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Cerebellar-Thalamic Connectivity in Schizophrenia

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The literature on alterations in brain structure and function in schizophrenia, particularly in relationship to impairments in cognitive, motor, and affective functions, has made it increasingly clear that changes in the function of a single brain region cannot explain the range of impairments seen in this illness.[1–4] This realization has led to a surgence of interest in studies examining neurobiological changes in schizophrenia from the perspective of brain networks and connections among brain regions and networks, with a particular focus on neural circuits known to work together to support sensory, cognitive, and emotional processes.[5] This shift in focus is consistent with long-standing hypotheses about schizophrenia as a "dysconnection" syndrome, where impairments in cognition and behavior occur because of a failure of coordinated action across multiple brain regions. As many researchers have noted,[6] versions of this hypothesis were put forth as early as the work of Wernicke[7] and Bleuler.[8] Further, theories about abnormalities in connections among brain regions have also played a central role in more recent theories of the pathophysiology of schizophrenia. For example, one such prominent theory, put forth by Andreasen and colleagues,[9] suggested that schizophrenia involves a disruption in the integration of cortical-subcortical-cerebellar circuits, a hypothesis termed "cognitive dysmetria."

Although the cognitive dysmetria hypothesis suggested the critical involvement of cerebellar, striatal, and thalamic circuits as well as cortical circuits, the majority of the work on structural and functional connectivity deficits in schizophrenia has focused on cortical and striatal dysfunction and disconnection,[10–14] with the need for additional work on the thalamus. Alterations in the structure[15–17] and function of the thalamus are prominent in the schizophrenia literature.[2,18–21] As shown in anatomical studies of primates, the thalamus is topographically organized into parallel pathways connecting specific thalamic nuclei to different regions of cortex brain regions,[22] helping to form parallel loops for various types of information processing between subcortical and cortical regions. A growing number of studies have examined deficits in thalamic connectivity in schizophrenia, with several studies finding alterations in the functional connectivity between the thalamus and regions in the prefrontal in individuals with schizophrenia,[23–27] consistent with the known anatomical connectivity of the thalamus.

Surprisingly few studies have examined cerebellar dysconnectivity in schizophrenia, or abnormalities in cerebellar-thalamic connections.[28–31] In part this may reflect the fact that until recently, the involvement of the cerebellum in nonmotor functions was not well-appreciated, perhaps making it a potentially less attractive target for work trying to understand the neural basis of cognitive and affective, as well as motor deficits in schizophrenia. However, there is now strong evidence that the cerebellum plays important roles in nonmotor cognitive and affective functions[32–37] though the precise mechanistic contributions that the cerebellum makes to these functions remains to be elucidated. Existing theories of cerebellar function suggest that it influences motor and higher cognitive functions through feed-back and feed-forward loops via the thalamus and pons, with the thalamus the obligatory relay for all efferent cerebellar projections to the cortex. In particular, it is thought that the cerebellum plays a key role in cognitive and affective control through error processing,[38] with potential roles for the cerebellum in reinforcement learning[39] and/or supervised learning.[40,41] Further, there is also strong evidence that the cerebellum, particularly the olivo-cerebellar loop, plays a key role in timing functions.[42]

A substantial amount of work has found that cerebellar regions display anatomical and functional alterations in schizophrenia,[43–47] and there is evidence for abnormalities in motor,[48] conditioning,[49–53] and timing functions[54–58] thought to be supported at least in part the cerebellum in schizophrenia. Further, several previous studies have found evidence of altered connectivity between the thalamus and the cerebellum.[28–31,59] However, much remains to be understood in terms of the nature of cerebellar and thalamic connectivity dysfunction in schizophrenia and related psychotic disorders. The 3 articles in this special section on thalamic and cerebellar functional and structure and connectivity in psychosis are contributions that attempt to address some of the critical unanswered questions in this domain. Specifically, these articles address the questions of the degree to which cerebellar connectivity impairments are present in white matter connections and in the topographic organization of modules in the cerebellum, the degree to which thalamic/cerebellar connectivity impairments are or are not specific to nonaffective vs affective psychosis, and the relationship of thalamic/cerebellar connectivity impairments to neurological signs during the course of psychosis development.

