HHS Public Access

Author manuscript

Mol Psychiatry. Author manuscript; available in PMC 2021 October 30.

Published in final edited form as:

Mol Psychiatry. 2021 August ; 26(8): 3666–3668. doi:10.1038/s41380-020-00935-9.

Cerebellar-thalamic circuits play a critical role in psychomotor function

Vijay A. Mittal[1], **Jessica A. Bernard**[2], **Sebastian Walther**[3]

[1]Departments of Psychology, Psychiatry, Medical Social Sciences, Northwestern University, Evanston, IL

[2]Texas A&M University, Department of Psychological and Brain Sciences, Texas A&M Institute for Neuroscience, Texas A&M University, College Station, TX, USA

[3]Translational Research Center, University Hospital of Psychiatry, University of Bern, Switzerland

To the Editor,

We read the recent conceptual review on the biochemical modulation of psychomotor mechanisms (1) with great interest. The distinction between purely motor functions, and the modulatory influence of non-motor functions such as cognition and emotion (putting the "psycho" in "psychomotor") provides a fresh perspective for understanding motor symptoms from a transdiagnostic perspective. However, we do believe the proposed model was incomplete in that it did not consider cerebello-thalamo-cortical-cerebellar (CTCC) circuits. We argue that "non-motor" influences on motor behaviors regulated by the cerebellar circuit also closely align with the authors' definition of "psychomotor", and further, provide additional considerations for framing an otherwise excellent model.

The authors highlight dopamine and cortical-striatal-thalamic circuits, as purely "motor" and indicate that "psycho"motor modulation occurs through serotonin and cortical networks (e.g., default mode network; DMN). However, this conception neglects CTCC "motor" circuits, which are also rich with afferent and efferent connections to networks that modulate motor, cognitive, and affective processing. We suggest extending the model of Northoff and colleagues (1) to include the cerebellum. Broadly, cerebellar circuits allow for the processing of information shared from the cortex with the cerebellum, allowing for fluid and coordinated movement and thought. One critical function is the precise timing of action and subjective time perception (2). Notably, the cerebellum is also innervated by serotonergic fibers (3), and neurotransmission includes GABAergic and cholinergic action. In addition, projections heavily interact with dopaminergic and glutamatergic systems (4). As such, the CTCC is in large part an extension to the dopaminergic model proposed by Northoff and colleagues (1), and cerebellar action in particular may in part further modulate the action

Corresponding: Vijay A. Mittal, Associate Professor of Psychology, Northwestern University, Vijay.mittal@northwestern.edu.

Author Statement: All authors contributed equally to the conceptual planning, drafting, and revision of the manuscript.

Conflicts: None

of these dopaminergic systems in the cortex (4). Similar to the mechanisms highlighted by the authors, CTCC mediated motor behaviors are influenced by “psycho”logical function as well. For example, consider Gerhard Anderson’s seminal work indicating that postural control is impacted by cognitive load, and cognitive performance is influenced by balance perturbation in turn (5). The CTCC has also been implicated in affective symptoms of schizophrenia. Brady and colleagues (6) demonstrated that CTCC connectivity is associated with negative symptom severity (e.g., affective flattening and slowing) and that symptom course improves with non-invasive brain stimulation. As our knowledge of this circuit grows and we investigate its contributions across diagnoses (e.g., clinically relevant abnormalities in motor balance, gait, coordination, timing, integration and learning) occur across a full range of psychiatric disorders), inclusion of this circuit in the broader model is of utmost importance.

