The Role of the Cerebellum in the Pathophysiology of Parkinson’s Disease

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ABSTRACT: Parkinson’s disease (PD), the most common neurodegenerative movement disorder, has traditionally been considered a “classic” basal ganglia disease, as the most obvious pathology is seen in the dopaminergic cells in the substantia nigra pars compacta. Nevertheless recent discoveries in anatomical connections linking the basal ganglia and the cerebellum have led to a re-examination of the role of the cerebellum in the pathophysiology of PD. This review summarizes the role of the cerebellum in explaining many curious features of PD: the significant variation in disease progression between individuals; why severity of dopaminergic deficit correlates with many features of PD such as bradykinesia, but not tremor; and why PD subjects with a tremor-predominant presentation tend to have a more benign prognosis. It is clear that the cerebellum participates in compensatory mechanisms associated with the disease and must be considered an essential contributor to the overall pathophysiology of PD.

The Basal Ganglia and Cerebellum

Superficially, the subcortical systems of the basal ganglia and cerebellum have much in common. Both systems influence cerebral cortical activity via the thalamus, are linked with the cerebral cortex via recurrent circuits, and affect multiple aspects of motor, cognitive, and affective behaviour. Whereas the exact way that each system influences motor output has not been fully elucidated, most models of the basal ganglia emphasize the importance of movement selection in the context of reward, and the basal ganglia are most active when a subject must perform an action that is internally guided (e.g. recalled from memory) from many potential candidates of action. The cerebellum, traditionally associated with motor control, now is considered to be essential for the development of...
"forward models," such as predicting the sensory consequences of motor actions\(^{19,20}\). Cerebellar activity is normally associated with externally guided movements where sensorimotor integration is important\(^{14,17,18,21}\). In fact, during an active/passive execution of a motor task consisting of flexion and extension of the elbow, 80-90\% of the neocerebellar signal can be attributed to sensory information processing\(^{14}\). This distinction of the roles of the basal ganglia and cerebellar circuits in externally and internally guided tasks, however, is not absolute. Indeed, several studies have demonstrated equal activity in the two pathways during these tasks\(^{22,23}\). In addition, there is some evidence that basal ganglia structures may be involved in externally guided tasks\(^{24}\), and cerebellar regions are more active during internally guided tasks\(^{23}\). The role of the two circuits in externally and internally guided tasks also may be impacted by the study paradigm and/or whether movement preparation or execution is examined. Nevertheless, the outputs from the basal ganglia and cerebellum project to neighboring thalamic nuclei (ventroanterior (VA) and ventrolateral (VL), respectively), which also demonstrate differential involvement in externally and internally guided tasks\(^{25,26}\). Anatomical studies using transneuronally transported viruses have demonstrated that projections from the basal ganglia and the cerebellum through the thalamus to the cortex constitute multiple 'parallel' channels forming circuits\(^{13}\).

There is little known about the pathophysiological changes of the cerebellum in PD. Imaging studies are equivocal, with some reporting decreased cerebellar volume in PD\(^{33}\) and others not\(^{28,29}\). Physiologically, Molnar et al\(^{40}\) demonstrated that PD subjects show decreased firing rates in the VA nucleus of the thalamus, the target of basal ganglia output nuclei, but no alterations in firing of cerebellar-associated VL (called Vim/VPLa in their paper) cells. This study in five PD subjects, however, did not detail the type of PD patients whom they studied and no follow-up studies were reported. Importantly, deep brain stimulation surgery targeting the ventralis intermedius (Vim) thalamic nucleus can capture the tremor associated with essential tremor or PD\(^{41}\), suggesting the role of cerebellum in tremorgenesis. Pathologically, classic pathology studies\(^{32}\) reported severe cell loss at the substantia nigra of the basal ganglia, but did not report any cell loss in the cerebellum. Similarly, PD subjects have increased α-synuclein in the substantia nigra and basal ganglia but not the cerebellum (Devi et al 2008)\(^{33}\). Recent studies suggest that the protein synphilin-1 interacts with α-synuclein and also is associated with Lewy bodies in sporadic PD\(^{34}\). Over-expression of wild-type or mutant synphilin-1 protein in a transgenic mouse model leads to both deficits in motor learning and performance, and pathological changes in cerebellar regions including ubiquitin-positive inclusions and degeneration of purkinje cells\(^{35}\). Furthermore, cerebellar purkinje cell axonal swelling ('torpedoes') is increased significantly in PD\(^{36}\). There are, however, no detailed pathophysiological studies focused on the role of cerebellar changes in PD, particularly those associated with the different aspect of symptoms, subtypes of disease, or its progression.

