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Cortico-Basal Ganglia and Cortico-Cerebellar Circuits in Parkinson's Disease: Pathophysiology or Compensation?

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The basal ganglia and the cerebellum are anatomically and functionally linked to the cerebral cortex through a series of well-established circuits. The disruption of dopaminergic projections in Parkinson's disease (PD) leads to an imbalance within these circuits, leading to motor and cognitive symptoms. The cortico-cerebellar (CC) network has often been viewed as a compensatory network, helping the dysfunction of the cortico-basal ganglia (CBG) circuits in PD. However, evidence for this compensatory role is scarce; most changes in cerebellar activity could equally be attributed to pathophysiological changes underlying PD. This paper will review the anatomy, interaction and function of the CBG and CC circuits, the pathophysiological, metabolic, and functional changes observed in PD, as well as the effect of levodopa and deep brain stimulation on these changes. We will use this framework to discuss the pathophysiological and compensatory mechanisms behind CBG and CC circuit activity in PD.

Keywords: Parkinson's disease, cerebellum, striatum, compensation, levodopa

Parkinson's disease (PD) is a debilitating neurodegenerative illness associated with the loss of dopaminergic neurons of the substantia nigra. Patients classically suffer from motor symptoms such as tremor, rigidity and bradykinesia, although cognitive deficits in executive functioning, memory, language, and visuospatial processing are also pervasive (Taylor & Saint-Cyr, 1995). The cortex, thalamus, basal ganglia, and cerebellum form a series of anatomically and functionally segregated circuits subserving a multitude of cognitive and motor functions. The disruption of these circuits through the degeneration of dopaminergic neurons in the substantia nigra leads to widespread changes in brain activity and connectivity. It is not yet known whether these extensive neural changes are strictly the result of PD pathophysiology or, alternatively, are manifestations of compensatory mechanisms in response to the disease. It has been suggested that the recruitment of cortico-cerebellar (CC) networks is one possible compensatory mechanism for the generation of movement in PD (Rascol et al., 1997; Palmer, Ng, Abugharbieh, Eigenraam, & McKeown, 2009), such as self-initiated and externally triggered movements. However, many of the changes in the CC circuits may be the result of disruptions caused by PD or by the prolonged used of dopaminergic medication. In this review, we will suggest that the pathophysiology behind changes in cerebral and cerebellar activity cannot be ignored, and that future research will be necessary in order to disentangle these two alternative hypotheses. To this end, we will first describe the anatomy and function of the cortico-basal ganglia (CBG) and CC circuits, as well as the pathophysiological, metabolic, and functional changes in these circuits as a result of the disease. We will then discuss the effect of levodopa and its side effects in the treatment of PD, deep brain stimulation (DBS), and provide suggestions for future research that may help distinguish between compensatory and pathophysiological mechanisms.

Cortico-Basal Ganglia Circuits

Anatomical Connections

It is well established that motor, sensory, and association areas of the cortex are extensively connected with specific subdivisions of the basal ganglia to form a series of "basal ganglia–thalamocortical" circuits. Several distinct circuits have been described, including the motor, oculomotor, limbic, and associative circuits (Alexander, DeLong, & Strick, 1986). These functionally and anatomically segregated pathways mainly relay information from functionally related cortical regions, the striatum, the pallidum and substantia nigra, and the thalamus. Understanding the connections within and between these circuits is crucial for procedures such as DBS, as an intervention in one area will have

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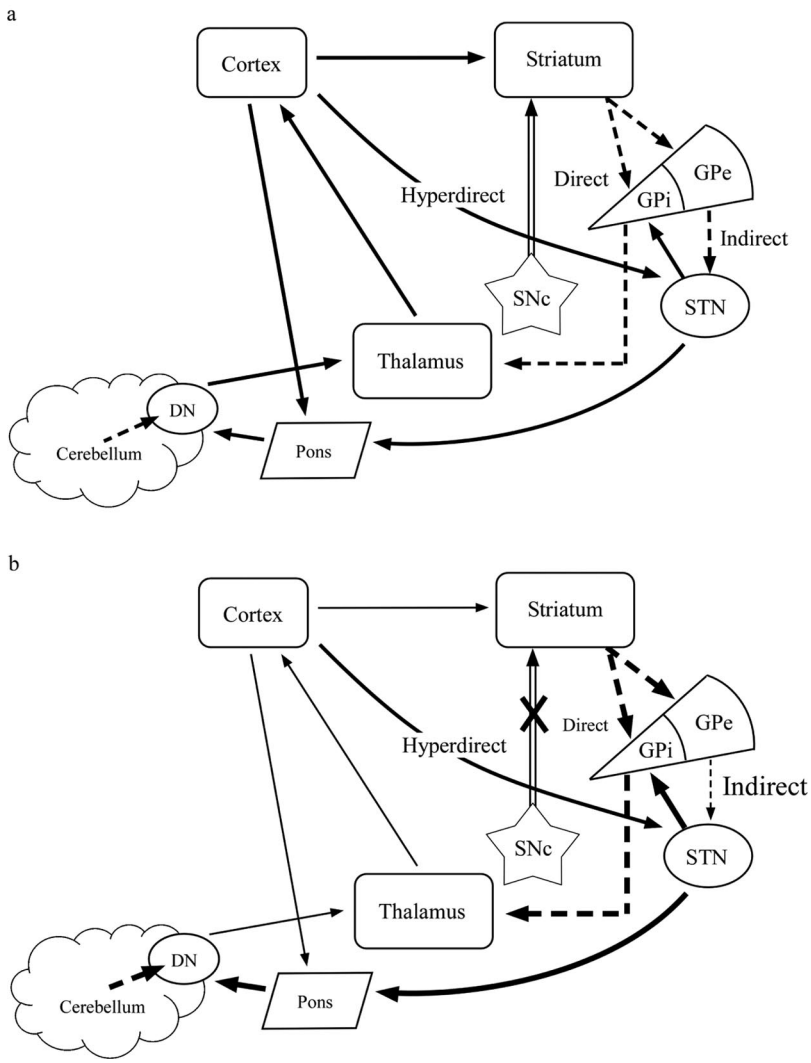

Figure 1. SNc = substantia nigra pars compacta; GPe = external segment of the globus pallidus; GPi = internal segment of the globus pallidus; STN = subthalamic nucleus. Schematic of the interaction between cortico-basal ganglia and cortico-cerebellar circuits in (a) healthy individuals and (b) Parkinson's disease. Solid lines represent excitatory connections, dotted lines represent inhibitory connections, double lines represent a mixture of excitatory and inhibitory effects. Arrow weight in (b) represents increases and decreases of synaptic output in PD as compared with healthy individuals. The change in synaptic output in the CC circuit is the hypothesized effect in tasks that involve the CBG pathway. Note that the nature of connections to and from the cerebellum are still under debate.

specific effects across a wide range of areas (Wichmann & DeLong, 2011). In the motor basal ganglia–thalamocortical circuit (see Figure 1), somatotopically organized information from the somatosensory, motor, premotor, and supplementary motor cortices is projected through the putamen (which receives input from the substantia nigra pars reticulata; SNr) to the ventrolateral nucleus of the thalamus, via the internal and external segments of the globus pallidus (GPi and GPe, respectively). The activity of the GPi is additionally modulated by the subthalamic nucleus (STN). Finally, the thalamus projects back to the cortex, forming a closed loop of tightly interconnected regions.

