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Review

Thalamic Connectivity System Across Psychiatric Disorders: Current Status and Clinical Implications

Wu Jeong Hwang, Yoo Bin Kwak, Kang Ik K. Cho, Tae Young Lee, Harin Oh, Minji Ha, Minah Kim, and Jun Soo Kwon

ABSTRACT

The thalamic connectivity system, with the thalamus as the central node, enables transmission of the brain's neural computations via extensive connections to cortical, subcortical, and cerebellar regions. Emerging reports suggest deficits in this system across multiple psychiatric disorders, making it a unique network of high translational and transdiagnostic utility in mapping neural alterations that potentially contribute to symptoms and disturbances in psychiatric patients. However, despite considerable research effort, it is still debated how this system contributes to psychiatric disorders. This review characterizes current knowledge regarding thalamic connectivity system deficits in psychiatric disorders, including schizophrenia, bipolar disorder, major depressive disorder, and autism spectrum disorder, across multiple levels of the system. We identify the presence of common and distinct patterns of deficits in the thalamic connectivity system in major psychiatric disorders and assess their nature and characteristics. Specifically, this review assembles evidence for the hypotheses of 1) thalamic microstructure, particularly in the mediodorsal nucleus, as a state marker of psychosis; 2) thalamo-prefrontal connectivity as a trait marker of psychosis; and 3) thalamo-somatosensory/parietal connectivity as a possible marker of general psychiatric illness. Furthermore, possible mechanisms contributing to thalamocortical dysconnectivity are explored. We discuss current views on the contributions of cerebellar-thalamic connectivity to the thalamic connectivity system and propose future studies to examine its effects at multiple levels, from the molecular (e.g., glutamatergic) to the behavioral (e.g., cognition), to gain a deeper understanding of the mechanisms that underlie the disturbances observed in psychiatric disorders.

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The thalamus is a subcortical structure that is the center of the thalamic connectivity system, through which most of our brain's neural computations flow, with multiple connections to cortical, subcortical, and cerebellar regions (1). As the node of this extensive system, the thalamus plays a pivotal role in the processing of sensory inputs and is an essential hub for cognitive processing, such as working memory, attention, flexible goal-directed tasks, sleep, and sensory perception. Recent investigative methods in neuroimaging have presented the thalamic connectivity system as a unique network of high translational and transdiagnostic utility in mapping the neural alterations that may potentially contribute to symptoms and deficits in psychiatric patients (2–5). Unlike the traditional neuroimaging approaches in which the thalamus was delineated and investigated, advancements in technology have enabled modern approaches to leverage the key pivotal properties of the thalamus: this structure is composed of multiple nuclei topologically arranged with respect to the cortex, each with distinct inputs and outputs, and therefore, thalamocortical connectivity patterns are, to a great extent, segregated. However, even with much effort, it is still debated how the thalamic connectivity system contributes to psychiatric disorders.

This narrative review aims to assess how currently available evidence reveals the contribution of thalamic connectivity system abnormalities to psychiatric disorders, as well as to evaluate the nature and characteristics of the components of the thalamic connectivity system. This article provides an overview of the structure and function of the thalamus, followed by evidence of thalamic connectivity system abnormalities in patients with schizophrenia, bipolar disorder, major depressive disorder (MDD), and autism spectrum disorder (ASD) by integrating studies across multiple levels of the system. We identified markers of disease-specific and general psychopathology in the thalamic connectivity system and assessed their nature and characteristics. Specifically, this review assembles evidence for the hypotheses of 1) thalamic microstructure, particularly in the mediodorsal nucleus, as a state marker of psychosis; 2) thalamo-prefrontal connectivity as a trait marker of psychosis; and 3) thalamo-somatosensory/parietal connectivity as a possible marker of general psychiatric illness. Finally, the article explores potential underlying mechanisms of thalamocortical dysconnectivity in psychiatric disorders. We discuss the current views on the downstream effects of cerebellar-thalamic connectivity on the thalamic connectivity system and propose future studies to examine its

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effects at multiple levels, from the molecular (e.g., glutamatergic) to the behavioral (e.g., cognition) levels. Gaining a deeper understanding of the underlying mechanisms of the thalamic connectivity system, as well as the identification of markers of disease-specific and general psychopathology, will facilitate the use of this network as a novel strategy for better treatment and even earlier prevention of psychiatric disorders.