While previously considered in isolation, recent evidence has demonstrated that the basal ganglia and cerebellum are anatomically connected. Bostan and Strick\(^{37}\) describe a disynaptic projection from the cerebellum to the basal ganglia and a reciprocal projection from the basal ganglia to the cerebellum. Hoshi and colleagues\(^{38}\), using transneuronal transport of rabies in non-human primates, revealed a disynaptic pathway that links the dentate nucleus (an output stage of the cerebellum) with the putamen (input nuclei of the basal ganglia) and the globus pallidus externa (GPe; output nuclei of the basal ganglia) via the thalamus. Thus, output from the cerebellum influences the striatum, the target of which includes striatal neurons in the indirect pathway of the basal ganglia. Similarly, Bostan et al observed a disynaptic connection linking the subthalamic nucleus and cerebellar cortex via the pontine nuclei\(^{37}\). We recently proposed how striato-thalamo-cortical and cerebello-thalamo-cortical circuits and their interconnections may be functionally organized\(^{39}\) (Figure). Interestingly, the projections identified by Bostan et al appear to be topographically organized, such that projections from the dentate nucleus to the primary motor and premotor areas originate from its motor domain, whereas projections from the dentate to prefrontal and parietal areas originate from its non-motor domain\(^{40}\). Furthermore, markers for dopaminergic transmission, normally most prominent in the basal ganglia, have been demonstrated to be present and altered in the human cerebellum in PD\(^{41}\).

In addition to anatomical studies, electrophysiological studies suggest a close interaction between the cerebellum and basal ganglia structures. Local field potentials between 12 and 25 Hz (β-band) have been observed widely in the cerebellar cortex\(^{42}\) and these are synchronous with activity in the cerebral cortex\(^{43}\). β-band oscillations also have been detected in the basal ganglia\(^{44}\), and while these basal ganglia oscillations are exaggerated in the parkinsonian state\(^{45-47}\), they still can be observed being dynamically modulated by simple motor tasks in the striatum of normal primates\(^{48}\). It is unclear if β-band oscillations occur in the cerebellum either in PD or in animal models of the disease. Nevertheless, these collective results suggest that coherent oscillations between cortical and subcortical motor structures (including the basal ganglia and cerebellum) assist in binding the activity of spatially distinct regions\(^{48}\).

The Cerebellum and Parkinson’s Disease Tremor

Although dopaminergic treatments are capable of improving symptoms of bradykinesia and rigidity, they are less reliable in improving tremor\(^{8}\), consistent with the observation that nigrostriatal dopamine deficiency correlates with bradykinesia but not tremor\(^{10}\). In animal models of tremor and parkinsonism, lesions of dopaminergic substantia nigra neurons alone do not produce tremor\(^{48}\). In the MPTP (1-methyl-4-phenyl 1,2,3,6-tetrahydropyridine) toxin model of parkinsonism, the majority of nonhuman primate species examined exhibit an action/postural tremor\(^{50}\) rather than the resting tremor typically observed in human PD. Thus, dopamine depletion in basal ganglia nuclei does not fully account for PD-related tremor.

