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

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Submitted 3 December 2014; accepted in final form 10 February 2015

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-thalamocortical (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 advanta-
geous in this regard.

The authors aimed to test their core hypothesis that cerebel-
lar 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 hy-
pothesis: 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 func-
tionally 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 cere-
bellar stimulation sites themselves needed to be identified. Site
I 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 stimula-
tion 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 connectiv-
ity 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 func-
tional connectivity of the entire core DMN. Additionally,
midline cerebellar stimulation increased functional connectivity
between the lobule VII node and nodes of the DAN. Sham stimu-
lation revealed no significant effects. The authors also
determined that neither lateral nor midline cerebellar stimula-
tion 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 cog-
nitive 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. Be-
cause 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 neuro-
navigation cerebellar rTMS experiments, the scalp-based land-
marks still correspond to the lateral portion of the anterior lobe
of the cerebellum, where Crus I and II reside, and the posi-
tioning 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 neuronavi-
gation, 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 stimula-
tion altered connectivity between the DMN and thalamic sub-
regions. 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 though 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 net-
works is a pertinent step for future TMS-fMRI investigations.
Overlapping lobular contributions to different networks raises
one potential concern. The anatomical topography of the cer-
bellum 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
network 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 estab-
lished 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 fulfill the aims of Halko et al. to modulate
specific cognitive networks. The fact that Halko et al. demon-
strate 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 monitor-
ing 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 tar-
gested 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 ab-
normalities, such as levodopa-induced dyskinesia in Parkin-
sone’s disease (Koch et al. 2009). Moreover, given that the
DMN is a task-negative idling network, the functional signif-
icance 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 ap-
proach 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.

ACKNOWLEDGMENTS
We thank Drs. Michael Vesia, Robert Chen, Joyce Chen, and Aaron Kucyi
for insightful discussion.

DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS
A.R., A.G., and R.C. interpreted results of experiments; A.R. drafted
manuscript; A.R., A.G., and R.C. edited and revised manuscript; A.R., A.G.,
and R.C. approved final version of manuscript.

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