THE THALAMUS AND THE THALAMIC CONNECTIVITY SYSTEM

The thalamus is a walnut-sized, paired structure that sits in the middle of our brain. It consists of approximately 60 topographically arranged nuclei, each of which has distinct inputs and outputs to cortical, subcortical, and cerebellar regions. The nuclei are largely segregated, with the exception of the thalamic reticular nucleus. Thalamic nuclei, predominantly organized in reciprocal feedback loops, receive input from layer 6 of largely nonoverlapping cortical areas. Thus, thalamocortical connectivity patterns have unique characteristics in that they are topographically arranged and segregated, and with the exception of the thalamic reticular nucleus and midline nuclei, the connectivity patterns are mostly confined to a single hemisphere and provide a major source of excitatory input to the cortex (Figure 1).

The functions of thalamic nuclei are defined by their inputs, and based on these inputs, thalamic nuclei can be categorized into two groups: first-order and higher-order (HO) nuclei (6). First-order nuclei relay driver input from the subcortex and relay the primary sensory information to the cortex. Such nuclei include the lateral geniculate nucleus, the medial geniculate nucleus, the ventral posterior nucleus, and parts of the ventral anterior/lateral nuclei, which relay visual information from the retina, auditory information from the inferior colliculus, somatosensory input from the medial lemniscus, and motor input from the deep cerebellar nuclei, respectively. In addition to receiving input from cortical layer 6 in reciprocal feedback loops as first-order nuclei do, HO nuclei receive additional input from layer 5 that is organized in a feedforward structure. Thus, HO nuclei receive driver input from layer 5 of upstream cortical areas and relay it to other cortical areas, forming cortico-thalamo-cortical, or transthalamic, pathways; in this manner, they work to relay information from one cortical area to another (7,8). Such nuclei in the brain include the mediodorsal nucleus (MD), which receives inputs from the amygdala, limbic system, basal ganglia, midbrain, and brainstem and has reciprocal connections with the prefrontal cortex (PFC) and pulvinar, which receives inputs from the superior colliculus and has reciprocal connections with the PFC and temporal, parietal, and occipital cortices. Through transthalamic pathways, HO nuclei send information based on activity in lower cortical areas to the target (higher) cortical areas, and while doing so, they can modulate or even block the message (9), selectively gating the information and positioning themselves as a key player in cortical processes such as cognitive functioning (Figure 1).

Lesion studies have revealed that different nuclei are associated with different behavioral changes, including cognitive functions and psychiatric symptoms [ventral lateral nucleus: sensory processing impairments, synesthesia (10); pulvinar: social cognition and attention impairments (11); MD: PFC-dependent abilities (12)]. The involvement of the MD and