It is important to highlight the differences between postural and resting tremor. The classic resting tremor observed in PD is low frequency (4-5 Hz), whereas postural tremor is of a higher frequency (~8-12 Hz). It has been suggested that rest and postural tremor in PD may be mediated by different neuronal pathways\(^{51}\). Postural tremor is the hallmark feature of essential
tremor in humans, although rest tremor also is noted in a large number of these patients. Cerebellar involvement in essential tremor is well accepted. Interestingly, when patients with essential tremor have had the disease for a long duration, or have started to develop PD, they also start to have more features of tremor at rest. Our clinical experience and review of the literature indicates that tremor patients only develop the tremor-dominant type of PD, not the akinetic-rigid type. The co-occurrence of resting tremor in essential tremor patients suggested that there may be a common link regarding to etiology of both types of tremor, and cerebellar dysfunction could well be that common link.

Several lines of evidence suggest the crucial involvement of the cerebellum and/or its circuitry in PD tremor. First, lesion experiments in primates have revealed that tremor can be induced only when there is damage to the nigrostriatal dopaminergic pathway and concomitant damage to the cerebellum or its connections, although, interestingly, these lesions result in postural rather than the rest tremor seen in humans. Second, oscillatory bursting at tremor frequencies in the cerebellum or its connections, although, interestingly, these lesions result in postural rather than the rest tremor seen in humans. Third, surgical lesions or long-term stimulation of the Vim consistently improves tremor symptoms, and the Vim has been established as an effective surgical site for treating PD tremor. Notably, Vim surgery does not ameliorate bradykinesia and/or rigidity. Lastly, recent functional imaging network analysis provides evidence that a distinct cerebello-thalamic-cortical circuit may mediate tremor in PD.

Several studies have observed abnormal activity in the cerebellum in relation to PD tremor. Positron emission tomography (PET) studies have demonstrated that resting activity of rostral, medial, and intermediate cerebellum (vermis and paravermis) is increased in PD tremor, and cerebellar hyperactivity of rostral vermis and paravermis is reduced when effective thalamic Vim stimulation arrests tremor. These results suggest that tremor suppression is primarily associated with decreased synaptic activity in the cerebellum. Consistent with these findings is the observation that grey matter volume in the right quadrangular lobe and declive of the cerebellum is decreased in PD patients with rest tremor.

Oscillatory activity in the cerebellum itself in patients with rest tremor has been reported. These findings strongly implicate the involvement of altered cerebellar activity in tremor in light of the fact that the P3rkinje cells in lobules IV-VI of the cerebellar cortex (where grey matter decreases are observed) provide input to the arm area of the primary motor cortex (M1). These data are consistent with the notion that the cerebellum may be one part of a circuit that is involved in the propagation and/or transmission of tremor and/or tremor can be a consequence of a complicated interplay between basal ganglia and cerebellar circuits as suggested recently by Helmich et al.

Tremor-dominant PD patients reportedly have a better prognosis since they have less dyskinesias and motor fluctuations in response to levodopa and less frontal lobe deficits compared to akinetic-rigid patients. The exact reason for the better prognosis in tremor-dominant PD is unknown, although it is possible that the better prognosis observed may be less due to basal ganglia pathology in tremor-dominant PD patients than that seen in the akinetic rigidity type of PD. This hypothesis has not been tested, however, and further studies are warranted.
Lewis et al recently investigated the role of tremor in PD by studying functional differences between PD subtypes using fMRI. Nine tremor-dominant PD, eight akinetic-rigid-dominant PD, and 14 control subjects completed a sequential finger tapping task followed by comparison of activity in striatothalamo-cortical and cerebello-thalamo-cortical circuits. Compared to controls, both tremor- and akinetic-rigid-dominant PD subjects displayed overall increased activity in striatothalamo-cortical and cerebello-thalamo-cortical pathways. Interestingly, the comparison of akinetic rigid- and tremor-dominant PD subjects revealed significant differences in cerebellar circuits, lending further support to the role of cerebellar circuitry in PD and underscoring the involvement of cerebello-thalamo-cortical pathways in tremorgenesis.

Cerebellar activity as a compensatory mechanism in PD

Motor symptoms in PD only occur after an estimated 50% of dopaminergic nigral cells and 60-80% of striatal dopamine levels have been lost. Further, imaging measures of pathological dopaminergic nigral cells and 60-80% of striatal dopamine levels correlated necessarily with clinical measures of disability, such as the Unified Parkinson’s Disease Rating Scale (UPDRS). The lack of observed motor pathology despite significant cell loss indicates the existence of redundancy and/or compensatory mechanisms that serve to delay the onset of symptoms and preserve an optimal level of motor function.