The motor CBG loop can further be divided into "direct" and "indirect" pathways, by which competing processes between the putamen, globus pallidus, STN and SNr determine overall thalamic activity (Alexander, Crutcher, & DeLong, 1991). Specifically, the direct pathway connects the striatum to the GPi/SNr by a single inhibitory projection. By contrast, the indirect pathway connects the striatum to the GPi via inhibitory projections to the GPe and the STN, and ultimately, excitatory connections to the GPi/SNr. An overall output is finally sent from the GPi/SNr to the thalamus; the direct pathway causes the striatum to disinhibit the thalamus, whereas the indirect pathway causes the striatum to inhibit thalamic activity (see Figure 1a). The signals from the direct and indirect pathways create a balance of opposing contributions, allowing movement to be regulated via thalamocortical connections. However, these pathways are not entirely independent, as evidence suggests that there are synaptic

connections between the direct and indirect motor CBG pathways (Yung, Smith, Levey, & Bolam, 1996).

There is also evidence for additional connections directly from the cortex to the STN (Monakow, Akert, & Kunzle, 1978), referred to as the "hyperdirect" pathway. One possibility would be that signals to the thalamus are first modulated by the inhibitory hyperdirect pathway, followed by the excitatory direct pathway, and finally by the inhibitory indirect pathway (Nambu, Tokuno, & Takada, 2002). The STN, reflecting the organization of the basal ganglia into motor and associative and limbic portions, functions as a major relay station and modulator in the processing of CBG information (Hamani, Saint-Cyr, Fraser, Kaplitt, & Lozano, 2004).

Neuromodulators

Dopamine is a prominent neurotransmitter in the basal ganglia, and, among other functions, plays a major role in movement through the CBG pathway. Although many different neurotransmitters are implicated in brain circuitry and PD, this review will focus on dopamine in particular. Dopaminergic projections are sent from the substantia nigra to the striatum, forming the nigrostriatal pathway. Additional dopaminergic projections run from the ventral tegmental area (VTA) to the nucleus accumbens (mesolimbic pathway) or frontal cortex (mesocortical pathway). In the context of the motor CBG circuit, dopamine has a contrasting effect on the direct and indirect pathways through a differential effect on D1 and D2 receptors (Gerfen et al., 1990; DeLong & Wichmann, 2007). Specifically, dopamine has a net inhibitory effect on the indirect pathway and a net excitatory effect on the direct pathway. The end result is that dopamine effectively favors the direct pathway, and its depletion or excess creates an imbalance in the two circuits, affecting activity in most cortical regions through the different CBG loops. This ultimately leads to the movement-related difficulties observed in different patient populations.

Cortico-cerebellar Circuit

Anatomical Connections

The CC circuit is similarly organized into functionally segregated pathways that connect regions of the cerebellar cortex with the cerebral cortex. Lateral portions of the cerebellar cortex send projections, via the dentate nucleus, to the thalamus, which in turn projects to specific cortical areas (see Figure 1). Retrograde transneuronal transport methods using neurotropic viruses have shown that these cortical areas include the motor, premotor, oculomotor, prefrontal, and posterior parietal cortex with minimal overlap between different termination sites (Clower, West, Lynch & Strick, 2001; Middleton & Strick, 2001; Strick, Dum, & Fiez, 2009). Projections from the cortex back to the lateral cerebellum pass either through the pons or the red nucleus and inferior olive (Leiner, Leiner, & Dow, 1989). Furthermore, the segregation of connections to the cerebral cortex is maintained in the cerebellar cortex (Kelly & Strick, 2003), such that the separate compartments of the cerebellum form closed anatomical loops with the specific cortical region to which they send projections, and from which they receive input (Strick et al., 2009).

The cerebellar cortex is organized into very regular molecular, Purkinje, and granular cell layers, suggesting that the type of information processing in the cerebellar cortex is mainly related to its associations with different cortical regions, rather than local circuitry (Ramnani, 2006). The dentate nucleus seems to consist of distinct sections that process motor and nonmotor information (Dum & Strick, 2003), with the nonmotor portion of the dentate nucleus substantially larger than the motor section (Matano, 2001). In fact, two main circuits have been described, notably the "motor" loop that projects from the motor and premotor cortex (PMC) to the dorsal part of the dentate nucleus, and the "prefrontal" loop that connects the prefrontal cortex Brodmann Area 9/46 and the ventral dentate nucleus (Glickstein, May, & Mercier, 1985; Orioli & Strick, 1989; Schmahmann & Pandya, 1995; Kelly & Strick, 2003). This segregation of motor and nonmotor connections from the dentate nucleus is maintained in the cerebellar cortex, with separate locations being connected to areas such as the primary motor cortex and Area 46 (Strick et al., 2009). Diffusion-tensor imaging examining the distribution of fibers in the cerebellar peduncle in humans and macaque monkeys in vivo has revealed that the majority of fibers in the macaque consist of motor fibers, whereas humans have a much larger prefrontal component (Ramnani et al., 2006). Thus, the cerebellum, similar to the basal ganglia, has underlying connections linked to both motor and cognitive functions (Strick et al., 2009).

Neuromodulators

Although the cerebellum receives mainly noradrenergic and serotonergic projections, there is also evidence for dopamine, acetylcholine, and histamine (Schweighofer, Doya, & Kuroda, 2004). In particular, dopaminergic neurons from the rat's VTA send projections to the cerebellar cortex (Ikai, Takada, Shinonaga, & Mizuno,1992). In fact, animal studies have shown that DARPP-32, a protein regulated by dopamine and adenosine 3′:5′-monophosphate (cAMP), is expressed in the cerebellar's Purkinje cells and may be involved in the regulation of long-term depression (LTD; Alder & Barbas, 1995). The cerebellum was long thought to contain almost no dopamine D2/D3 receptors compared with the striatum (Hall et al., 1994). Consequently, D2/D3-receptor binding [^{11}C]raclopride positron emission tomography (PET) studies have sometimes used the cerebellum as a reference tissue for raclopride binding (e.g., Hilker et al., 2003; Ko et al., 2008; Steeves et al., 2009). Other evidence suggests, however, that the cerebellar cortex contains a high density of dopamine D3 receptors that may help regulate locomotor activity and provide a form of cellular modulation by dopamine (Sokoloff, Giros, Martres, Bouthenet, & Schwartz, 1990; Bouthenet et al., 1991; Barik & de Beaurepaire, 1996; Schweighofer et al., 2004). The presence and the modulation by dopamine imply that cerebellar activity may be affected by dopamine depletion in PD, and consequently by dopamine replacement therapy.