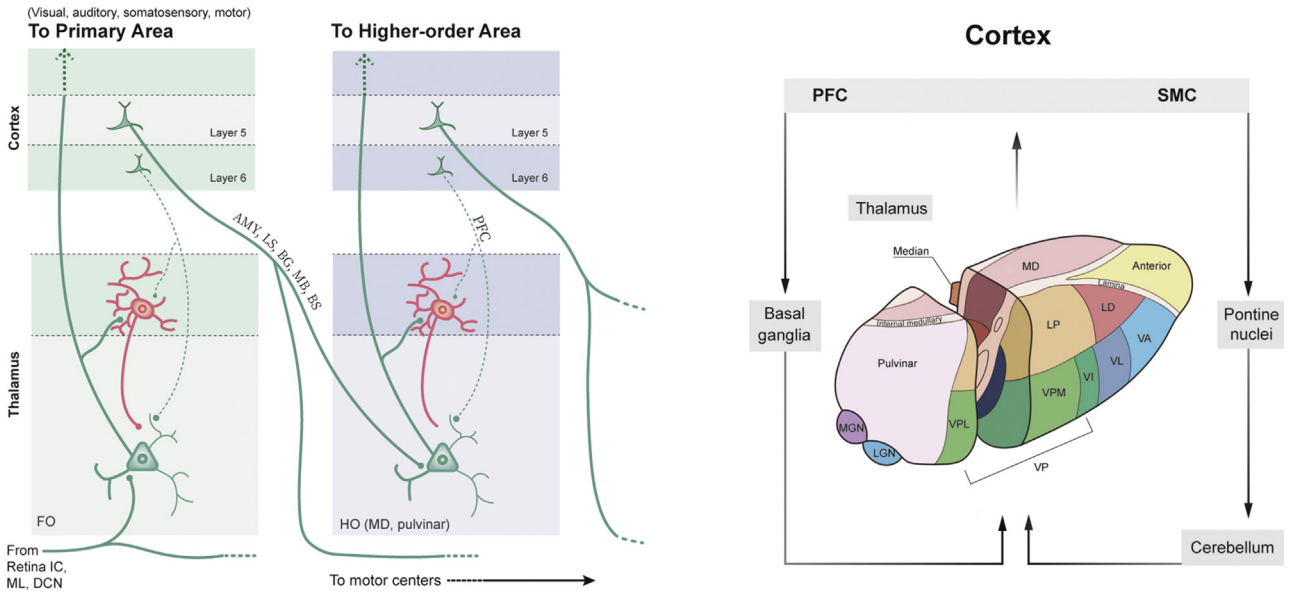

Figure 1. Schematic diagram of the thalamic connectivity system at the neural and systemic levels. (Left) Schematic diagram showing the neural transmission of first-order (FO) and higher-order (HO) thalamic nuclei. (Right) Schematic diagram of pathways between the frontal and parietal cortices to the thalamus. AMY, amygdala; BG, basal ganglia; BS, brainstem; DCN, deep cerebellar nuclei; LD, lateral dorsal nucleus; LGN, lateral geniculate nucleus; LP, lateral posterior nucleus; LS, limbic system; MB, midbrain; MD, mediodorsal nucleus; MGN, medial geniculate nucleus; ML, medial lemniscus; PFC, prefrontal cortex; Retina IC, retina and intercollicular pathways; SMC, somatosensory cortex; VA, ventral anterior nucleus; VI, ventral intermediate nucleus; VL, ventral lateral nucleus; VP, ventral posterior nucleus; VPL, ventral posterolateral nucleus; VPM, ventral posteromedial nucleus.

PFC in cognitive functioning is being examined in detail across various species. In mice, an optogenetic study reported distinct roles of afferent and efferent projections between the mediodorsal PFC and MD in supporting goal attributes (13). The differential roles of the PFC and MD in cognitive control were further investigated in monkeys, and unlike MD neurons, which specialized in decision making and response selection, PFC neurons specialized in preferential encoding of the environmental state (14). In humans, a recent neuroimaging study revealed an association between improved cognitive abilities and increased thalamocortical connectivity in the pulvinar, MD, intralaminar nucleus, and nuclei of the lateral group (15).

THALAMIC CONNECTIVITY SYSTEM ABNORMALITIES IN PSYCHIATRIC DISORDERS

Schizophrenia

Schizophrenia is a severely debilitating disorder characterized by positive and negative symptoms and cognitive deficits. Abnormalities involving thalamic deficits have been extensively investigated in schizophrenia. Multiple large consortium and meta-analytic studies have reported reduced thalamic volume in patients with chronic schizophrenia, as well as those with first-episode psychosis (FEP) (16–18). The significance of the region to schizophrenia pathophysiology has been extensively demonstrated. Thalamic volume is the strongest classifier distinguishing between patients with FEP and healthy control subjects (19); furthermore, an increased thalamic volume is associated with improved cognitive functioning in patients with schizophrenia (20).

HO nuclei, such as the MD and pulvinar, are heavily implicated in schizophrenia pathophysiology. As revealed by postmortem studies, patients with schizophrenia have reduced neuron counts, density, and total volume in the MD, anterior nucleus, and pulvinar (21). Abnormalities in density and volume in the MD and pulvinar have also been confirmed in vivo in multiple neuroimaging studies [for a review on the thalamus in schizophrenia, see (22,23)]. Furthermore, it is suggested that these structures could be a hub of not only cognition but also cortical structural changes in schizophrenia, with their progressive loss of volume being associated with structural abnormalities of the cortex (24). Moreover, their densities show state-like characteristics, and they are reduced only in patients with FEP and not in their unaffected relatives (2,25).