Part of the reason the cerebellum has not heretofore been considered as a primary site for systems-level compensation in PD is the difficulty in differentiating actual compensatory changes from direct disease-related changes. This requires a rigorous definition of compensation. For the purpose of this paper, we define compensation to mean, “any change, morphological or functional, seen in the damaged brain, that acts to maintain performance of the impaired function.”

The cerebellum may be involved in the increased reliance on external visual or auditory cues observed in PD. Likely the most dramatic case of the use of visual cues is that of kinesia paradoxica. In kinesia paradoxica, PD subjects described as “frozen” have anecdotally gained the sudden ability to move in urgent situations. One explanation put forth for this phenomenon is that intact cerebellar pathways may allow patients to bypass the compromised basal ganglia pathway, enabling them to utilize vision to guide their movements. The properties of the stimuli that are effective in helping patients guide their movements (e.g., transverse stripes on the floor) are similar to those of visual signals that are relayed by mossy fibers via the posterior parietal cortex and the pontine nuclei to the cerebellum. The receptive fields of the visual neurons along this pathway tend to be tuned to horizontal gratings in the lower visual field, therefore, a staircase or stripes on the floor may activate the neurons along the visual cortex → posterior parietal → pontine nuclei → mossy fiber → cerebellum pathway. Thus, the clinical observation that PD patients become increasingly reliant on external visual cues to successfully perform movements represents a compensatory strategy that involves a switch to more visually guided motor networks and likely cerebellar pathways.

Motor urgency, closely related to kinesia paradoxica, recently has been shown to involve cerebellar circuits. In a study by Ballanger et al, participants were instructed to stop a rolling ball with a button-controlled electromagnetic catch. They were instructed to stop as many balls as possible when prompted by an auditory cue. Patients demonstrated increased activation of the cerebellum generally, and when comparing the “urgent” externally cued to the externally cued task there was increased activation in the contratrolateral cerebellum. Interestingly, the speed of movement demonstrated a significant negative covariation with regional cerebral bloodflow (rCBF) in left parasagittal cerebellar hemisphere, with shorter movement time associated with greater activation in the cerebellum. These findings lend further support to the proposition that patients recruit the cerebellum in order to compensate for basal ganglia dysfunction so as to increase movement velocity in urgent contexts.

Lewis et al examined a monozygotic twin pair discordant for PD with fMRI while they performed both externally and internally guided finger tapping sequences. Single photon emission computed tomography (SPECT) with [I-123](-)-2-β-carboxymethoxy-3-β-(4-iodophenyl) tropane (β-CIT) was used to confirm disease status, which revealed severe loss of transporter binding in the PD twin, whereas the non PD twin was normal. No significant differences were found between the twins in the striato-thalamo-cortical pathway during the externally

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DLFPC = dorsolateral prefrontal cortex; PET = positron emission topography; SPECT = single-photon emission computed tomography; PD<sub>T</sub> = tremor-dominant Parkinson’s patients; PD<sub>AR</sub> = akinetic and rigid-dominant Parkinson’s patients; SN = substantia nigra
guided task. In contrast, the PD twin demonstrated increased activity in the cerebello-thalamo-cortical circuit relative to the non-PD twin during the externally guided task. This cerebello-thalamo-cortical hyperactivity was relatively normalized by levodopa. During the internally guided task, the PD twin demonstrated decreased activation compared to the non-PD twin in both circuits. L-dopa medication normalized the hypoactivation in the contralateral striato-thalamo-cortical pathway, but appeared to over-correct activation in the ipsilateral striato-thalamo-cortical and bilateral cerebello-thalamo-cortical circuits. Similarly, an earlier study by Cerasa et al investigated the neurofunctional basis of externally and internally guided movements in PD patients and controls, with an overall signal increase in patients compared to controls in the cerebellum, putamen, supplementary motor area (SMA), and thalamus during their externally guided task. Unlike Lewis et al, however, the authors observed increased recruitment of the cerebello-thalamo-cortical circuit in patients during the internally guided task. This difference may be explained by the use of a timing task by Cerasa et al, which likely engages the cerebellum more than the sequencing task used in Lewis et al. It is important to note, however, that the role of the striato-thalamo-cortical and cerebello-thalamo-cortical circuits in externally and internally guided tasks is influenced by many factors (e.g., study paradigm, aspect of movement examined, measurement method, etc.) and thus the distinction is not absolute (see, for example Cerasa et al and Gowen and Miall)