Dopamine, norepinephrine (also known as noradrenaline) and epinephrine are catecholamines synthesized from tyrosine through a series of metabolic events (Nagatsu, Levitt, & Udenfriend, 1964). It is important to note that there are substantial noradrenergic projections to the cerebellum from the locus coeruleus and ventral tegmental area, regions significantly affected in PD (Hornykiewicz, 1975; Szot, 2012). Decreases in cerebellar norepi-

nephrine levels have been shown in PD patients (Kish, Shannak, Rajput, Gilbert, & Hornykiewicz, 1984), as well as the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) monkey model of PD (Pifl, Schingnitz, & Hornykiewicz, 1991).

Synaptic Connections Between CBG and CC Loops

Initially, the CBG and CC circuits have been considered to be anatomically distinct. In particular, the cerebellum and basal ganglia relay information to separate regions of the thalamus (Asanuma, Thach, & Jones, 1983), and retrograde labeling using the herpes simplex virus (HSV) has shown that the segregation of CBG and CC circuits remains at the level of the cortex, cerebellum, and dentate nucleus as well as in the thalamus and the substantia nigra (for a review, see Middleton & Strick, 2000). However, more recent evidence suggests that there are direct connections between the CBG and CC circuits (Bostan & Strick, 2010). Studies using the rabies virus and retrograde labeling in nonhuman primates report bisynaptic projections from the STN to the cerebellar cortex via pontine nuclei (Bostan, Dum, & Strick, 2010) and tri-synaptic connections between the GPe and the dentate nucleus (Hoshi, Tremblay, Feger, Carras, & Strick, 2005). A synaptic link between the CBG and CC pathways implies that changes in one circuit may affect the other circuit. This has implications for diseases such as PD (see Figure 1b), as connections between the CBG and CC circuits mean that dynamic fluctuations in the CBG pathway related to disease pathophysiology can affect the activity observed in the CC pathway.

CBG and CC Loop Function

Functional magnetic resonance imaging (fMRI) studies have provided evidence of CBG involvement in movement planning, initiation, motor learning, timing control, and their modulation by task complexity (Alexander et al., 1991; Rao et al., 1997; Boecker et al., 1998; Mattay et al., 1998; Jenkins, Jahanshahi, Jueptner, Passingham, & Brooks, 2000; Cunnington, Windischberger, Deecke, & Moser, 2002; Taniwaki et al., 2003; Elsinger, Harrington, & Rao, 2006; Purzner et al., 2007; Boecker, Jankowski, Ditter, & Scheef, 2008; Doyon et al., 2009; François-Brosseau et al., 2009). Furthermore, single-cell recording studies in monkeys have demonstrated the involvement of the putamen and caudate nucleus in self-initiated and externally triggered movements, where some neurons would respond to self-initiated movements only, and others to both self-initiated and externally triggered movements (Romo, Scarnati, & Schultz, 1992; Romo & Schultz, 1992). Activity in the substantia nigra has been observed for both internally and externally guided actions and movements (Boecker et al., 2008). Taken together, these findings suggest that the striatum is especially involved in the planning and the execution of novel and self-initiated movements (Elsinger et al., 2006; Boecker et al., 2008).

Consistent with the motor and nonmotor anatomical connections of the CC pathway, the cerebellum consists of specific topographically organized compartments used for the integration of motor and nonmotor functions (e.g., emotion, working memory, and language) (Stoodley & Schmahmann, 2009). There are also task-dependent and task-independent neurons in the dentate nucleus that respond to the planning phase of internally and externally cued movements (Middleton & Strick, 2000). Functional MRI studies have additionally demonstrated that slightly different regions of the dentate nucleus are activated during movement planning and execution (Kim, Ugurbil, & Strick, 1994), and that the lateral cerebellum is involved in the planning phase (Boecker et al., 2008). When looking at the temporal involvement of motor regions in the planning and execution of simple self-paced movements, both cortical and cerebellar regions show gradual spatial and temporal changes (Hülsmann et al., 2003); activity within the cerebellum shifted spatially in the same time-frame as the activity shift from the anterior cingulate cortex to the supplementary motor area (SMA) and the PMC.

The acquisition of complex motor skills can be divided into motor-sequence learning and motor adaptation. Motor-sequence learning consists of the gradual performance of a specific sequence of movements, whereas motor adaptation denotes the ability to compensate for changing environments (Doyon, Penhune, & Ungerleider, 2003). The CBG and CC circuits have been shown to be strongly involved in sequence learning and motor adaptation, respectively (Doyon & Ungerleider, 2002; Doyon et al., 2003; Doyon & Benali, 2005). Doyon and his colleagues have proposed that both types of learning initially recruit regions within the CBG and CC pathways. When learning is more advanced and the subject has reached asymptotic performance, however, there is a shift of representation between the regions within the CBG or the CC loop, depending on the type of learning. At that stage, sequence learning relies mostly on the CBG loop, whereas motor adaptation depends predominantly on the CC loop (Doyon et al., 2003; Doyon et al., 2009). It has been shown that motor learning is affected even in early PD (Shin & Ivry, 2003), with considerable changes in brain activity (Mentis et al., 2003). Since this framework allows for a clear distinction between the CBG and CC pathways functionally, it holds great promise for future research aiming to address whether or not the CC circuit is recruited in PD to compensate for CBG deficiency.

Parkinson's Disease

Motor and cognitive symptoms can arise in parallel with the disruption of normal function of the putamen and caudate nucleus, with almost complete dopamine depletion seen in the putamen (Kish, Shannak, & Hornykiewicz, 1988). In PD patients, nigrostriatal dopamine depletion leads to a net increase in STN and GPi discharge, but a decrease in GPe discharge, creating an imbalance in the direct and indirect pathways (DeLong & Wichmann, 2007; see Figure 1b). Specifically, the indirect pathway becomes hyperactive and the direct pathway becomes hypoactive, resulting in an excess of inhibitory output from the globus pallidus, and leading to bradykinesia and rigidity (Bergman, Wichmann, Karmon, & DeLong, 1994). In addition, according to the functional deafferentation hypothesis, the increase in GPi tonic activity leads to cortical inhibition (Albin, Young, & Penney, 1989). The depletion of dopamine in the motor system is associated with important functional changes that can affect the function of many other brain regions going beyond solely motor functions.