The most commonly used method to evaluate the thalamic connectivity system in schizophrenia calculates the connectivity between the thalamus and 5 or 6 cortical regions (3,4,26). Interestingly, when applied to diffusion tensor imaging (DTI)–based structural connectivity and task-free functional connectivity studies, regardless of magnetic strength [e.g., 3T or 7T (27)], this method yields consistent results of reduced thalamo-prefrontal and increased thalamo-somatosensory/parietal connectivity patterns in patients with chronic schizophrenia, patients with FEP, and individuals at clinical high risk for psychosis, as well as patients with early-onset schizophrenia (28). Furthermore, it has been reported that task-free functional dysconnectivity does not show a progressive deterioration in schizophrenia (29). Currently, thalamocortical dysconnectivity consisting of reduced thalamo-prefrontal and increased thalamo-somatosensory/parietal connectivity is considered a core neurobiological abnormality in schizophrenia [for further reading, see (23,30,31)]. Recently developed methods to investigate the interconnectivity of the thalamus, cerebellum, and cortex revealed dysconnectivity among the thalamus, cerebellum, and temporal cortex (32–34), which highlights the widespread involvement of the thalamus in brain activity and suggests the cerebellum as the next key region to investigate.

Bipolar Disorder

Bipolar disorder is characterized by cycles of mania and depression. The volume of the thalamus is reduced in bipolar disorder in postmortem and neuroimaging meta-analysis studies (35,36). However, when thalamic volume was investigated in individuals with prodromal bipolar disorder, the individuals showed no reductions (37). Similarly, in a recent voxel-based meta-analysis, the anterior thalamic radiation, a white matter structure that is also associated with emotion regulation difficulties in this disorder (38), was compared between patients with bipolar disorder and prodromal individuals. While patients with bipolar disorder showed reduced fractional anisotropy and increased radial diffusivity, no such deficits were seen in individuals at risk for bipolar disorder (39), suggesting that disruptions in the thalamic connectivity system do not occur or are too subtle to be detected in the very early stages of bipolar disorder.

Another intriguing aspect of thalamic connectivity system abnormalities in bipolar disorder is that thalamic volume abnormalities in bipolar disorder tend to be weaker than those in schizophrenia, which is suggested to relate to the increased neurodevelopmental disruption in schizophrenia relative to bipolar disorder (18,36). Interestingly, a similar trend was also shown in thalamocortical connectivity deficits in bipolar disorder. In a meta-analysis of task-free functional connectivity studies, bipolar disorder showed similar patterns of thalamocortical dysconnectivity to schizophrenia, and as with thalamic abnormalities, it showed a similar or lower degree of deficits in thalamocortical dysconnectivity relative to schizophrenia (31). Furthermore, the recent evidence of significant associations between decreased thalamo-prefrontal connectivity and increased thalamo-somatosensory/parietal connectivity suggests that these dysconnectivity patterns could be a part of a common mechanism shared by schizophrenia and bipolar disorder.

Major Depressive Disorder

MDD is characterized by substantial impairments in emotional and cognitive processing. Accumulating evidence suggests deficits in the thalamus in MDD. MD in particular has been reported to show increased metabolism and blood flow (40). Patients with MDD show reduced thalamic volume (41), and clinical implications have been reported for its negative association with symptom severity (42). Further studies using electroconvulsive therapy showed improvement in thalamic volume and its positive associations with clinical improvements in patients with MDD after electroconvulsive therapy (43–45).

In addition to the clinical associations, studies have also demonstrated treatment-responsive characteristics of the thalamic connectivity system in MDD. When task-free functional connectivity between the thalamus and the mood-regulating cortical areas is compared between patients with treatment-resistant and non–treatment-resistant MDD, treatment-resistant patients show reduced connectivity and greater spontaneous thalamic activity (46). Higher thalamic activity has also been reported to be correlated with lower clinical improvement in response to antidepressants in MDD (47), indicating its heavy involvement in MDD pathophysiology.

