Modulation of cerebello-cerebral resting state networks by site-specific stimulation

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Rastogi A, Ghahremani A, Cash R. Modulation of cerebello-cerebral resting state networks by site-specific stimulation. J Neurophysiol 114: 2084–2086, 2015. First published February 11, 2015; doi:10.1152/jn.00977.2014.—Converging evidence from neuroimaging and neuromodulation literature suggests that the cerebellum plays a broad role in motor as well as cognitive processes through its participation in resting-state networks. A recent study by Halko et al. (J Neurosci 34: 12049–12056, 2014) demonstrates, for the first time, the ability to modulate functional connectivity of some of these distinct resting-state networks using site-specific repetitive transcranial magnetic stimulation (rTMS) of the cerebellum. In this Neuro Forum, we discuss and critically analyze this study, emphasizing important findings, potential therapeutic relevance, and areas worthy of further inquiry.

resting-state fMRI; cerebellum; rTMS; plasticity

The cerebellum was understood to be involved in a myriad of nonmotor in addition to motor functions long before the advent of modern neuroimaging. Impaired executive function in patients with confined cerebellar stroke or atrophy invoked the cerebellum as a key structure in cognition (Schmahmann 2010). Despite this lag between early case-based investigations and nuanced cerebellar imaging methods, converging evidence now implicates the cerebellum in processes nearly as diverse as the cerebral cortex itself. These range from emotion and cognition to time perception, memory, and language, as well as traditionally accepted sensorimotor processes (Schmahmann 2010). A seminal series of anatomic experiments in monkeys revealed that a multitude of neocortical areas, especially from the prefrontal cortex, receive projections from specific cerebellar lobules (Bostan et al. 2013). More recently, resting state network functional connectivity measured with functional magnetic resonance imaging (fMRI) has confirmed cerebellar involvement in multiple brain wide networks that subserve diverse functions.

As a subject lies in the scanner and the brain is not engaged in external tasks, its spontaneous activity manifests in intrinsic resting-state neural networks with interconnected nodes (O’Reilly et al. 2010). Functional connectivity is demonstrated by synchronous oscillatory activity between different nodes, which together form resting-state networks. Regional differences in the cerebellum can now be made on the basis of lobular involvement in different resting-state networks. Different lobules and other cerebellar areas likely act as nodes that are functionally connected to cerebral areas, thereby forming distinct cerebello-cerebral networks. Based on an a priori degree of parcellations, cerebellar lobules can be separated into a five-network model (Habas et al. 2009) or a more popular seven-network model (Buckner et al. 2011), which includes visual, somatomotor, dorsal attention, ventral attention, limbic, frontoparietal, and default mode networks. (For an overview of these networks, please refer to the illustrations by Buckner et al. 2011.)

Interest in the contribution of the cerebellum to cognitive and motor processes as well as potentially associated disorders has grown in recent years. This pursuit can be aided through the use of repetitive transcranial magnetic stimulation (rTMS). rTMS is a noninvasive brain stimulation method in which rapid magnetic pulses are delivered to targeted brain regions to excite or suppress neuronal circuits. This not only allows for the study of cortical excitability, connectivity, and plasticity but also enables the determination of causal effects of modulating one area on other interconnected areas. Functional connectivity serves as a measure of node-node coupling reflecting excitability changes within the networks. Several recent studies have explored the effects of rTMS on the cerebello-thalamo-cortical (CTC) motor pathway (Carillo et al. 2013; Koch et al. 2008, 2009). These studies have demonstrated a direct influence of cerebellar stimulation on intrinsic circuitry in the motor cortex. However, the influence on cognitive networks remains underinvestigated. Answering the basic question of exactly what cerebellar rTMS is changing is an imperative prerequisite for devising therapeutic interventions for motor and nonmotor network disorders alike, including Parkinson’s and Alzheimer’s diseases. The confluence of rTMS and fMRI can be advantageous in examining network dynamics and plasticity. Most studies of the cerebellum have used exclusively one technique, and only now are they beginning to be used together. Therefore, investigating resting-state network modulation by rTMS is useful if the functionally heterogeneous nature of the cerebellum is to be understood.

