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EDITORIAL

Modulation of Cerebellar Activity in Schizophrenia: Is It the Time for Clinical Trials?

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Theories involving the cerebellum in the pathophysiology of schizophrenia have a long tradition, rising and falling throughout the history of psychiatry. Now, preliminary studies suggest the modulation of cerebellar activity could actually relieve symptoms of schizophrenia.

In his seminal work "*Dementia praecox and paraphrenia*," Kraepelin reports that schizophrenia could be accompanied by cerebellar signs, such as disorders of equilibrium, staggering, adiadochokinesia, and tremor. He attributed these observations to Dufour, also credited with the hypothesis of "cerebellar" forms of dementia praecox. Interestingly, in a later chapter, he also mentions the presence of atrophic changes in the cerebellum, as noted by Klippel and Lhermitte (*please refer to the* Supplementary Material *file for additional references*). At the time, the cerebellum was exclusively considered for its role in motor functions, and motor symptoms was deemed less important in the clinical picture of the disorder. The advent of drug treatment further overshadowed the importance of *primary* motor symptoms in schizophrenia, with the exception of extrapyramidal and catatonic symptoms[1]; the cerebellum, too, was seemingly forgotten for the decades that followed.

We imagine it must have been surprising, then, when one of the first neuroimaging studies ever conducted on schizophrenia highlighted the presence of abnormalities located in the cerebellum. Weinberger and colleagues' reported signs of cerebellar atrophy mainly in the vermis,[2] while subsequent neuroimaging and postmortem studies observed other abnormalities or failed to detect meaningful differences from controls. The significance of such findings was relatively obscure, once the authors excluded they were due to chronic alcohol use or drug treatment. Still, it was hypothesized that cerebellar abnormalities could contribute to the pathogenesis of schizophrenia, possibly through a newly discovered cerebellar influence on dopaminergic tone.[2] In addition, one study suggested that the electric stimulation of the cerebellum might exert some therapeutic effect. Nonetheless, during the following years, the role of the cerebellum in the pathophysiology of schizophrenia was again overshadowed by other compelling "mainstream" accounts.

The 90s saw another reemergence of the interest on this topic, following the reconceptualization of cerebellar functions introduced by Schmahmann.[3] On the basis of lesion studies and other lines of evidence, researchers discovered that the functions of the cerebellum extended well beyond the sensorimotor domain, including higher-order cognitive and affective functions. Various studies contributed to redefine the set of topographically organized connections linking cerebellar areas with association and paralimbic cerebral cortices. On this basis, the cerebellum is now deemed to function as a multimodal "*Universal Cerebellar Transform,*" constantly generating and updating internal predictive models across different modalities (motor, cognitive, and/or affective).[3] Individuals with cerebellar lesions, in fact, can develop cognitive, affective, and meta-cognitive dysfunctions that in part resemble the fundamental deficits of schizophrenia.[3] In this regard, Andreasen and colleagues developed their "Cognitive Dysmetria" hypothesis, proposing a prominent role for cerebellar dysfunction in the pathophysiology of schizophrenia.[4] In their view, abnormal function of the cerebello-thalamo-cortical circuit would lead to a lack of integration between neural stimuli across multiple modalities which, in turn could lead to develop different symptoms, including delusions, hallucinations, cognitive deficits, and affective dysregulation.[4] The Cognitive Dysmetria model is termed "neo-Bleulerian," since it encompasses a pathological *disconnection* or *lack of coordination* between different brain functions or areas.

Nearly four decades later, advanced neuroimaging techniques still consistently recognize that schizophrenia is associated with cerebellar structural and functional abnormalities, such as gray matter reduction and altered connectivity in the cerebellar-thalamo-cortical circuit. Interestingly, such features are also observed among subjects at high-risk and seem associated with worse functional outcomes. Parker and colleagues has recently further revamped the interest on this topic by studying a preclinical model obtained in rats through antagonism of the D1 receptor in the prefrontal cortex. The authors elegantly showed that optogenetic stimulation of the cerebellum (in the rat analogue of the human dentate nucleus) was able to recover neural activity in the medial frontal cortex and the performance in a cognitive task that had been both disrupted by D1 antagonism. Another intriguing preclinical study by Carta and colleagues recently demonstrated the presence of direct connections between cerebellar nuclei and the ventral tegmental area, one of the major dopaminergic hubs in the brain. Here, optogenetic stimulation resulted in the direct modulation of reward-related and social behavior. These studies readily prompt the question whether the time has come for possible clinical applications of the Cognitive Dysmetria model, more specifically, whether the modulation of cerebellar activity may entail therapeutic effects in patients suffering from schizophrenia (*see Supplementary Materials for additional references*).

Actually, studies that have taken on this challenge are already available, while some others are ongoing (*see Supplementary Materials for additional references*). Available studies are few and display methodological limitations, but their results seem promising. A pioneer study had been conducted by Heath and colleagues in 1980 on 15 patients with treatment-resistant schizophrenia, who were implanted a cerebellar pacemaker with encouraging results. Although improvement of symptoms was reported, the authors did not specify in which domain they occurred. This line of research restarted in the 2010s by exploiting repetitive transcranial magnetic stimulation and transcranial direct current stimulation as elective tools to directly modulate cerebellar activity, with fewer side effects. Studies targeted almost exclusively the cerebellar vermis, part of the so-called "*limbic cerebellum*" involved both in motor and emotional processing. In most cases, cerebellar stimulation led to significant improvements of negative and/or depressive symptoms, measured with mainstream rating scales. Regrettably, no study made a distinction between primary negative, cognitive, or motor symptoms and their drug-induced counterparts. The recent study of Brady and colleagues, however, was accompanied by a functional neuroimaging assessment. Interestingly, the improvement of negative symptoms was specifically and strongly correlated with an increase of functional connectivity between the dorsolateral prefrontal cortex and the cerebellum. Improvements of cognitive performance, including attentional, visuospatial abilities, and procedural learning were also reported in the few studies that included such evaluations. The potential to ameliorate negative or cognitive symptoms is particularly noteworthy for clinical practice insofar they are largely responsible for residual disability but very few therapeutic alternatives currently exist. The major drawback of such studies, however, are methodological: above all, the design seldom included randomization.

Given these premises, we believe a strong case could be made for further studying the modulation of cerebellar neural pathways as a therapeutic intervention in schizophrenia. Now that various, safe tools to modulate cerebellar activity are available, this may be readily translated into the clinical world.[5] The time seems similarly ripe for further, rigorous experimental challenge of the Cognitive Dysmetria model and its implications. Future studies should examine the spectrum of psychotic disorders, possibly incorporating specific domains that may be linked with cerebellar function among the outcomes. Such are motor dysfunctions, time processing deficits, language, meta-cognitive, and other higher-order cognitive impairment.[3] In addition, recent recommendations on the distinction between primary vs secondary symptoms would need to be considered. Ideally, future studies would also include neuroimaging and electroencephalographic assessments to help clarifying the role of cerebellar abnormalities in the context of other neurobiological findings, as well as identifying the neural mechanisms of clinical change. It should be examined, for instance, if the modulation of the cerebello-thalamo-cortical circuit, recently indicated as a robust trait of vulnerability to psychosis,[6] or direct connections with dopaminergic areas are specifically implicated in clinical improvements. Similarly, future studies should elucidate whether structural and functional cerebellar abnormalities are widespread across the psychotic spectrum or they only interest specific subgroup of patients. If such studies were conducted, we believe they would not only benefit patients, but also help to shed light on the elusive pathogenesis of schizophrenia.

Supplementary Material

Supplementary data are available at *Schizophrenia Bulletin* online.

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