Similar to the schizophrenia literature, the thalamocortical connectivity of patients with MDD has been investigated using 5 or 6 cortical regions of interest. DTI-based anatomical connectivity and task-free functional connectivity studies have reported decreased thalamo-prefrontal connectivity and increased thalamo-temporal and thalamo-somatosensory/parietal connectivity patterns (5,48–52). Among these, thalamo-temporal connectivity has been reported to have particular clinical significance in MDD. Task-free thalamo-temporal connectivity has been shown to have a positive correlation with symptom severity (49) and to occur irrespective of age of onset, unlike thalamo-prefrontal functional connectivity, which is significantly reduced in adult-onset MDD (48). To date, thalamo-temporal connectivity is one of the most clinically implicated connectivities in MDD.

Autism Spectrum Disorder

ASD is a highly heritable neurodevelopmental condition associated with impairments in reciprocal social communication and patterns of rigid or repetitive behavior. There is substantial evidence supporting structural and functional thalamocortical connectivity deficits in ASD. Structurally, increased DTI-based thalamo-somatosensory connectivity and decreased DTI-based thalamo-prefrontal, thalamo-parietal, and thalamo-temporal connectivity patterns have been reported (53,54). Functionally, studies have demonstrated reduced task-free thalamo-prefrontal connectivity and increased task-free thalamo-temporal connectivity (53,54). A recent study using a large dataset from the Autism Brain Imaging Data Exchange reported increased task-free thalamo-prefrontal, thalamo-temporal, and thalamo-sensorimotor functional connectivity patterns, with more pronounced effects in temporal cortical areas, including the temporoparietal junction (55). Further corroborating the notion of thalamo-temporal hyperconnectivity in ASD, a study reported that the pathophysiology of ASD is more likely related to thalamo-cortical hyperconnectivity (i.e., temporoparietal and posterior cingulate cortices) than to amygdala-cortical hypoconnectivity (56), as well as reduced effective connectivity (57). However, despite the strong findings supporting thalamo-temporal connectivity deficits in ASD, the meaning or clinical relevance remains to be elucidated because studies have yet to reveal significant correlational relationships.

STATE- VERSUS TRAIT-RELATED THALAMIC CONNECTIVITY SYSTEM DEFICITS IN PSYCHIATRIC DISORDERS

Among psychiatric disorders, schizophrenia is one of the most comprehensively studied disorders in terms of investigating individuals in different phases of the course of illness, which includes individuals at clinical high risk for psychosis, patients with FEP, and patients with chronic schizophrenia, as well as individuals at genetic or familial high risk. This approach has enabled investigating and elucidating trait-/state-related markers and thus has provided information regarding potent endophenotypes and biomarkers. As described in the previous sections, thalamic connectivity system deficits are currently being reported at multiple levels of analysis across multiple psychiatric disorders, with some of the patterns being shared across some disorders, such as altered thalamo-prefrontal and thalamo-somatosensory/parietal connectivity patterns and microstructural reductions in the MD (Figure 2).

Thalamo-Prefrontal Connectivity: A Trait Marker of Psychosis?

Reductions in thalamo-prefrontal connectivity are shared to different degrees, both structurally and functionally, among schizophrenia, bipolar disorder, and MDD, implicating this as a