Further, in recent work, the interactions of subcortical systems involved in psychomotor function are of note. While the importance of the CTCC has been established, interactions between the cerebellum and basal ganglia stand to be of great importance for our understanding of psychomotor function in psychiatry and the formation of new hypotheses in this field. Several studies in non-human primates have now established the direct connections between these two critical circuits (4). These connections allow for back and forth modulation of cerebellar and basal ganglia function, and in turn, may play a key role in psychomotor function (see Figure 1). Dysfunctional activation patterns have been seen across both psychiatric and neurological conditions in these regions (4), pointing to their potential importance in understanding this critical domain of function. As Northoff and colleagues (1) so clearly outlined, striatal function through dopaminergic modulation is key for maintaining balanced activity in the motor system. However, it may be the case that cerebellar action upon this system, in addition to dopaminergic modulation, may also be a major contributor to balanced sensorimotor function. Indeed, direct connections may be the key for linking theories that explain heterogeneous characteristics of psychosis such as cognitive dysmetria (centering on the cerebellum and CTCC circuits) (7), with updated dopamine models (focusing on basal ganglia circuits) (8). We would suggest that including this sub-circuit into the framework as well. In addition, we propose investigating the CTCC’s role in abnormal motor behavior in psychiatry, assuming decreased neural activity in premotor cortices and M1 with concurrent increases in neural activity in basal ganglia, thalamus and cerebellum in subjects with behavioral inhibition. For example, Moussa-Tooks have demonstrated aberrant effective connectivity between cerebellum and basal ganglia in schizophrenia during motor synchronization (9). Alternatively, given our recent proposal that cerebellar internal model function is degraded in patients with psychosis (10), decreased activation in the cerebellum may be associated with slowing and poorer motor performance.

In addition to omitting CTCC circuits, there are a few other important considerations we would like to highlight. First, the authors have put much emphasis on their own findings from a series of excellent resting-state fMRI studies, in which they used available data sets of patients with major depressive or bipolar disorder, who were classified into agitated depressed, inhibited depressed, or manic based on single item ratings of agitation or retardation from general rating scales with very little symptom load. Thus, this information has to be interpreted with some caution, as in-depth analyses of altered motor system

activity would require scanning patients with sufficient symptom load, ideally assessing motor behaviors with objective instrumentation (e.g. actigraphy) or entire validated rating scales (). Related to this point, resting-state fMRI studies should be complemented with concurrent MRI technologies, such as task fMRI, perfusion MRI or diffusion tensor imaging (DTI). Thus, while there is promise for this idea, we think that at the current stage framing it as a hypothesis may be more effective in encouraging the field to conduct the types of follow up work necessary to serve as the foundation for a unifying psychomotor theory. Examples of such approaches include a DTI study that indicated links between neurological soft signs and progressing cerebellar-thalamic tract abnormalities (11), a task fMRI experiment that detected associations with rule learning deficits and abnormal cerebellar activation (12), and a resting-state functional connectivity investigation that reported a relationship between aberrant timing and cerebellar network dysfunction (13), each conducted in samples of youth at clinical high-risk (CHR) for psychosis. Beyond schizophrenia spectrum disorders, studies have demonstrated associations between instrumental assessments of motor behavior and perfusion MRI/DTI in depression and bipolar disorder (14–15). Further, we would encourage the use of standardized measures of motor function and when possible, parallel imaging parameters to allow for comparison across sites.

Second, the authors have focused on the entire sensorimotor network (SMN), while the cortical motor areas are quite distinct. A number of reports in depression or schizophrenia demonstrated that resting brain activity is increased in premotor areas and decreased in ventromedial prefrontal cortex in patients with reduced motor activity as measured with actigraphy (14). Therefore, the assumption of reduced activity within the SMN in patients with behavioral motor inhibition is ambiguous. In fact, increased neural activity within the supplementary motor area (SMA) seems to be specific to psychomotor retardation as observed in catatonia. Indeed, a recent report suggests that hyperactivity in the SMA can be ameliorated via *inhibitory* repetitive transcranial magnetic stimulation over the SMA (16), a mechanism that would not work in hypoactive SMN. The psychomotor conception would be strengthened by incorporating and explaining SMN nuance as well as conflicting findings.

In summary, we would like to recognize that this work is important and that a new comprehensive model is exactly what has been needed to push the field forward in this promising area. We hope that our observations and suggestions can be used to improve what promises to be a highly impactful perspective of psychomotor symptoms for years to come.

Acknowledgments:

Funding: NA

References

1). Northoff G, Hirjak D, Wolf RC, Magioncalda P, Martina M. All roads lead to the motor cortex: psychomotor mechanisms and their biochemical modulation in psychiatric disorders. Mol Psychiatry 2020. 10.1038/s41380-020-0814-5

2). Sokolov AA, Miall RC, Ivry RB. The cerebellum: adaptive prediction for movement and cognition. Trends Cog Sci. 2017;21(5):313–332.