Increased cerebello-thalamo-cortical activity also may be involved in the progression of PD. Sen et al recently gathered fMRI scans two years apart from five PD and five control subjects while they performed both externally and internally guided tasks. All PD subjects had unilateral symptoms at baseline that developed into bilateral symptoms at the follow-up time point. Importantly, significant differences over time between PD patients and controls were observed in the cerebello-thalamo-cortical circuit during the internally guided task. In addition, patients demonstrated more recruitment in the cerebello-thalamo-cortical circuit when the internally guided task was performed by the hand that transitioned from unaffected to symptomatic. This finding suggests that the emergence of symptoms on the less affected side may reflect a breakdown of a previously relatively more intact striato-thalamo-cortical pathway, which may lead to compensatory recruitment of the cerebello-thalamo-cortical circuit and permit successful performance on an internally guided task. Conversely, the increased cerebello-thalamo-cortical activity may represent increased pathological processes in PD progression, although this study could not delineate definitively between compensatory and/or pathological processes (see next section ‘Cerebellar Activity and Forward Models in PD’).

Yu and colleagues used BOLD contrast fMRI to examine patients and controls while they performed automatic and cognitively-controlled thumb pressing movements. In both conditions, patients demonstrated an augmented BOLD signal increase in the cerebellum and M1 relative to controls, whereas they displayed less activation in putamen and SMA. Further, PD subjects showed a significant negative correlation between activation in the ipsilateral cerebellum and contralateral putamen. Although this may be a compensatory increase in cerebellum activity as a result of putaminal deficiency as suggested by the authors, it is hard to distinguish an epiphenomenon from true compensatory activity unless the motor performance correlates with the hyperactivity.

One possible method to assess compensatory changes is to require patients to perform tasks that are challenging for them or tasks that increase in difficulty. This approach relies on the assumption that disease-related changes are relatively static across variations in task difficulty, whereas compensatory mechanisms, which are recruited to maintain or improve performance, should show a monotonic relationship with the difficulty of the task. In the following discussion, we present data that are consistent with this assumption, although we recognize that rigorous definitions of how to differentiate between disease and compensatory changes are an ongoing source of debate.

Parkinson’s disease patients increasingly rely on cerebellar structures when the motor demands of the task increase in level of difficulty. Palmer et al recently examined motor reserve as a compensatory mechanism in PD. Active motor reserve, a concept drawn from cognitive reserve, is defined as increased recruitment of a task-related network that monotonically increases with task difficulty in healthy participants in order to maintain performance. This is distinguished from novel area recruitment (NAR), whereby novel areas or networks are recruited as additional resources to maintain a near-normal level of performance as task difficulty increases. In this study, PD participants and healthy controls were asked to provide sinusoidal force production at three different speeds (0.25, 0.5, and 0.75 Hz) while in the magnetic resonance scanner. Multiple linear regression analyses revealed that activity linearly increased with movement speed in regions of the basal ganglia in healthy controls, most notably in bilateral putamen and thalamus. Off medication, PD patients maximally recruited this same network at lower speeds, suggesting that PD subjects tap into motor reserve earlier to maintain task performance. To perform the task at higher speeds, patients needed to recruit new areas by shifting to a compensatory network that included the cerebello-thalamo-cortical loop. These observations are likely to reflect compensatory changes since patients maximally recruited the normal motor network during the lowest level of task difficulty, but then engaged areas of the cerebello-thalamo-cortical network as the task became more challenging. Supportive of this hypothesis is the fact that the compensatory activity in the cerebello-thalamo-cortical network increased monotonically as task difficulty increased.