Lesions of the cerebellum also cause a range of deficits, from motor to nonmotor symptoms, depending on the location of the lesion (Strick et al., 2009). It has been shown that changes in the CC pathway are involved in resting tremor, as well as the sup-

pression of tremor during voluntary movements (Deuschl et al., 2000). Lesions of the superior cerebellar peduncle seemed to alleviate Parkinsonian tremor (Cooper, 1956), although the removal of cerebellar lobes does not seem to treat tremor consistently. Recent work with macaque monkeys has shown a correlation between persistent Purkinje cell activity in the cerebellum and dopaminergic degeneration (Heman et al., 2012). Deep brain electrode recordings in PD and essential tremor patients (Pedrosa et al., 2012), as well as in the MPTP model of PD (Guehl et al., 2003) also indicate that there are tremor-related cells in the thalamus. It has been suggested that it is the disruption of competitive balance between cerebellar and basal ganglia output that leads to certain types of tremor in PD (Stein & Aziz, 1999; Deuschl et al., 2000). More specifically, Helmich and colleagues hypothesize that the disruption of the CBG pathway sends transient fluctuating signals to the CC circuit, leading to tremor (Helmich, Janssen, Oyen, Bloem, & Toni, 2011). In accordance, a recent voxel-based morphometry study has shown a decrease in cerebellar gray matter in patients with PD that present with tremor (Benninger, Thees, Kollias, Bassetti, & Waldvogel, 2009).

Metabolic Alterations in PD

Some of the first functional neuroimaging studies in PD were aimed at understanding the change in metabolism and activity fluctuations. Fluorodeoxyglucose (^{18}F) (FDG) PET results suggested a decreased global metabolism, with additional decreased inferior parietal and increased basal ganglia metabolism (Kuhl, Metter, & Riege, 1984; Martin et al., 1984; Schapiro et al., 1993). Using a scaled subprofile model (SSM) to study spatially distributed networks (Moeller & Strother, 1991), Eidelberg et al. (1994) were able to detect a pattern of metabolic increases and decreases related to PD pathology, the PD-related pattern (PDRP), reproducible across Parkinsonian patients and tomographs (Moeller et al., 1999). Although there was no difference between healthy control and PD patient global brain metabolism levels, authors found a major topographic profile consisting of metabolic decreases in the lateral frontal, paracentral, and parietal association cortices, and increases in the lentiform nucleus, thalamus, pons, and 'cerebellum (Eidelberg et al., 1994). Furthermore, the individual topographic profile score correlated with the patients' Hoehn & Yahr (1967) stage and motor Unified Parkinson's Disease Rating Scale (UPDRS) symptom severity score. The PDRP is also strongly associated with STN activity, and lesioning the STN in return affects the PDRP activity (Su et al., 2001). The PDRP can be detected at an individual level before the onset of symptoms, giving it great potential for early diagnosis. The metabolic increases and decreases of this topographic profile accentuate with disease progression; longitudinal data show an increase in metabolism in the pedunculopontine nucleus, STN, GPi, and motor cortex, and a decrease in metabolism in prefrontal and parietal association cortices over disease progression (Huang et al., 2007). Furthermore, Mure et al. (2011) recently used FDG PET to describe a PD tremor-related pattern (PDTP) that plays an important role in Parkinsonian tremor, and which consists mainly of structures involved in the CC pathway.

The altered patterns of brain metabolism could reflect a form of network adaptation to disease pathology (Eidelberg, 2009). However, results from these methods do not allow the distinction between compensatory mechanisms and pathological consequences of circuit imbalance. Because the structures implicated in the PDRP and PDTP are linked through the CBG and CC circuits, fluctuations in one will cause fluctuations in the other, resulting in widespread changes in metabolism that increase as the disease progresses.

Task-Related Neuroimaging in PD

Many neuroimaging studies have reported hypo- and hyperactivations in patients with PD compared with healthy controls during motor and cognitive tasks. In this section we will focus on the basis of these patterns, and whether hyper-activations in the cerebellum in particular can be attributed to compensatory mechanisms.

The classic model of motor deficits in PD (Albin et al., 1989) depicts that the increased inhibitory drive to the thalamus leads to a decreased excitatory drive to the cerebral cortex. Consistent with this model, observations of original functional neuroimaging studies in PD indeed found decreases in motor, premotor, and prefrontal cortex activity (Playford et al., 1992). A series of studies, however, later showed overactivity in certain cortical regions (Sabatini et al., 2000; Haslinger et al., 2001), indicating that patients with PD do not simply have a hypoactive cortex. Models have been suggested to account for these changes in activity; one proposition was that hypo- and hyperactivity patterns in PD were related to a distinction between motor and cognitive tasks, respectively (Mattay et al., 2002). Based on our previous work with set-shifting tasks (the Montreal and Wisconsin Card Sorting Tasks), we have observed that the increases and decreases in cortical activity seen in patients with PD are related to whether the striatum is necessary for the task at hand or not (Monchi et al., 2004; Monchi et al., 2007; Monchi, Marinu, & Strafella, 2010), rather than whether the basis of the task is motor or cognitive. More specifically, we have observed a decrease in activity in the prefrontal regions of patients with PD off medication compared with control participants for tasks that require the striatum in healthy controls (e.g., planning a set-shift; hypoactivation). In contrast, when performing tasks that do not require the striatum (e.g., task execution without changes in rules) in healthy controls, patients with PD showed significant prefrontal and parietal increases in activity (hyperactivation; Monchi et al., 2007). Moreover, in a given task where healthy participants recruit the striatum, patients with PD will show a reduction in cortical activity as the model by Albin, Young and Penney (1989) suggests. On the other hand, in tasks where healthy participants do not recruit the striatum, patients with PD present increases in cortical regions usually unrelated to the task. These hyperactivations may be related to compensatory mechanisms, but it has been proposed that they are due to an exacerbation of dopaminergic tones in the cortex originating from the VTA. Indeed, since dopamine neurons in the substantia nigra degenerate much earlier in the disease than those in the VTA, activity during motor and cognitive tasks of the cortical regions to which they project will be related to their integrity, and will be modulated differently by dopamine-replacement therapy (Monchi et al., 2010; MacDonald & Monchi, 2011).