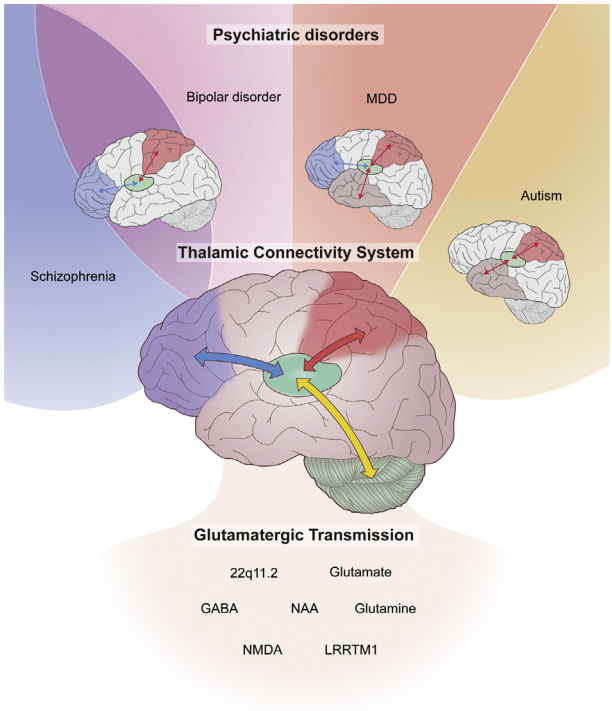

Figure 2. A diagram of multiple levels of the system leading to thalamic connectivity system disruptions. The proteins and genes highly implicated in psychiatric disorders are often essential in glutamatergic transmission in the brain, particularly within the thalamic connectivity system, which comprises the thalamus and thalamic connectivity patterns. These effects are taken up to show disease-specific or general psychopathology characteristics within the system. Schizophrenia and bipolar disorder share reduced thalamo-prefrontal connectivity and increased thalamo-somatomotor/parietal connectivity. Major depressive disorder (MDD) is characterized by reduced thalamo-prefrontal connectivity and increased thalamo-temporal and thalamo-somatomotor/parietal connectivity patterns, and autism is characterized by increased thalamo-temporal and thalamo-somatomotor/parietal connectivity patterns. Shaded blue, red, pink, green, and gray areas indicate the prefrontal cortex, somatomotor/parietal cortex, temporal cortex, thalamus, and cerebellum, respectively. GABA, gamma-aminobutyric acid; NAA, *N*-acetylaspartate.

transdiagnostic connectivity feature in psychosis (5,52,58–61). Considering the strong implication of the relevance of thalamo-prefrontal connectivity in cognition, which has been supported by animal and human studies, it may be a fair view to attempt to understand these differences in terms of cognitive functioning deficits, in particular executive functioning, which are seen across disorders and prodromal states (62–65). Indeed, thalamo-prefrontal connectivity has been shown to be associated with cognition at rest in psychosis (59), dependent on cognitive demand during tasks in schizophrenia (66), and can also be increased by cognitive remediation training (67). Together with the DTI-based structural connectivity study reporting the association of thalamo-prefrontal connectivity with working memory (68), the current literature implicates thalamo-prefrontal connectivity in cognitive function in psychosis.

However, further evidence demonstrating reductions in both structural and functional thalamo-prefrontal connectivity in early-stage psychosis, individuals at clinical high risk for psychosis, and those with genetic high risk for psychosis may require the current interpretation of this phenomenon to be re-evaluated (26,69–75). Notably, asymptomatic relatives/siblings of schizophrenia share decreased thalamo-prefrontal connectivity but not increased thalamo-sensorimotor connectivity (72,74), suggesting that this biological phenotype may be considered a useful intermediate phenotype in linking genetic effects to schizophrenia pathophysiology. Indeed, schizophrenia-related genes have been confirmed to be associated with MD–dorsolateral PFC connectivity (76,77). Taken together, current evidence suggests that reduced thalamo-prefrontal connectivity may represent a heritable trait and vulnerability factor for psychosis. Thalamo-prefrontal connectivity has also been reported to be reduced in ASD. However, no study has yet compared deficits with schizophrenia, bipolar disorder, or MDD. Such studies, together with longitudinal studies, will help fully corroborate this notion.

Thalamo-Somatomotor/Parietal Connectivity: A Marker of General Psychiatric Illness?

Studies have consistently reported increased thalamo-somatomotor/parietal connectivity across psychiatric disorders. For example, studies have reported that increased thalamo-somatomotor/parietal connectivity is shared across schizophrenia, bipolar disorder, and MDD (5,52,58–60) but is not seen in asymptomatic relatives/siblings of patients with schizophrenia (72,74); however, the relevance of this deficit remains unclear because it is one of the understudied components in the thalamic connectivity system. Notably, thalamo-somatosensory/parietal connectivity has been shown to be modulated by electroconvulsive therapy in MDD and schizophrenia (45,69). Studies on this phenomenon are limited, but it is currently postulated to reflect the expression of these mental illness phenotypes or related secondary factors (72). Interestingly, reports have consistently demonstrated, as previously described, significantly increased thalamo-somatomotor/parietal connectivity in ASD. Furthermore, it has been reported that thalamocortical connectivity deficits are shared genetically across psychiatric disorders (78).

