Cerebellar Role in Parkinson’s Disease

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Abstract

Parkinson’s disease (PD) is a common neurodegenerative disorder associated with motor and cognitive impairments. The mechanisms underlying the pathophysiology and treatments have traditionally focused on basal ganglia-thalamo-cortical pathways due to striatal dopamine loss, but more recent evidence has highlighted the role of the cerebellum. Here we review evidence from neuroimaging and non-invasive brain stimulation that demonstrate altered cerebellar activity in PD may be both a pathophysiological and compensatory mechanism depending on dopaminergic medication and symptoms.
Parkinson’s disease (PD) is the second most common neurodegenerative disorder. It is associated with a wide range of cognitive and motor impairments, including bradykinesia, rigidity, resting tremor, and postural instability (Jankovic, 2008). PD is thought to arise from progressive degeneration of dopaminergic neurons in the substantia nigra, resulting in dysfunction of striato-thalamo-cortical pathways. Dopaminergic medication (levodopa) is considered the most common and effective treatment in early stages of PD and is thought to improve symptoms by increasing striatal dopamine levels. An alternative but more invasive treatment is deep brain stimulation, which is applied to specific basal ganglia nuclei including the subthalamic nucleus and internal globus pallidus, or brainstem nuclei (Jankovic, 2008; Wu & Hallett, 2013).

Often overlooked is the role of the cerebellum in PD. Interactions between the cerebellum and basal ganglia have traditionally been thought to occur only at the cortical level. However, recent studies in macaques have demonstrated reciprocal connections between the basal ganglia and cerebellum via the thalamus and pontine nucleus (Bostan, Dum, & Strick, 2013). Through retrograde transneuronal transport of rabies virus, disynaptic projections have been identified between the cerebellar cortex and subthalamic nucleus via the pontine nucleus, and between the dentate nucleus and striatum via the thalamus (Bostan et al., 2013). Further, neuroimaging studies in humans have found that PD patients have altered cerebellar activation during motor execution, motor learning, and at rest (Wu & Hallett, 2013). The altered cerebellar activation could reflect either a pathophysiological impairment related to abnormal basal ganglia activity, or a compensatory mechanism to overcome dysfunction in the striato-thalamo-cortical circuitry.

This review highlights three recent reports (Bologna et al., 2015; Di Biasio et al., 2015; Festini et
al., 2015) involving neuroimaging and non-invasive brain stimulation in PD patients that investigate the role of the cerebellum in PD.

Altered cerebellar connectivity in PD

Functional connectivity (FC) refers to the degree to which one or more brain regions show similar fluctuations in oscillatory activity to a seed region (O’Reilly, Beckmann, Tomassini, Ramnani, & Johansen-Berg, 2010). Resting-state functional connectivity, measured with functional magnetic resonance imaging (fMRI), assesses intrinsic brain activity while a subject is at rest. With striatal seed regions, several studies have found reduced cortical-striatal connectivity in PD (for review see Tahmasian et al., 2015). However, Liu et al. (2013) found enhanced connectivity between the dentate nucleus and cerebellum compared to healthy controls. This study and most others have scanned PD patients in the OFF state, or in the drug-naïve state, in order to evaluate functional abnormalities independent of any confound from dopamine therapy (Tahmasian et al., 2015). However, assessing PD patients in the ON state may provide insight on the mechanisms mediating improved functions on dopaminergic medication.

Festini et al. (2015) investigated whether cerebellar connectivity is altered by levodopa, and whether network connectivity relates to motor and cognitive function. The authors hypothesized that greater resting cerebellar connectivity would be associated with enhanced motor and cognitive function, in support of a compensatory cerebellar role. Twenty-five mild-to-moderate stage PD patients and 23 healthy older adults completed functional resting state scans, neuropsychological assessments using the Montreal Cognitive Assessment (MOCA), motor assessment using the motor section of the United Parkinson’s Disease Rating Scale (UPDRS-III), and manual dexterity testing using the Grooved pegboard task. They investigated cerebellar-whole brain connectivity and within-cerebellar connectivity using seed regions in the right
cerebellar hemisphere previously shown to be involved in motor and cognitive functions. For the whole brain analysis, they compared the average time course of activity in the seed lobule to the time course of activity of every other voxel in the brain. Behavioral regressions were performed to relate cerebellar-whole brain connectivity to motor and cognitive performance. Similar analyses were conducted for within-cerebellar connectivity.

PD patients OFF medication showed more widespread cerebellar-whole brain connectivity compared to patients ON medication. Healthy older adults showed intermediate levels of cerebellar-whole brain connectivity, suggesting that levodopa may over-compensate for the hyperactive cerebellar activity observed OFF medication. For patients OFF medication, increased cerebellar-whole brain connectivity was associated with better Grooved Pegboard performance using the more affected hand, but worse MOCA performance.