3). Oostland M, van Hooft JA. Serotonin in the Cerebellum. In Essentials of Cerebellum and Cerebellar Disorders (pp. 243–247). 2016. Springer, Cham.

4). Bostan AC, Strick PL. The basal ganglia and the cerebellum: nodes in an integrated network. Nat Rev Neurosci. 2018;19: 338–350. [PubMed: 29643480]

5). Andersson G, Hagman J, Talianzadeh R, Svedberg A, Larsen HC. Effect of cognitive load on postural control. Brain Res Bull. 2002;58(1):135–139. [PubMed: 12121823]

6). Brady RO, Gonsalvez I, Lee I, Ongur D, Seidman LJ, Schmahmann JD, et al. Cerebellar-prefrontal network connectivity and negative symptoms in schizophrenia. Am J Psychiat. 2019; 176(7): 512–520. [PubMed: 30696271]

7). Andreasen NC, Paradiso S, O'leary DS. "Cognitive dysmetria" as an integrative theory of schizophrenia: a dysfunction in cortical-subcortical-cerebellar circuitry?. Schizophr Bull, 1998;24(2):203–218. [PubMed: 9613621]

8). Howes OD, Kapur S. The dopamine hypothesis of schizophrenia: version III—the final common pathway. Schizophr Bull, 2009;35(3): 549–562. [PubMed: 19325164]

9). Moussa-Tooks AB, Kim DJ, Bartolomeo LA, Purcell JR, Bolbecker AR, Newman SD, et al. Impaired effective connectivity during a cerebellar-mediated sensorimotor synchronization task in schizophrenia. Schiz Bull. 2019;45(3): 531–541.

10). Bernard JA, Mittal VA. Dysfunctional activation of the cerebellum in schizophrenia: a functional neuroimaging meta-analysis. Clin Psychol Sci. 2015;3(4): 545–566. [PubMed: 26392921]

11). Mittal VA, Dean DJ, Bernard JA, Orr JM, Pelletier-Baldelli A, Carol EE, et al. Neurological soft signs predict abnormal cerebellar-thalamic tract development and negative symptoms in adolescents at high risk for psychosis: a longitudinal perspective. Schizophr Bull. 2014;40(6):1204–1215. [PubMed: 24375457]

12). Bernard JA, Orr JM, Dean DJ, Mittal VA. The cerebellum and learning of non-motor associations in individuals at clinical-high risk for psychosis. NeuroImage: Clin. 2018; 19:137–146. [PubMed: 30035011]

13). Osborne KJ, Damme KS, Gupta T, Dean DJ, Bernard JA, Mittal VA. Timing dysfunction and cerebellar resting state functional connectivity abnormalities in youth at clinical high-risk for psychosis. Psychol Med. 2020;3:1–10.

14). Cantisani A, Stegmayer K, Bracht T, Federspiel A, Wiest R, Horn H.et al. Distinct resting-state perfusion patterns underlie psychomotor retardation in unipolar vs. bipolar depression. Acta Psychiatric Scand. 2016;134(4): 329–338.

15). Bracht T, Steinau S, Federspiel A, Schneider C, Wiest R & Walther S. Physical activity is associated with left corticospinal tract microstructure in bipolar depression. Neuroimage Clin. 2018;20:939–945 [PubMed: 30308380]

16). Walther S, Alexaki D, Schoretsanitis G, Weiss F, Vladimirova I, Stegmayer K.et al. Inhibitory Repetitive Transcranial Magnetic Stimulation to Treat Psychomotor Slowing: A Transdiagnostic, Mechanism-Based Randomized Double-Blind Controlled Trial. Schizophren Bull Op, 2020;1(1): sgaa020.