Some authors were able to observe changes in the patterns of cerebellar activity using neuroimaging via a study of bradykinesia in PD, which represents a slowness in movement initiation (Hallett, 1990). In an H_2O^{15} PET study, Turner, Grafton, McIntosh, DeLong, and Hoffman (2003) also observed regions normally

involved in a task to be hypoactive, and different regions normally not involved in the task to be hyperactive. The authors used a "visuomanual tracking task" with three increasing velocities to investigate bradykinesia in patients with PD. PD Participants did not perform more temporal errors than healthy controls, but their movement amplitudes decreased to remain synchronized with the moving target. Interestingly, when comparing velocity-related activity between PD patients and controls, only the cerebellum showed a decrease in activity in PD, suggesting its involvement in bradykinesia. The authors also addressed the debate regarding the link between overactivation and compensatory mechanisms in PD, and proposed that the observed overactivation in the cerebellum may be a correlate of PD pathology (Turner et al., 2003).

In contrast, using single-photon emission computed tomography (SPECT), Rascol et al. (1997) argued for a compensatory role of the cerebellum by showing that, compared with healthy controls and PD patients on medication, PD patients off medication had an increase in ipsilateral cerebellum and a decrease in SMA activity during a sequential finger-to-thumb opposition task. One could have just as well argued, however, that due to the neuronal connections, the pathophysiology of PD generates an imbalance that leads to an increase in cerebellar activity. (For a review on compensatory mechanisms in PD, see Appel-Cresswell, de la Fuente-Fernandez, Galley, & McKeown, 2010.) Similarly, Sen, Kawaguchi, Truong, Lewis, and Huang (2010) described an increase in CC loop involvement in internally generated movements with disease progression that can again be attributed to either compensation or pathophysiology. Yu, Sternad, Corcos, and Vaillancourt (2007) have also argued for a compensatory role of the CC pathway by correlating CBG and CC region activity. The authors have shown a negative correlation between the contralateral putamen and ipsilateral cerebellum in PD patients during a motor-timing task, indicating that, as the CBG pathway is affected and shows decreases in activity, the CC pathway compensates by increasing its activity. A shift in this balance, however, could still simply be due the pathophysiological imbalance. Palmer et al. (2009) were driven to similar conclusions using a sinusoidal force task of varying frequencies to demonstrate that, as movement frequency (and therefore difficulty) increases, PD patients first increasingly recruit the CBG and CC circuits, and then recruit additional areas in the bilateral cerebellum and primary motor cortex. In this study, the authors worked with the assumption that disease-related activation changes are constant, whereas compensatory changes are not. The communication between the two circuits can lead to altered dynamics relating to disease pathology, and these dynamics vary through direct synaptic input with the level of activity necessary for the task at hand. It is possible, then, that not only compensatory regional involvement varies with task difficulty, but the level at which the same regions are affected by the disease vary as well.

Another interpretation of the compensatory role of cerebellar and cortical regions comes from a study on movement automaticity. Wu & Hallett (2005) showed that when performing automatic movements, patients with PD have increased activity in the cerebellum, premotor area, parietal cortex, precuneus and prefrontal cortex compared with healthy aged participants. Although there were no behavioral differences between PD patients and healthy controls, patients needed more time to reach automaticity, suggesting that the increases in activity are part of compensatory mechanisms. There is however no evidence of any correlation of activity in these regions with performance. One could also argue that since patients have more difficulty performing the movement sequences automatically, the differences in cerebral activity may be due to the pathophysiological changes in PD. In a subsequent study, Wu et al., (2011) report a decrease in cortico-striatal and striato-cerebellar effective connectivity in PD during self-initiated finger tapping movements, but an increased cortico-cerebellar connectivity. Once again, as there were no differences in performance between PD patients and healthy controls, and no correlation with performance was described, these changes in effective connectivity can be due to compensatory mechanisms or pathophysiological changes. Mattay et al. (2002) showed a significant correlation with cortical activity and the number of errors made during a working memory task. More specifically, the increases in cortical activity correlated with the number of errors during an n-back working memory task when patients were off medication. We would like to underline the importance of the observation that these increases in activity are linked with a decrease in performance, further implying that increases in activity cannot be simply attributed to compensatory mechanisms.

Another reason the cerebellum is thought to be involved in compensatory mechanisms stems from the observation that patients with Parkinson's disease present difficulty in performing self-initiated voluntary movements (Benecke, Rothwell, Dick, Day, & Marsden, 1987), but perform better when visual cues are available (Georgiou et al., 1994). The cerebellum is strongly modulated by visual feedback (Debaere, Wenderoth, Sunaert, Van Hecke, & Swinnen, 2003), which is thought to be the basis of paradoxical movements observed in PD (Glickstein & Stein, 1991). Signals through connections between the visual cortex and cerebellum may bypass the CBG pathway and allow an otherwise immobile PD patient to catch a ball being thrown to them or get up and run in the case of a fire. In agreement with this theory, a study where patients performed externally cued movements in urgent situations showed significant cerebellar involvement in PD patients (Ballanger et al., 2008). More specifically, patients were asked to perform self-initiated, externally cued (EC) and externally cued-urgent (ECu) arm movements to a contact plate. In the ECu condition, participants had to reach to the contact plate fast enough to stop a ball, rolling on a ramp, from falling. Ballanger et al. (2008) showed that patients performed movements faster in the context of a "temporally pressing situation." Furthermore, when comparing the ECu with the EC condition, PD patients had greater activity in the cerebellum that correlated with movement speed. Based on cerebellar, basal ganglia and thalamic surgeries, there appears to be a competitive balance between the CBG and CC pathway inputs within the thalamus (Stein & Aziz, 1999), the disruption of which would lead to the rigidity and tremor observed in PD. Moreover, a recent study has shown that patients presenting primarily with tremor have a different brain-activity profile than those presenting with akinesia and rigidity (Lewis et al., 2011). During internally guided hand movements, patients with tremor displayed increases in activity in the cerebellum and thalamus, whereas patients with akinesia/rigidity showed increases in the putamen and globus pallidus.

In summary, while it is relatively clear that CBG hypoactivations are linked to PD pathophysiology, frontal hyperactivations are still under debate, with some authors proposing a compensatory role and others a dopamine imbalance linked to the relative

preservation of the mesocortical system compared with the nigrostriatal pathway. The controversy is even greater regarding the role of the changes in patterns of cerebellum activity observed in PD compared with controls. An imbalance between the affected CBG pathway and an intact cerebellum could mean that the cerebellum becomes recruited in order to compensate for the CBG pathway, and therefore displays increases in activity. Evidence suggests, however, that the cerebellum is not intact in PD. Furthermore, an increase of activity does not necessarily mean it is beneficial, and the lack of association between increases in activity and improvement in performance in most of the studies mentioned above does not support a compensatory role. Although both may be involved, the association of the cerebellum with tremor and bradykinesia would, rather, suggest that such activity is related to the pathophysiological changes in PD.