This gap between cerebellar imaging and cerebellar rTMS research has now been bridged in a study by Halko et al. (2014), who were the first to combine rTMS and fMRI to determine the causal influence of cerebellar stimulation on functional connectivity in resting-state networks. The researchers applied an rTMS technique known as intermittent theta burst stimulation (iTBS), which is based on cellular theta burst stimulation and is able to transiently increase the excitability of neuronal circuits (Huang et al. 2005). Halko et al. targeted the cerebellar node of the default mode network (DMN) and demonstrated that cerebellar iTBS could perturb individual
networks in a site-specific manner. It is worth noting that cerebellar TBS is a low intensity TMS method and is not painful. Other cerebellar TMS methods such as single-pulse cone-coil stimulation generally require higher intensities and may cause some discomfort to participants. TBS is advantageous in this regard.

The authors aimed to test their core hypothesis that cerebellar stimulation at any site would change functional connectivity within an entire associated network. That is, changes would occur not just between cortical nodes and the single stimulated cerebellar node, but additionally between other cortical nodes that were not directly targeted with rTMS. This reflects an especially novel exploration, since previous cerebellar rTMS studies have not examined internodal changes that were not directly stimulated. From this stems their more specific hypothesis: iTBS to the lateral cerebellum specifically increases functional connectivity within the DMN. The authors also tested a secondary hypothesis that cerebellar midline iTBS would have no effect on the DMN but would increase functionally connectivity within a separate network called the dorsal attention network (DAN). This, much like the sham stimulation, served as a control condition. Hence, there were three randomized stimulation conditions: 1) Crus I or Crus II right lateral cerebellum, 2) lobule VII midline cerebellum, and 3) sham stimulation. Before rTMS was performed, the cerebellar stimulation sites themselves needed to be identified. Site 1 was localized with a resting-state scan individually, whereas selection of site 2 was based on a previous MRI study and was defined anatomically rather than functionally. Sham stimulation was delivered as a control to mimic the percept of real stimulation without magnetic output. For each subject, baseline resting-state scans were first obtained before stimulation. iTBS was then performed, after which poststimulation resting-state scans were obtained. This is known as an imaging-stimulation-imaging paradigm. Finally, in terms of analysis, seed-based correlations were computed individually from a priori regions of interest (ROIs), effectively creating a functional connectivity map of the DMN and DAN.

The authors found that Crus I and II stimulation significantly increased functional connectivity between these cerebellar nodes and DMN cortical nodes, including the medial prefrontal cortex, posterior cingulate cortex, and inferior parietal lobule bilaterally. Remarkably, rTMS was able to increase in functional connectivity of the entire core DMN. Additionally, midline cerebellar stimulation increased functional connectivity between the lobule VII node and nodes of the DAN. Sham stimulation revealed no significant effects. The authors also determined that neither lateral nor midline cerebellar stimulation altered functional connectivity within the motor network. The double dissociation of cerebellar stimulation was striking. Crus I and II stimulation only affected the DMN, whereas lobule VII stimulation only affected the DAN. To summarize, the authors demonstrated not only that cerebellar stimulation could influence cognitive networks but also that distinct cognitive networks could be modulated depending on stimulation site and, moreover, that changing the excitability of one node can change the entire network as a whole and not just node-to-node coupling, a completely novel finding. Not only does this demonstrate spatial specificity, but it also confirms the overarching hypothesis of network modulation. In addition to clinical implications, which are discussed below, this may render multisite rTMS network stimulation superfluous. Because all nodes experience changes in functional connectivity from one stimulation site only, multiple nodes may not need to be stimulated at once to observe network-wide changes.

In addition to the primary findings, there are some aspects of the study that warrant further discussion. Within the context of recent research, it is surprising that Halko et al. (2014) did not observe any sensorimotor network changes in any stimulation condition. Previous studies by Koch et al. (2008, 2009) and Carillo et al. (2013) have demonstrated that TBS targeted to the lateral cerebellum is able to induce bidirectional plastic changes in primary motor cortex (M1), including changes in M1 intracortical circuits. Although these three prior studies used standardized scalp coordinates based on previous neuronavigation cerebellar rTMS experiments, the scalp-based landmarks still correspond to the lateral portion of the anterior lobe of the cerebellum, where Crus I and II reside, and the positioning is not dissimilar to that used by Halko et al. Even though Halko et al. specifically targeted the DMN node of the cerebellum, given the overlapping topography of cerebellar network areas and motor changes in the prior rTMS studies, some changes in the somatomotor network might have been expected. This finding in no way detracts from the authors’ novel findings and conversely raises the important question as to whether previous studies using lateral stimulation to target motor networks also might have inadvertently induced changes in cognitive networks. It also highlights the use of neuronavigation, which may offer superior spatial specificity for future studies seeking to target specific networks, especially for a brain structure as convoluted as the cerebellum.