Specifically, Kim and Hetrick extend graph theoretical studies of cortical topography and connectivity to the cerebellum, with a focus on structural connections. They show that individuals with schizophrenia have reduced white matter integrity in cerebellar lobules I–IV and V, lobules that have been hypothesized to play a key role in sensorimotor function.[33] The overall modularity of cerebellar networks was similar in individuals with schizophrenia and healthy controls, but the modular pattern of organization of the cerebellum was significantly altered in schizophrenia, in a way that might suggest abnormal segregation of prefrontal inputs into the cerebellum.

Anticevic et al focused more on thalamic connectivity, asking whether there are similar or distinct patterns of abnormal connectivity from medial dorsal vs lateral geniculate thalamic nuclei in schizophrenia and in individuals with bipolar disorder who do and do not have psychosis. They found that both the medial dorsal and lateral geniculate nuclei showed patterns of *under* connectivity with prefrontal and cerebellar regions in schizophrenia, but a pattern of *increased* connectivity with sensory motor regions. In contrast, neither the bipolar patients with psychosis nor the individuals without psychosis showed altered thalamic to cerebellar connectivity. Importantly, they found that the reduction in medial-dorsal thalamus to cerebellar connectivity was significantly greater in schizophrenia as compared with bipolar disorder, both with and without psychosis. These data provide evidence for important potential diagnostic differences in thalamic to cerebellar connectivity and suggest the need for further cross-diagnostic comparisons of cortical-striatal-thalamic-cerebellar connectivity to understand which components of this network show shared impairments across different disorders involving psychosis vs which may be more specific to affective or nonaffective forms of psychosis.

Mittal et al examined the integrity of the superior cerebellar peduncles, the white matter tracts connecting the cerebellum and the thalamus in young adults with prodromal symptoms of psychosis (eg, "ultra high risk" individuals, or UHR). This allowed them to ask novel questions about the course of cerebellar to thalamic connectivity deficits in the emergence of psychosis, and about their relationship to sensory motor deficits. They found that at baseline, the UHR individuals showed significantly elevated neurological soft signs in sensory and motor domains. However, the UHR individuals did not differ from healthy controls in terms of white matter integrity in the superior cerebellar peduncles. Over the course of a 12-month follow-up, the healthy controls showed continued development of the superior cerebellar peduncles, as evidenced by increases in fractional anisotropy, while the UHR individuals showed a decline in fractional anisotropy, leading to significant group differences at follow-up. Even more importantly, neurological soft signs at baseline predicted a significant decline in white matter integrity over the course of follow-up, as well as more severe negative symptoms at follow-up. Thus, these data provide evidence for altered development of the white matter tracts connecting the thalamus and the cerebellum among individuals with early risk signs of psychosis. Further, these data provide a crucial link between thalamic-cerebellar connectivity and both motor and sensory function even very early in the course of psychosis.

Taken together, these 3 articles provide new information about the nature of cerebellar and thalamic connectivity abnormalities in relationship to psychosis, with evidence at both the structural and functional level. However, these results also raise intriguing questions that should be the pursuit of future research. Importantly, these data suggest the need for a closer examination of the developmental course of thalamic and cerebellar connectivity deficits in relationship to the emergence of psychosis, as a way to determine whether such deficits are predictors of risk or endophenotypes vs markers of illness course or emergence. In addition, these data point to the need for cross-diagnostic studies that examine the shared vs unique impairments in thalamic and cerebellar connectivity across illnesses that may or may not involve psychosis, both at the functional and structural level. Lastly, it will be critical to more mechanistically link these thalamic and cerebellar structure, function, and connectivity deficits to theories of illness development and impairments in cognition, emotion, and motor function. The work on the computational role of the cerebellum in different aspects of learning provides a pathway by which to do so, especially if this work can be linked to putative functional roles for the thalamus and the striatum in interaction with the cortex. There are a number of existing computational models of both the symptoms of psychosis and different aspects of cognition that postulate specific roles for particular components of the striatum and the cortex.[60–64] These models are relatively well developed and have already been harnessed to try to understand the neurobiology of psychosis.[65–70] However, compared with other components of the circuit, there has been relatively little computational work on the specific role of the thalamus,[71,72] and thus future computational modeling that integrates roles for the cerebellum and thalamus along with the striatum and cortex would help generate testable predictions that could advance our understanding of the functional significance of cortical-striatal-thalamic-cerebellar circuit abnormalities in psychosis.

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