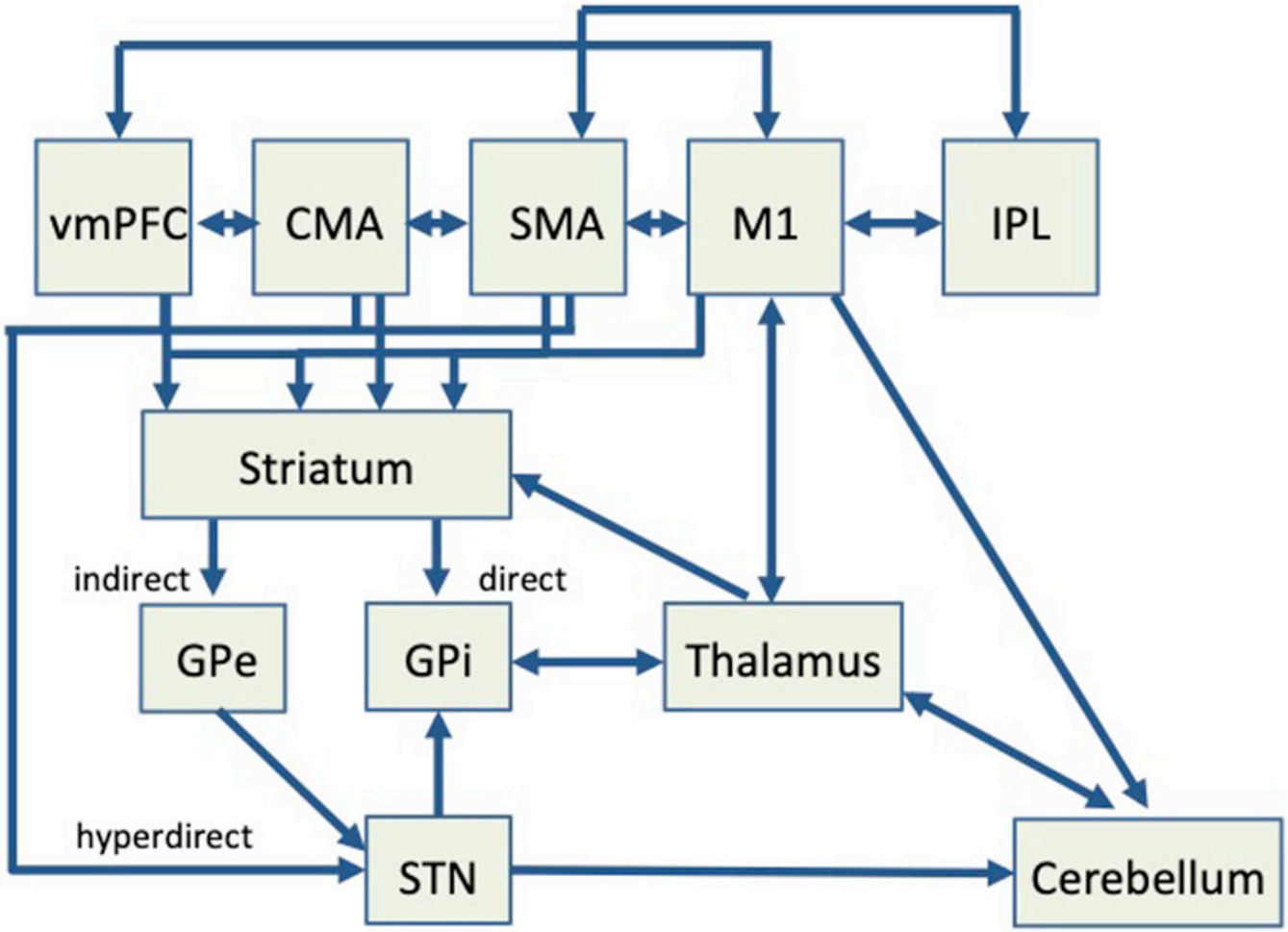

Figure 1. Psychomotor circuit interactions between cortical motor areas, basal ganglia, thalamus, and cerebellum.

The cerebellar-thalamic-cortical-cerebellar circuit is a significant component in a broader psychomotor system. Abbreviations: vmPFC – ventromedial prefrontal cortex; CMA – cingulate motor area; SMA - supplementary motor area; M1 – primary motor cortex; IPL – inferior parietal lobe. GPe – external globus pallidum; GPi – internal globus pallidum; STN – subthalamic nucleus.