Levodopa Treatment

Levodopa is a common choice of treatment for PD, and is used in the hopes of restoring activity in the CGB networks through dopamine replacement. Levodopa has been shown to decrease the PDRP by suppressing metabolic activity in the putamen, motor cortex and cerebellum. In fact, using FDG PET, Feigin et al. (2001) reported that the degree of PDRP decline correlated significantly with symptom improvement. The authors also observed a significant correlation between UPDRS motor symptom ratings and metabolic decreases in the area of the globus pallidus and ventral thalamus.

Although levodopa has no effect on global cerebral blood flow, it has been shown to reestablish activity in the SMA (Buhmann et al., 2003; Jenkins et al., 1992). It has been suggested that the changes in cortical activity seen after levodopa administration could be attributed to its focusing effects (Ng, Palmer, Abugharbieh, & McKeown, 2010) of otherwise spatially spread-out activity (Monchi et al., 2004). It has been suggested that this focusing effect may be due to a dopamine-induced increase in signal-to-noise ratio of cellular activity (Winterer, 2006). Moreover, Ng et al. (2010) showed that spatial changes in activity patterns could be observed in the contralateral motor cortex and ipsilateral cerebellum at low movement frequencies, whereas a change in amplitude can only be detected at higher frequency movements. Levodopa has additionally been shown to sometimes normalize task-related activity and improve performance on motor and cognitive tasks (Mattay et al., 1998; Cools, Stefanova, Barker, Robbins, & Owen, 2002). When patients in the early stages of PD performed volitional movements, levodopa was shown to restore the activity of the lateral PMC and SMA, but with no improvement on execution times (Haslinger et al., 2001). Although cerebellar changes would also be expected, acquisition parameters did not include the cerebellum in the field of view. Others have demonstrated a worsening of performance on a motor sequence-learning task as well, which correlated with the regional cerebral blood flow (rCBF) of occipital association areas (Feigin et al., 2003). Interesting was that an H_2O^{15} PET study showed an increase in spatial errors of movement that correlated with changes in the cerebellum (Feigin et al., 2002), arguing against a compensatory role. Using the Wisconsin Card Sorting Task (WCST; with patients on and off levodopa in fMRI, we have previously shown that levodopa does not restore prefrontal cortex activity during the WCST (Jubault et al., 2009). In accordance with these results, we have recently indicated that even within a motor task that solicits both motor and cognitive CBG regions, levodopa has an effect on the motor CBG circuit, but not the cognitive one (Martinu et al., 2012). Although the effect of levodopa on motor symptoms is beneficial, improvement can be seen in some tasks whereas performance on others worsens (Gotham, Brown, & Marsden, 1988; Cooper et al., 1992). Taken together, the effect of levodopa seems to strongly depend on the regions implicated in the task at hand, and too much dopamine can be detrimental to processes linked to mesocortical pathway and the ventral striatum. For example, tasks that require the activity of the dorsal striatum may show improvement after levodopa administration, whereas tasks that depend on ventral striatal activity will show a worsening (Monchi et al., 2010; MacDonald et al., 2011; MacDonald & Monchi, 2011).

We have recently used an SI and ET task to describe the effect of levodopa on the CBG circuit in patients with PD using fMRI (Martinu et al., 2012). Healthy controls and patients at Stage I and II of PD were asked to use their right or left hand to either press a sequence of buttons following visual cues, button by button and (externally triggered task), or create a "random" sequence on their own (self-initiated task), with no working memory component. Task-related activations were contrasted with a simple single-button repeat control. PD patients participated in two scanning sessions, both following overnight withdrawal of dopaminergic medication. For one session, patients were asked to take their levodopa one hour before scanning. We observed that healthy controls recruit the putamen at different levels for our SI and ET tasks, with the SI task requiring higher activity levels. This effect was greatly reduced in patients off medication, and levodopa partially restored the putamen's activity. Results also indicated that cerebellar activity in self-initiated and externally triggered movements follows that of the putamen (see Figure 2). Activity in the cerebellum of patients with PD was also greatly reduced for both self-initiated and externally triggered movements. Most importantly, however, levodopa significantly increased the activity in the cerebellum for both types of movements, restoring activity at least partially to that observed in healthy controls. We suggest that the activity pattern observed is due to the direct connections between the CBG and CC loops, and that levodopa therefore leads to a boost in activity in the striatum as well as the cerebellum. Our results with this paradigm further support the notion that the pathophysiology of PD affects cerebellum function, and give further support to the implication of the cerebellum in the development of levodopa-induced dyskinesia (LID).

Briefly, these different studies show that dopaminergic medication is beneficial for activity in the dorsal striatum and related cortical regions in PD, but not necessarily for ventral striatum circuit activity (especially at the beginning of the disease). Although it has been observed that dopaminergic therapy can affect cerebellar activity as well, it is not yet clear whether this is linked to a direct effect of dopamine on the cerebellum or to the interactions between the CC and CBG circuits.

Dyskinesia

Levodopa has few short-term side effects (Hauser & Zesiewicz, 2007), but its long-term administration leads to the development of LIDs in about 50% of patients (Rinne, 1989; Montastruc, Rascol,