Within-cerebellar connectivity analyses revealed similar group differences. For patients ON medication, greater within-cerebellar connectivity was associated with better performance on MOCA and Grooved Pegboard and reduced disease severity according to the UPDRS-III. Similar relationships were observed for patients OFF medication with stronger connectivity being associated with improved performance and less disease severity, although there were some instances in which greater connectivity was associated with worse disease severity (i.e. between right Crus II and right Crus I).

Overall, the authors suggested a cerebellar connectivity spectrum, where PD patients OFF medication show greater resting state cerebellar connectivity than healthy older adults, who show greater connectivity than PD patients ON medication. The association between greater cerebellar connectivity and improved behavior suggests that cerebellar involvement in PD is compensatory. However, since this was not universal across the cognitive and motor tasks and
varied depending upon seed region, cerebellar involvement may also be pathological. The modulation of cerebellar connectivity by dopamine and mixed results with behavioral correlations support previous suggestions that levodopa can have both beneficial and detrimental effects on behavior, and that the cerebellum may be either compensatory or pathological in PD. One complexity to this interpretation relates to the heterogeneity of PD symptoms. PD can be broken down into two main subtypes: tremor dominant and akinetic-rigid (Wu & Hallett, 2013). This raises the question as to whether cerebellar connectivity changes and their relation to motor/cognitive behavior differ by subtype. Festini et al. did not investigate this question, but their thorough analysis using both cerebellar whole brain and within-cerebellar connectivity provides strong evidence for the role of the cerebellum in PD. Additional studies clarifying these cerebellar changes according to PD subtype will further advance our understanding.

Cerebellar role in PD-related somatosensory impairment

One limitation of fMRI is that connectivity patterns in relation to behavior are correlational rather than causational. Theta burst transcranial magnetic stimulation (TBS) is a non-invasive brain stimulation technique that can transiently excite or inhibit brain activity in a targeted region, allowing researchers to investigate the causal role of specific brain regions on behavior (Hallett, 2007). Specifically, continuous theta burst stimulation (cTBS) inhibits cortical excitability through mechanisms of long-term depression. If suppression of cerebellar activity impairs function in PD patients, a cerebellar compensatory mechanism would be supported. Alternatively, suppression of cerebellar activity may improve function in PD patients, indicating that the cerebellum plays a pathological role in PD (Wu & Hallett, 2013). The latter was
supported by Koch et al. (2009) who found that repeated sessions of inhibitory cerebellar
stimulation improved levodopa-induced dyskinesias in PD patients.

Somatosensory temporal discrimination threshold (STDT), a measure of sensory
integration, is typically impaired in PD patients. The reduced ability to perceive two stimuli as
sequential, e.g. higher STDT threshold, has been traditionally associated with impaired basal
ganglia function. If the cerebellum contributes to abnormal STDT in PD, inhibitory cerebellar
stimulation should improve STDT. To test this hypothesis, Di Biasio et al. (2015) measured
STDT before and after cerebellar or sham cTBS in 15 mild-to moderate PD patients OFF
medication and aged-matched controls. For real stimulation, cTBS was delivered over the lateral
cerebellum ipsilateral to the more affected side in PD patients. As a control, sham stimulation
was applied to the neck muscles. Eight of the 15 patients also participated in an additional
session ON medication.

Before cTBS, STDT values in PD patients OFF medication was higher (i.e. worse
sensory integration) compared to patients ON medication and healthy subjects. Cerebellar cTBS
but not sham cTBS reduced STDT values in the more affected hand in PD patients OFF
medication, but did not alter STDT values in healthy subjects or PD patients ON medication.
Cerebellar cTBS but not sham cTBS reduced motor cortex excitability in both healthy subjects
and PD patients OFF medication.

The lack of an effect of cTBS on STDT in PD patients ON medication may relate to the
state-dependent nature of TBS, such that the state of the underlying brain activity during
stimulation influences the direction and magnitude of the after effect of TBS (Hallett, 2007).
Therefore, differences in cerebellar activity depending upon medication status could determine
the effectiveness of cTBS upon STDT; levodopa could have normalized abnormal cerebellar
activity, which in turn prevented any further modulation by cTBS. Given that differences in cerebellar activity have been found between PD patients ON medication and healthy controls (Festini et al., 2015), and that the effects of stimulation are state-dependent (Hallett, 2007), one may still have expected a differential group effect by cerebellar cTBS. However, their findings may relate to a ceiling effect, such that both groups already had high sensory discrimination function that could not be further improved by cTBS. In contrast, for PD patients OFF medication, a presumed cerebellar hyperactivity may have contributed to impaired STDT at baseline. Like levodopa, cerebellar inhibitory stimulation may then normalize cerebellar-thalamocortical circuitry to improve STDT. Similarly to Festini et al.’s conclusion, these results suggest it is important to consider the role of dopamine in determining whether the cerebellum is compensatory or pathological. The present results indicate that the cerebellum may be pathological in patients without dopamine, and that cerebellar inhibitory stimulation may have therapeutic potential for improving sensory function.