It would be interesting to examine whether seeding of other key nodes in the somatomotor network outlined by Buckner et al. (2011), including the premotor cortex, supplementary motor area, primary somatosensory cortex, and midcingulate sulci, could reveal additional motor network changes. Support for this idea may lie in the voxelwise correlations between the DMN and thalamus (Halko et al. 2014). Only lateral stimulation altered connectivity between the DMN and thalamic subregions. The densely packed thalamic nuclei are difficult to discern even under the high spatial resolution of a 3T MRI. Approximately 60% of the output fibres originating from the cerebellum belong to the motor domain of the dentate nucleus relaying through the posterior ventrolateral thalamus (Dum and Strick 2003). Without MNI coordinates of peak thalamic activity, it is difficult to map the activity of specific nuclei (Halko et al. 2014), although it is conceivable upon visual inspection to partially attribute the activity to motor regions of the thalamus.

Resolving the effects of lateral stimulation on motor networks is a pertinent step for future TMS-fMRI investigations. Overlapping lobular contributions to different networks raises one potential concern. The anatomical topography of the cerebellum has overlapping functional distinctions depending on which network model is used. For example, whereas Halko et al. (2014) considered Crus I and II in only the DMN, Habas et al. (2009) classified Crus I and II as nodes in the executive control and salience detection networks and not in the DMN; the DMN was localized to lobule IX (on the midline) and a small cluster in the right hemisphere of lobule VIIb. Therefore, an immediate issue relates to the selection of optimal network subdivisions to capture meaningful changes in functional con-
connectivity from focal cerebellar stimulation. One solution is to simply group motor and nonmotor cerebellar regions established by O’Reilly et al. (2010) called the sensorimotor and supramodal zones, respectively. However, although such a model might be better able to grossly distinguish motor and nonmotor effects and whether or not cerebellar stimulation could target motor or nonmotor networks in isolation, it would be unsuitable to fulfil the aims of Halko et al. to modulate specific cognitive networks. The fact that Halko et al. demonstrate the modulation of an entire network underscores the importance of such subdivisions to detect all node-node changes in functional connectivity.

Finally, a number of studies suggest that cortical plastic changes may not be immediate but take 10–20 min to develop (Koch et al. 2008, 2009). Future studies could explore the dynamics of network plasticity by sliding window analysis or comparison of multiple successive scans following rTMS. The sliding window technique is a relatively new way of monitoring dynamic functional connectivity using one continuous longer resting-state scan. In this technique, a short statistical window typically lasting 40 s is gradually moved across the time series of the resting-state scan to constantly compute functional connectivity between network nodes (Hutchison et al. 2013). Knowing the duration of changes in functional connectivity achieved using rTMS would be of relevance for interventional therapies.

Halko et al. (2014) have for the first time demonstrated that resting-state networks may be modulated using spatially targeted rTMS, thus bridging the gap between two seemingly disparate fields. Network imaging is a powerful tool, and the authors use it to advance a new frontier in noninvasive brain stimulation research. They also speculate on the therapeutic significance of rTMS to treat cognitive disorders including severe depression, Alzheimer’s disease, and schizophrenia. Because of the complex etiology of these disorders, clinical use may still be a distant prospect. However, elucidating the motor network issues detailed above will likely translate into the treatment of more direct and immediately apparent CTC abnormalities, such as levodopa-induced dyskinesia in Parkinson’s disease (Koch et al. 2009). Moreover, given that the DMN is a task-negative idling network, the functional significance of modulating this particular network remains to be explored. It is conceivable that modulation of the salience network, as demonstrated in Halko et al. by midline cerebellar stimulation, might have more functional relevance. Whether patient groups have a significant capacity for plasticity at the network level is unknown. For example, cortical plasticity is reduced in clinical Alzheimer’s disease (Battaglia et al. 2007), but plasticity at the network level remains poorly understood. With further study we share the authors’ vision of modulating targeted networks in future treatment protocols for resting-state network aberrations.

In sum, the broader implications of the current study are threefold. First, the combined use of rTMS and fMRI conjoins two separate fields of cerebellar research. Second, this approach allows for the modulation of networks as a whole and not just individual node-node coupling. Third, although its use is still in development, disorders of network connectivity may be ameliorated by targeted rTMS. Halko et al. (2014) have steered network neuroscience into exciting new territory, and their findings encourage additional exploration in this area.

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DISCLOSURES

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AUTHOR CONTRIBUTIONS


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