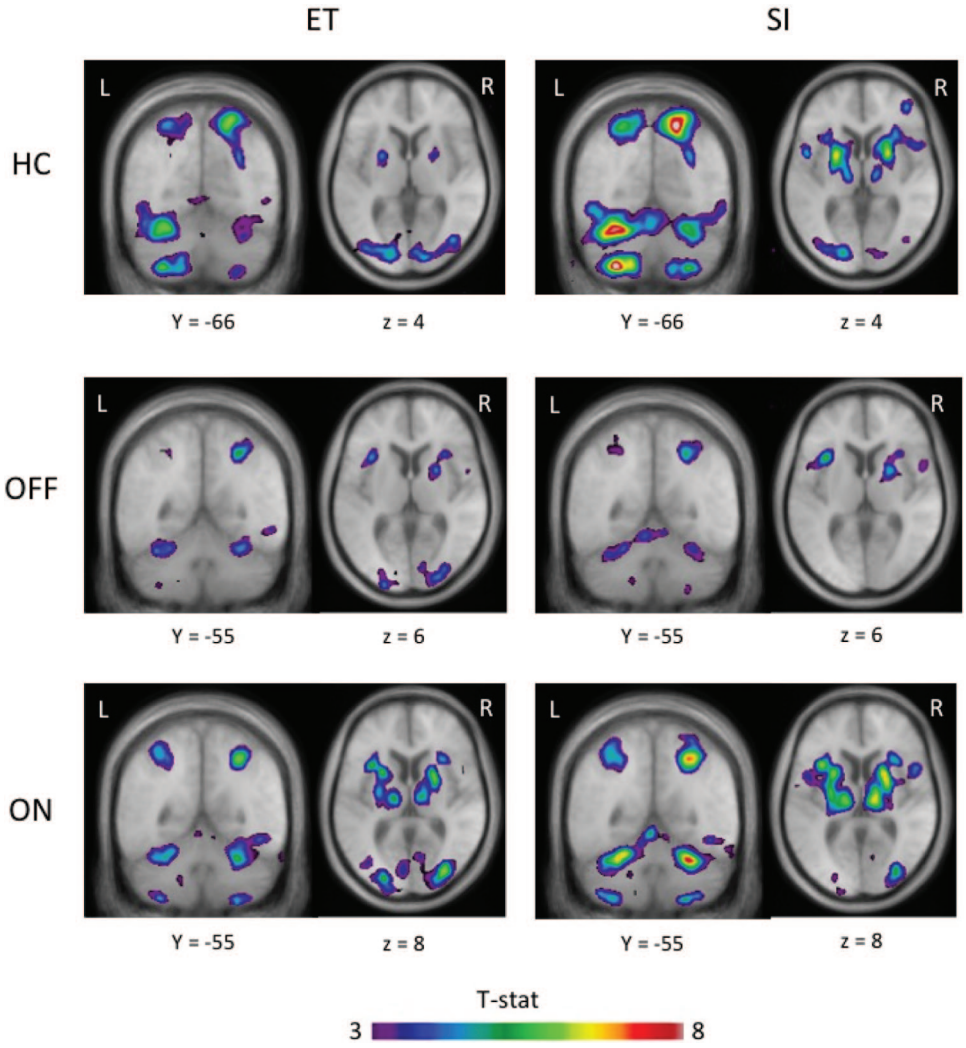

Figure 2. Activation peaks during ET and SI movements in healthy controls and PD patients before and after levodopa. Location of peaks in the ET versus control (left) and SI versus control (right) for the three groups of healthy controls (top), PD patients off medication (middle) and on medication (bottom). Anatomical images shown are the average of the T1 acquisitions of all participants transformed into stereotaxic space. The functional peaks are shown for *t*-stat values between 3 and 8. Healthy controls have significant activity in CBG and CC circuits during ET and SI movements. Patients show a decrease in CBG and CC loop activity before levodopa administration, and an increase in CBG and CC circuit activity after levodopa administration.

Senard, & Rascol, 1994). These are mainly manifested by chorea and dystonia at the peak of drug dose (Bezard, Brotchie, & Gross, 2001), and are difficult to treat once they appear (Fahn, 2000). The course of treatment methods and the order of administration for the highest benefit and lowest number of side effects were long under debate, because maintaining constant dopamine levels throughout the length of the disease is difficult (Quinn, 1995; Durif, 1999; Khan, 2012). One study reports that over five years, 45% of patients in their levodopa group developed dyskinesias compared with 20% in the dopamine agonist group (Rascol et al., 2000). The development of LIDs is associated with a series of changes in genes and proteins involved with dopamine receptors, as well as with nondopamine transmitters (Bezard et al., 2001). In the context of the present manuscript, LIDs also provide a means of further investigating functional changes in CBG and CC pathways in PD. More specifically, dyskinesias are linked with an imbalance between the direct and indirect motor pathways, and in particular, with a decrease in GPi activity (Lozano, Lang, Levy, Hutchison, & Dostrovsky, 2000), although the latter does not account for the symptoms in their entirety. PET studies have shown an overactivation of motor regions in dyskinetic patients (Brooks, Piccini, Turjanski, & Samuel, 2000). Using ^{11}C-diprenorphine PET, the authors suggest that dyskinesias are mediated by changes in opioid-receptor binding in the basal ganglia, resulting in the overactivity of frontostriatal projections (Piccini, Weeks, & Brooks, 1997; Brooks et al., 2000). More recently, Nimura et al. (2004) have shown the implication of sigma-receptors in LIDs. These receptors are localized in the substantia nigra, red nucleus, and

cerebellum (Jansen, Faull, Dragunow, & Leslie, 1991). Sigma-active neuroleptics have been shown to cause dystonic responses in rats after an injection to the red nucleus, and their effect on behavior correlated with their affinity with sigma receptors (Matsumoto et al., 1990). Using ^{11}C-nemonapride PET with PD patients presenting with LIDs, Nimura et al. (2004) detected sigma-receptor-binding potential in the cerebellum; the authors showed a correlation of $r = .893$ between receptor-binding potential in the cerebellum and LID severity. Moreover, an almost complete disappearance of LID symptoms after pallidal surgery coincided with a decrease in receptor-binding potential. Although the function of these receptors in LIDs and the reason for their up-regulation after levodopa administration is still unclear, these results imply that important changes associated with levodopa administration may take place in the cerebellum.

Repetitive transcranial magnetic stimulation (rTMS) has been suggested as a potential treatment for LIDs. Stimulation over the SMA or the primary motor cortex has been shown to reduce LIDs transiently (Koch et al., 2005; Brusa et al., 2006). More specifically, Koch et al. (2005) showed that 1Hz (inhibitory) rTMS stimulation over the SMA reduced dyskinesias, whereas 5Hz (excitatory) rTMS increased them. More recently, however, Koch et al. (2009) have attempted theta-burst stimulation (TBS), a sequence that can produce changes for over 30 min over the cerebellum of patients with LIDs. A single session of inhibitory continuous TBS (cTBS) over the cerebellum was able to reduce LIDs (Koch et al., 2009), and one week of cTBS treatment showed considerable symptom improvement, along with a decrease in cerebellar metabolism, as shown by FDG PET (Brusa et al., 2012). Taken together, these results suggest that the metabolic and receptor changes in PD lead to an imbalance between the CBG and CC pathway, and underline the importance of the cerebellum's role in dyskinesias, further implying that changes in cerebellar activity may be linked to disease pathology.

Deep Brain Stimulation

Deep brain stimulation (DBS) is a very effective form of treatment, mostly used in advanced stages of PD when symptoms and medication side effects (e.g., dyskinesia and motor fluctuations) become too severe. One main advantage of DBS is that, unlike ablation, stimulation is reversible and adjustable. The most common targets of DBS in PD are the STN and GPi (Volkmann, 2004; Østergaard & Sunde, 2006; Deuschl et al., 2006; Wider, Pollo, Bloch, Burkhard, & Vingerhoets, 2008), although DBS of the ventral intermediate nucleus of the thalamus seems to be the most effective to treat tremor (Lyons & Pahwa, 2008). Stimulations often consist of bilateral stimulations of 60–185-Hz pulses (Wichmann & DeLong, 2011). STN-DBS in particular seems to be effective, as it helps patients reduce their medication doses and consequently, dyskinesias (Rodriguez-Oroz, Zamarbide, Guridi, Palmero, & Obeso, 2004). The exact mechanisms behind DBS treatment, however, are unclear. It appears that the effect of STN stimulation has different effects on cell bodies, afferent and efferent axons, modulated by stimulation parameters, leading to both complex excitatory and inhibitory effects on the GPi (Wichmann & DeLong, 2011).

