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Cerebellar Dysfunction and Schizophrenia: From “Cognitive Dysmetria” to a Potential Therapeutic Target

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That cerebellar dysfunction may be involved in the pathogenesis of schizophrenia is by no means a completely new hypothesis. Approximately 20 years ago, Nancy Andreasen, M.D., Ph.D., and colleagues (1, 2) proposed a “cognitive dysmetria” theory to explain the diversity of behavior deficits within the schizophrenia spectrum. They posited that dysfunction of cerebello-thalamo-cortical circuitry is the most fundamental neurobiological change underlying a variety of observed clinical symptoms in patients with schizophrenia. Such change further leads to difficulties in synchronizing and integrating neural computations and processing in order to generate orderly and meaningful behaviors. Almost at the same time, Schmahmann and Sherman (3) studied clinical patients with lesions confined to the cerebellum and concluded that patients with cerebellar impairments (especially in the posterior lobe) are characterized by a set of cognitive, emotional, and social symptoms that highly resemble those observed in schizophrenia, such as deficits in planning, cognitive shifting, abstract reasoning, visual and spatial memory, and verbal fluency, as well as blunting of affect, depression, and inappropriate social behaviors. The “cerebellar cognitive affective syndrome” is now recognized as having extensive overlap with psychosis.

Our understanding of the cerebellum has evolved from the traditional view of its primary function in motor coordination to a more comprehensive picture that it participates in a broad range of cognitive functions in humans (4, 5). In parallel to this conceptual evolution, recent studies using data acquired from large-scale neuroimaging consortia have provided converging evidence for associations between the structure and function of the cerebellum and schizophrenia. In particular, in at least two large, independent data sets involving a total of more than 3,700 individuals, cerebellar volume has been found to be significantly reduced in patients with schizophrenia and significantly correlated with psychotic symptoms (6, 7). Moreover, a study of clinical high-risk subjects demonstrated cerebellar-thalamo-cortical dysconnectivity as a state-independent neural trait for prediction of psychosis (8). While these findings have brought new momentum to the two-decades-old cognitive dysmetria theory, the question arises as to whether cerebellar alterations indeed reflect a

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primary neuropathology that participates causally in schizophrenia or rather a secondary phenomenon related to either cognitive deficits or other latent pathological changes in the disorder. In other words, does cerebellar dysfunction lead to cognitive dysmetria, compensate for cognitive dysmetria, or signify a consequence of cognitive dysmetria?

In this issue of the *Journal*, Brady and colleagues (9) present a two-step study to approach this question by combining resting-state functional MRI, state-of-the-art brain network analysis, and brain stimulation. Considering the fact that negative symptoms are strongly associated with cognitive impairments and are a major rate-limiting feature of long-term functional outcomes in schizophrenia, these investigators started with a completely data-driven approach to exhaustively search for connectome-wide associations with negative symptoms in a sample of 44 patients diagnosed with schizophrenia spectrum disorders. Using multivariate distance matrix regression, a method that compares between-subject similarities of whole-brain connectivity maps on each voxel, followed by a post hoc seed-based connectivity analysis, they discovered that the connectivity between dorsolateral prefrontal cortex (DLPFC) and midline posterior cerebellum showed the strongest correlation with negative symptoms across the whole brain during resting state. Specifically, patients with higher negative symptoms had significantly lower cerebellar-prefrontal connectivity, suggesting that disrupted synchronization in the cerebellar-prefrontal circuitry underlies negative symptoms and possibly also cognitive dysfunction.

In the second part of the study, Brady and colleagues investigated whether the altered connectivity between the cerebellum and DLPFC could be a causal mechanism for negative symptoms or rather an epiphenomenon. They performed a repetitive transcranial magnetic stimulation (rTMS) trial targeting the posterior cerebellum in an independent group of patients (N=11) to examine whether rTMS could boost the functional connectivity of the cerebellar-prefrontal circuitry and in turn ameliorate clinical symptoms. In theory, if cerebellar-prefrontal dysconnectivity causes negative symptoms, one would expect that a restoration of such connectivity would help reduce symptom severity. In contrast, if the observed dysconnectivity is reflective of a compensatory effect or an epiphenomenon, a restoration of such connectivity would be expected to have little or no effect on symptoms. Intriguingly, after a 5-day (4 hours per day) rTMS administration, most patients in the sample showed an increase in cerebellar-prefrontal connectivity, the degree of which was significantly correlated with improvement in negative symptom severity. Notably, more than 60% of total variance in symptom change could be attributed to the change in cerebellar-prefrontal connectivity, corroborating a possible causal relationship from disrupted connectivity in cerebellar-prefrontal circuitry to negative symptoms in schizophrenia.

The findings from this study are interesting in the way that they have updated the cognitive dysmetria hypothesis by providing direct evidence for a potential causal influence of cerebellar dysfunction in the pathogenesis of schizophrenia. One underlying mechanism that may potentially bridge the gap between cerebellar dysfunction and behavioral deficits is alterations in error processing, which depends on information transfer and integration in the cerebellar-cortical circuitry. Recent research (10) has shown that cerebellar deep nuclei directly send outputs to the dopamine neurons in the midbrain ventral-tegmental area, which

in turn regulate the entire mesocortical dopamine system, including the DLPFC. As a result, cerebellar dysfunction may change the phasic firing of the ventral-tegmental area dopamine neurons by which the prediction errors are encoded. Such changes may subsequently exert distorted weights on the predicted probabilities of outcome expectations of the interactions between the individual and the outside world, thereby generating a series of “negative” responses to social and cognitive engagements such as blunting of affect, poverty of speech, anhedonia and avolition. In addition, such changes may also affect the downstream function of the dopamine D₁ receptors located in the DLPFC, together contributing to the negative symptoms in schizophrenia.

The study by Brady and colleagues offers an excellent model for probing brain-behavior relationships in psychiatric neuroscience by combining functional neuroimaging with neuromodulation techniques. As highlighted by the authors in the article, “it establishes a causal relationship between resting-state functional connectivity and disease expression in a psychiatric illness, moving the field away from purely correlational studies” (9). Such advancement could certainly not only further our understanding of the biological mechanisms underlying mental disorders but also shed light on potentially novel and promising intervention strategies, especially for symptoms for which we lack any effective treatments. For example, with the knowledge that cerebellar dysfunction possibly causes negative symptoms in schizophrenia, which may be corrected by brain stimulation of the cerebellum, investigators in future clinical trials would be encouraged to test the efficacy of cerebellar rTMS in the treatment of negative symptoms in large populations. In so doing, schizophrenia research may benefit from a bench-to-bed translation from mechanism-oriented neuroscience studies to evidence-guided clinical therapies.

This study also raises some questions that need to be answered in the future. First, it is unclear whether the observed symptoms were indeed directly triggered by dysfunction in the cerebellar-prefrontal circuitry. For instance, one may argue that rTMS may indirectly influence the functions of other networks in the brain, and these secondary modulations could more directly contribute to alleviations of negative symptoms. Second, in view of the small sample size in this study, it is unclear whether rTMS intervention could differentially benefit specific subgroups of patients stratified by, for example, gender, duration of illness, baseline symptom severity, comorbidity, and so forth. Given the fact that some of the patients in the studied sample did not respond to rTMS (as shown in Figure 2 in the article), the mechanisms determining whether a patient is a responder or nonresponder are equally interesting and worthy of investigation in future studies. Notwithstanding these limitations, the results of this study encourage cerebellar dysfunction as a promising neural target that may potentially help advance the understanding and treatment of this complex mental disorder.

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