) and HC (triangles), with error bars representing standard errors. Interaction effects between group and condition are reported below each subplot.