As the treatment effect and regional metabolism changes of STN-DBS are generally similar to ablation (Su et al., 2001), one would expect stimulation to have an inhibitory effect on the STN, decreasing cortical inhibition. However, according to neuroimaging (Hershey et al., 2003; Payoux et al., 2004; Asanuma et al., 2006; Grafton et al., 2006) and electrophysiological recordings (Hashimoto, Elder, Okun, Patrick, & Vitek, 2003), it appears that STN and GPi output is in fact increased. The stimulation of the STN was shown to increase rCBF to the midbrain, globus pallidus and thalamus, but to reduce blood flow to the SMA and PMC (Hershey et al., 2003). These changes correlated with motor improvement in PD (Karimi et al., 2008). Using $H_2^{15}O$ PET, Payoux et al. (2004) showed that PD patients at rest had significant reductions in rCBF in the sensorimotor cortex, PMC, anterior cingulate, SMA, and cerebellum during high-frequency STN-DBS. When patients performed fist-clenching movements in the stimulator-on condition, patients displayed a significant increase in activity of the sensorimotor cortex, cingulate cortex and ipsilateral cerebellum. The authors report that these activations were in fact due to the reduction of activity at rest, rather than an increase in activity during movements. Interestingly, rCBF of the cerebellum off-stimulator in this study correlated positively with patients' akinesia (Payoux et al., 2004). Additional PET studies also found rCBF increases in the STN and lentiform nucleus, and rCBF decreases in the thalamus and cerebellum at rest during STN stimulation (Hilker et al., 2004; Geday, Østergaard, Johnsen, & Gjedde, 2009). Furthermore, DBS appears to cause task-specific adaptation changes in brain activity, possibly via decreases in pathologic network activity (Grafton et al., 2006). Indeed, STN-DBS, just like levodopa, has been shown to reduce PDRP, inherently reducing cerebellar overactivity (Trošt et al., 2006; Asanuma et al., 2006), suggesting that STN-DBS leads to symptom improvement through the alteration of network communication within and between the CC and CBG pathways. These studies suggest that the reduction of activity in the cerebellum following STN-DBS goes hand in hand with symptom improvement, further supporting the hypothesis that overactivity in the cerebellum is associated with the pathophysiology of PD.

Concluding Remarks

In this review, we have shown the important implication of both the CBG and CC pathways in Parkinson's disease, and the changes related to levodopa administration and DBS. Direct evidence that the patterns of activity of the cerebellum and the CC loop are truly compensatory is still lacking, and traditional neuroimaging studies showing increases or decreases in activity always depend on interpretation. It has been suggested that externally cued movements are mainly processed by the CC loop and remain intact for the most part, whereas internally cued movements are processed through the dysfunctional CBG loop (Lewis et al., 2007).

Based on the results reviewed, we propose that the CC pathway activity in PD does not remain intact, as is often suggested, but that it is also affected by the disease, and related to some of the observed symptoms. In other words, the CBG and CC circuits are very closely related through direct interactions as well as cortical associations, and the changes in PD affecting the CBG circuits will therefore also affect the CC pathway. Changes in cerebellar activity should consistently correlate with improvements in performance in order to show clear compensatory involvements. The opposite seems to have been shown so far (Feigin et al., 2002).

Although both compensatory and pathophysiological changes are most likely present in PD, the interpretation of neuroimaging studies as supporting one or the other must be done with care.

An increase in cerebellar activity after levodopa administration can be due to different reasons, such as by a direct effect of dopamine on cerebellar receptors, or indirectly though the connections between the CC and CBG pathways, as previously suggested by Stevenson et al. (2011). Additional research will be necessary to establish the effect of levodopa on the cerebellum.

It has been suggested that oxidative stress and mitochondrial dysfunction plays an important role in the cell degeneration in PD (Jenner, 2003). A recent PET study has demonstrated an enhancement of oxidative stress in PD patients that increased with disease progression, suggesting that neurodegeneration in PD is associated with oxidative stress (Ikawa et al., 2011). Paradoxically, levodopa has prooxidant properties that promote free radical formation, and lead to cell death in cellular models of PD (Martignoni et al., 1999; Sabens, Distler, & Mieyal, 2010), explaining the growing number of side effects with long-term administration. The increase in activity after levodopa administration seems to be detrimental in the long run, leading to symptoms such as dyskinesia. Indeed, one major confound in most PD studies (including our own) is that one cannot completely distinguish between the pathophysiology of the disease and the accumulated effect of dopaminergic medication. It may be useful in the future to study cerebellum function via neuroimaging in nonmedicated, de novo PD patients.

It is interesting to note that the CC pathway has been shown to be strongly involved in dystonia, also originally considered a disorder of the basal ganglia (Niethammer, Carbon, Argyelan, & Eidelberg, 2011), and the cerebellum may not necessarily be involved in compensatory mechanisms (Sadnicka et al., 2012). Inversely, several types of spinocerebellar ataxias, primarily disorders of the cerebellum, have also been shown to lead to considerable basal ganglia degeneration (Seidel et al., 2012).

The limitations of neuroimaging make the distinction between compensatory mechanisms and disease pathophysiology difficult. TMS may prove to be a useful tool in the study of living PD patients. We propose a few ways in which the compensatory mechanisms may be separated from the pathophysiological changes in PD. By using tasks of sequence learning and motor adaptation, one can separate, for the most part, activity between the CBG and CC loops. As mentioned above, when participants reach the final stages of learning, sequence learning tasks are mainly operated by the CBG loop, whereas motor adaptation tasks by the CC loop. Following inhibitory TBS over the cerebellum, both PD patients and healthy controls should show a decrease in performance on the adaptation task. On the other hand, if cerebellar activity in PD compensates for CBG loop dysfunction, patients with PD should show a decrease in performance on sequence learning tasks, and there should be no effect on performance of healthy controls. In contrast, if cerebellar activity is related to pathophysiology, performance of PD patients on sequence learning tasks should be improved. A similar protocol in a task that recruits the cerebellum or basal ganglia selectively, such as the SI and ET model suggested by Lewis et al. (2007) should lead to similar conclusions. More specifically, their task consists of SI movements associated with CBG loop activity, whereas the ET movements are associated with CC loop activity. Inhibitory cerebellar TBS in PD patients should decrease performance of SI movements if cerebellar activity is compensatory.

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