Although further studies are needed, it is possible to speculate based on current knowledge that this observation of increased thalamo-somatomotor/parietal connectivity may be reflective of a factor that is present in various psychiatric disorders (i.e., a general psychopathology factor, or p factor) or perhaps underlies them (i.e., a general psychopathophysiological factor). Previous studies have found that a higher p factor was associated with structural disturbances within the cerebello-thalamo-cortical circuit (79). If this truly is the case, it could explain our rather slow advancements in gaining deeper understanding of this deficit, even with the rigorous performance of correlation analyses with multiple measures, such as clinical scores and cognitive function. It could be, as suggested in a review study by Giraldo-Chica and Woodward (30), that we are not testing the correct measures and need to broaden our perspective to find other, perhaps new, measures.

Thalamic Microstructure in the MD: A State Marker of Psychosis?

Recent neuroimaging methods have enabled in vivo segmentation of the thalamus into nuclei using the topographic properties of the thalamus. This new and exciting method has yet to be applied across multiple psychiatric disorders but has already shown promising results in the study of psychosis. Current neuroimaging findings, together with postmortem findings in schizophrenia, suggest that the most strongly implicated thalamic nuclei are the MD and pulvinar (2,80), which are also strongly implicated across psychiatric disorders (81). Studies have revealed volumetric reductions in the MD and pulvinar in psychosis and youths with psychosis spectrum symptoms (80) and microstructural reductions in FEP (2). Several studies investigating genetic associations have reported that unless multivariate analyses are applied to detect very subtle changes, volumetric integrity is preserved in healthy relatives of patients with schizophrenia despite their high genetic loading (82,83). A study further investigated thalamic microstructural integrity in a sample of unaffected relatives of those with psychosis, in whom reduced thalamo-orbitofrontal connectivity was previously reported (71), to elucidate whether such disruptions were associated with the thalamic microstructure; however, the microstructure was intact and volumetric integrity was preserved (25). Further examinations are required, but the current line of evidence suggests state-like characteristics of the MD and pulvinar, which may provide a foundational basis for a new avenue of reverse-translational studies related to the thalamic connectivity system for developing better treatments and better detection strategies.

INVOLVEMENT OF THE CEREBELLUM IN THALAMOCORTICAL DYSCONNECTIVITY

There are yet a limited number of studies postulating the common source of thalamocortical dysconnectivity, particularly in thalamo-prefrontal and thalamo-somatosensory/parietal connectivity patterns observed in schizophrenia and bipolar disorder. However, recent findings have indicated that the impact of cerebellar neurons on different thalamic nuclei varies substantially and highlight the possibility that cerebellar

output differentially controls various parts of the thalamocortical network (84–89). Manipulating cerebellar output affects sensorimotor integration by somatosensory and motor cortices and thereby directs thalamocortical activity related to voluntary movements (90–92). Furthermore, emerging evidence has supported the functional topography of sensorimotor, cognitive, and affective subregions in the cerebellum, with each distinct process linked to different processing regions across the brain (e.g., anterior cerebellum: sensorimotor areas; posterior cerebellum: PFC and parietal association cortices).

Studies have also reported cerebellar-thalamic connectivity deficits. In schizophrenia, it has long been postulated via the cognitive dysmetria theory that cerebello-thalamo-cortical circuitry disruptions lead to impairments in the coordination of mental processes (93). In addition to the structural circuitry having reduced integrity (94), being associated with cognitive functioning (95), and being disrupted from preclinical to chronic stages of schizophrenia (96), cerebello-thalamo-cortical circuitry holds value as a strong classifier between patients with first-episode schizophrenia and healthy control subjects (97). Functionally, it is hyperconnected and is a robust state-independent neural signature for psychosis prediction and characterization (98) and a heritable trait in schizophrenia (99). Similarly, the critical role of the cerebellar circuitry and the presence of disruptions in this circuitry have also been reported in bipolar disorder (100), MDD (101), and ASD (102). Evidence has demonstrated that connectivity between the thalamus and cerebellum is a common biological mechanism underlying multiple psychiatric disorders, particularly psychotic disorders (103).