Cerebellar involvement in resting tremor

Resting tremor associated with PD has traditionally been linked to abnormal oscillatory activity in the basal ganglia. However, a newly proposed “dimmer-switch model” from neuroimaging work suggests that tremor onset (i.e. turning on the switch) involves basal ganglia circuitry whereas tremor magnitude (i.e. dimmer modulation) involves cerebellar-thalamocortical projections (Helmich, Hallett, Deuschl, Toni, & Bloem, 2012). Altering cerebellar activity may interact with abnormal basal ganglia function through parallel loops in primary motor cortex or via reciprocal connections with the basal ganglia (Wu & Hallett, 2013).
Bologna et al. (2015) investigated the effect of cerebellar cTBS on motor cortical excitability and resting tremor in PD patients. Cerebellar cTBS (real, sham) was delivered over the lateral cerebellum ipsilateral to the tremor-affected side in PD patients, or ipsilateral to the dominant hand in healthy age-matched controls. Motor cortical excitability and tremor were assessed using clinical (tremor-specific sections of UPDRS-III) and kinematic (magnitude and frequency of tremor) measurements before and after cTBS. Cerebellar cTBS inhibited motor cortical excitability in both PD patients and healthy controls, which is inconsistent with Carrillo et al. (2013) who found altered cerebellar projections to motor cortex in PD patients. This discrepancy may relate to differences in patient selection; Bologna et al. tested tremor-dominant PD patients whereas Carrillo et al. tested akinetic-rigid PD patients.

In the Bologna et al. study, cerebellar cTBS failed to modulate tremor according to both clinical and kinematic assessments. Since there was no correlation between motor cortex excitability and tremor, the authors suggested that tremor may be mediated through cerebellar-basal ganglia reciprocal connections via the striatum and subthalamic nucleus (Bostan et al., 2013). Unlike the previous cTBS report, PD patients were only tested OFF medication. Therefore, it is unclear whether these results can be generalized to patients ON medication. Furthermore, whether the cerebellum plays a differential role in tremor in PD patients classified as mixed or akinesia-rigid subtypes requires further investigation.

Both Di Biasio et al. (2015) and Bologna et al. (2015) provide insight on the causal role of the cerebellum in sensory and motor function. Both were double-blind sham controlled investigations, and included healthy age matched controls. One limitation in both studies is the heterogeneity in PD patient selection, especially with the wide range of disease duration from 1-
15 years. Additional studies with more homogeneous patient selection may provide greater insight on the therapeutic application of TBS.

**Conclusion and Future Directions**

Although PD research has traditionally focused on basal ganglia dysfunction, the reviewed studies support a cerebellar role in PD. Differences in cerebellar activity may be considered a pathological mechanism related to basal ganglia dysfunction, or a compensatory mechanism. The nature of the cerebellar involvement is complex and is likely influenced by dopamine, patient subtypes, and the particular symptom or function assessed. Festini et al. found stronger evidence for a compensatory role, since the majority of motor and cognitive functions were associated with greater cerebellar connectivity. Di Biasio et al. found that inhibiting the cerebellum enhanced STDT in PD patients OFF medication, indicating that the cerebellum may play a pathological role in STDT. Lastly, Bologna et al. failed to find evidence for a role of the cerebellum in tremor, which may suggest that the cerebellum does not specifically play a pathological or compensatory role in tremor. However, these results contrast with previous neuroimaging and TMS evidence (Wu & Hallett, 2013) and underscore the importance of PD patient selection.

Future investigations of the effects of cerebellar cTBS on sensorimotor and cognitive functions could be further enhanced by combining TBS and fMRI to determine the causal influence of cerebellar stimulation upon functional connectivity (Halko, Farzan, Eldaief, Schmahmann, & Pascual-Leone, 2014). For instance, Halko et al. (2014) demonstrated that TBS over the lateral cerebellum in young healthy adults influenced the default mode network whereas TBS over the medial cerebellum influenced the dorsal attention network. Less clear is the
functional relevance of altering these networks. Since cerebellar resting state connectivity is
modulated by dopamine (Festini et al., 2015) and the effects of TBS are state-dependent (Hallett,
2007), resting state connectivity may be a useful predictor for individual responsiveness to TBS
and help clarify its therapeutic potential. Lastly, given that PD is largely heterogeneous in nature,
a combined approach would help clarify whether particular symptoms of PD are mediated by
particular functional networks. Ultimately, this could lead to stronger conclusions regarding
whether the cerebellum plays a pathological role driven by striatal dysfunction or a
compensatory role to overcome striatal dysfunction.
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