Compensatory changes in functional and effective connectivity

Rather than examining discrete loci for hyper/hypo activation, a number of studies have examined changes in connectivity between brain regions as a purported compensatory mechanism. Studies alluding to “connectivity” can refer to functional connectivity, the temporal correlation between spatially distinct neurophysiological events, or effective connectivity, a connectivity pattern that reveals the strength and directionality of information flow. A recent study compared the functional connectivity in the motor network between healthy controls and PD patients off and on levodopa during the resting state by using resting-state fMRI.
Patients off medication demonstrated decreased connectivity in the SMA, left DLPFC, and left putamen, and increased connectivity in the left cerebellum, left M1, and left parietal cortex. Administration of levodopa relatively normalized these connectivity patterns in patients. These results are consistent with the regional hypo- and hyperactivation patterns seen in the prior imaging studies discussed above.

A study that jointly examined amplitude and connectivity changes found distinct changes in connectivity between PD subjects and controls. Most notably, PD subjects alone demonstrated increased interhemispheric connectivity within the cerebello-thalamo-cortical pathway. Only amplitude changes, however, were modulated by task difficulty. These results indicate that connectivity changes may represent more permanent plastic changes that are relatively task-independent.

Cerebellar activity and forward models in PD

Recently, Stevenson et al investigated the response of PD subjects to less informative and extraneous visual stimuli during motor performance. Subjects performed large-amplitude arm movements as part of a visually guided tracking task where the position of the tracked target became progressively ambiguous as it ‘jittered’ about a desired trajectory at different amplitudes. Healthy human subjects demonstrated the ability to de-weight ambiguous visual feedback during motor tasks in order to preserve motor performance. However, the motor performance of PD subjects off medication significantly deteriorated with increasing ambiguous visual input. This may be a result of cerebellar dysfunction in PD, as evidence indicates cerebellar forward models are used to mitigate the effect of sensory uncertainty on motor performance. Thus, while the use of visual feedback may allow for improvements in motor performance in PD, parkinsonian motor performance is particularly sensitive to visual feedback that is uncertain and extraneous, suggesting the functional effect of cerebellar compensation in PD may be task dependent.

CONCLUDING REMARKS

Many clinical features of PD cannot be attributed exclusively to basal ganglia dysfunction. The work described in this review provides evidence for the role of the cerebellum in PD symptomatology and compensation for the damaged and dysfunctional striato-thalamo-cortical pathway. Altered cerebellar connectivity, as well as compensatory activity, however, may come with a price. In demonstrating the key position the cerebellum has in providing compensation for basal ganglia dysfunction through its reciprocal connections with the basal ganglia, Hoshi and colleagues queried, “when basal ganglia activity is abnormal, is cerebellar input part of the problem or part of the solution?” In addition to the importance of the cerebellum in providing redundancy and compensatory activity in PD, it also has been implicated in tremor generation, which may confound our understanding of the role of the cerebellum in PD. Patients diagnosed with the tremor-dominant subtype have a better prognosis and typically slower disease progression than patients with akinetic-rigid dominant PD. A smaller role for compensatory cerebellar activity in tremor-dominant PD patients may be one explanation for the slower progression and lower occurrence of dyskinesia observed in this PD subtype. Several studies have demonstrated increased recruitment of cerebello-thalamo-cortical circuits in PD, and we have shown a clear difference in this pathway between tremor- and akinetic-rigid-dominant PD subtypes. Moreover, cerebello-thalamo-cortical circuits appear to be involved in PD progression, as there is increased activation in the cerebello-thalamo-cortical pathway as subjects transition from unilateral to bilateral symptoms. Further studies have demonstrated changes in functional connectivity in the cerebello-thalamo-cortical pathways in PD. Collectively, these results affirm that the cerebellum should be increasingly recognized as being essential for the pathophysiology of PD.

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