Downstream Effects of Cerebellar Circuitry on the Thalamic Connectivity System

Studies elucidating detailed relationships between the thalamus and cerebellum can reveal the downstream effects of disruptions in the cerebellum and cerebellar circuitry on the thalamus, providing evidence for consequential downstream effects of thalamic disruption on the cortex. However, it is very difficult to explore these causal relationships in humans because 1) current neuroimaging methods are insufficient for the task, 2) invasive measures are needed, and 3) these relationships must be examined in longitudinal studies with long follow-up durations. Nonetheless, it is crucial to aim to provide information on these fundamental mechanisms in our brain. Particular study designs (such as translational and reverse-translational designs) and powerful, high-precision technologies show significant promise, potentially enabling such questions to be addressed with previously unattainable spatial and temporal resolution. To date, only a small number of studies are available, but in one recent study with a reverse-translational design, dysfunctional delta rhythms in the medial frontal cortex during an interval timing task were explored in an animal model. Both frontal and cerebellar neurons were modulated, and subsequent optogenetic cerebellar stimulation in mice normalized the dysfunctional frontal networks, which has also been observed in patients with schizophrenia, highlighting the direct impacts of the cerebellum on frontal networks, particularly in cognitive processing (104). Neuroimaging studies, although they cannot address direct causality, have revealed that cerebellar gray matter reductions may be associated with modulation of cerebellar-thalamic connectivity and the frontoparietal network (105). When investigating whether thalamic dysconnectivity patterns were shared with other nodes in a larger system, the corticostriatal-thalamic-cerebellar circuit, cerebellum, and striatum showed similar patterns of disruption, highlighting that thalamic connectivity deficits may not be focal disruptions but may be understood as a part of disturbances in a larger system, such as the corticostriatal-thalamic-cerebellar circuit, or perhaps in the context of a brain-wide level of NMDA receptor disruptions (106). Future studies are warranted to explore the effects of NMDA receptor disruptions in the cerebellar circuitry on the thalamic connectivity system.

CONCLUSIONS

Overall, there are shared and distinct patterns of deficits in the thalamic connectivity system across schizophrenia, bipolar disorder, MDD, and ASD. The disease-specific deficits include reduced thalamo-prefrontal connectivity in schizophrenia and bipolar disorder and increased thalamo-temporal connectivity in MDD and ASD. However, we do not yet know the relative degree of deficits across illnesses or, due to methodological differences across studies, the differential localization of deficits within the system. More exploration into sources causing thalamic connectivity system disruption needs to be conducted, although in this review, we provide the possibility that the cerebellum and cerebellar circuits would be a fruitful model to study. Furthermore, current evidence supports thalamo-prefrontal connectivity as a heritable trait and a marker of vulnerability to psychosis, and additional studies may be required to fully substantiate this notion, but thalamo-somatomotor/parietal connectivity is a possible general psychiatric illness marker. Taken together, current evidence supports the transdiagnostic validity of the thalamic connectivity system, and future studies elucidating further details of this system are highly warranted.

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ARTICLE INFORMATION

From the Department of Brain and Cognitive Sciences (WJH, YBK, HO, MH, JSK), Seoul National University College of Natural Sciences; Department of Neuropsychiatry (MK, JSK), Seoul National University Hospital; Department of Psychiatry (JSK), Seoul National University College of Medicine; Institute

of Human Behavioral Medicine (JSK), Seoul National University Medical Research Center, Seoul; Department of Psychiatry (TYL) and Research Institute for Convergence of Biomedical Science and Technology (TYL), Pusan National University Yangsan Hospital, Yangsan, Republic of Korea; and the Department of Psychiatry (KIKC), Psychiatry Neuroimaging Laboratory, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts.

Address correspondence to Jun Soo Kwon, M.D., Ph.D., at kwonjs@snu.ac.kr.

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