# Chapter 9
# Cognitive and Perceptual Impairments in Parkinson's Disease Arising from Dysfunction of the Cortex and Basal Ganglia

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## 9.1 Introduction

Parkinson's disease (PD) traditionally has been considered a motor disorder, being characterized by the cardinal motor symptoms of tremor, rigidity, slowness of movement, and impairments of posture, gait, and balance. Clinical and research emphasis on the substantia nigra and dopamine has resulted in a decades-long focus on this neurotransmitter in regard to PD etiology and treatment (Goetz 2011). In recent years, there has been growing recognition that the non-motor symptoms of the disease are important contributors to quality of life that are not relieved by dopaminergic treatment (Cronin-Golomb 2013). Understanding their etiology and course may lead to the development of interventions to ease the burden experienced by those with PD.

Current research on the non-motor symptoms of PD is focused on cognition and perception and on the diagnosis and treatment of cognitive decline (Litvan et al. 2011, 2012). This focus has derived in part from the work of Braak and colleagues on the neuropathological staging of PD through examination of synucleinopathy (density of Lewy bodies and Lewy neurites) (Braak et al. 2006). This program of research established that lower-brainstem areas (important to arousal and hence to attention) are affected early, before the first motor signs of PD (Chaudhuri et al. 2011; Gaenslen et al. 2011; Gaig and Tolosa 2009; Jacob et al. 2010; Postuma et al. 2012). In later stages, the pathology extends to cortex—first to prefrontal and high-order sensory association areas (stage 5), subsequently to premotor and secondary

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sensory association areas, and finally potentially to primary cortex (stage 6) (Braak et al. 2004). The presence of Lewy bodies and cortical loss is associated with impairments in cognition.

The basal ganglia are important to cognitive as well as motor activity. Imaging studies have found that the putamen and caudate are associated with an action's motor and cognitive components, respectively (Monchi et al. 2001). The caudate head may operate in executive processing (Seger and Cincotta 2005, 2006), sharing connectivity with the dorsolateral prefrontal cortex (PFC) (Selemon and Goldman-Rakic 1985). Executive functioning tasks that involve set-shifting, planning, problem-solving, monitoring, and sequencing elicit both lateral PFC and striatal activity (Monchi et al. 2001; Provost et al. 2010; Tinaz et al. 2008). Of relevance to visuospatial cognition and attention, functional connectivity and diffusion tensor imaging analysis have demonstrated that posterior parietal cortex, especially the angular gyrus region within the inferior parietal lobe, shares strong connections with the caudate (Uddin et al. 2010), and decreased cortical thickness has been reported in PD in the right inferior parietal lobule (Pagonabarraga et al. 2013) and parieto-occipital sulcus (Tinaz et al. 2011), among other areas. Sustained attention and inhibitory control are associated with a bilateral, though slightly right-lateralized, network of regions in the PFC (Aron et al. 2004; Esterman et al. 2013), particularly the inferior frontal gyrus/opercular cortex and its connections to the anterior cingulate cortex, and dorsolateral PFC. An fMRI study of PD by Tinaz and colleagues (2008) found abnormal activation in distinct PFC areas and left caudate, indicating compromise of frontal-basal ganglia circuits. Observations of reduced subcortical volume (Ibarretxe-Bilbao et al. 2009), reduced integrity of white matter tracts (Cochrane and Ebmeier 2013), and functional hypometabolism (Hosokai et al. 2009) suggest that these frontal-basal ganglia regions are compromised in PD.

The mechanisms of PD-related motor and non-motor deficits implicate basal ganglia pathology and the resulting dysfunction of basal ganglia-thalamo-cortical dopaminergic circuitry (Barnes et al. 2010; Kwak et al. 2010), but there is as yet no clear understanding of the pathophysiology underlying these various symptoms. Studies demonstrating functional changes in the basal ganglia and cerebral cortex suggest that PD is a complex network disorder in which abnormal basal ganglia activity has profound effects on the excitability of, and synchrony between, multiple cortical regions involved in perception, motor planning and execution, and cognitive function (Galvan and Wichmann 2008; Hammond et al. 2007). Brain activity dynamically changes independently of whether or not the brain is engaging in a particular cognitive task. Indeed, it has long been proposed that spontaneous activity during rest contributes significantly to the variability observed in stimulus responses (Arieli et al. 1996; Fox et al. 2007). The brain's natural resting state was initially considered to be a passive condition serving as a baseline against which other cognitive processes could be compared. This view of rest as a passive state has been replaced with the current idea that the brain's resting state is a

dynamic state of maintenance activity (Papo 2013). A default mode network comprising the medial prefrontal lobes, posterior cingulate cortices, precuneus, inferior parietal, and lateral temporal cortices displays increased activity at rest and decreased activity during cognitively demanding tasks (Raichle et al. 2001). The organization of spontaneous resting activity in the brain is thought to reflect a history of past task-induced activations and serves to modulate future network responses (Ohl et al. 2001; Yao et al. 2007). Resting state activity is predictive of performance on a range of cognitive tasks in healthy young adults as well as in individuals with damage to basal ganglia structures, as in PD (Kounios et al. 2008; Lebedev et al. 2014).

## 9.2 Cortico-Striatal Connectivity and Cognition

Intrinsic functional connectivity research in PD has focused on cortical networks including the default mode network, the dorsal attention network, and the cognitive control network. Functionally, the default mode network is proposed to subserve internally directed cognition and self-monitoring (Andrews-Hanna 2012). The dorsal attention network, including the frontal eye fields and bilateral intraparietal sulci, supports external attentional control (Szczepanski et al. 2013). The cognitive control network, also referred to as the central executive network, includes regions of posterior parietal cortex and dorsolateral PFC and responds strongly to externally oriented higher-order cognition (i.e., goal-directed executive processes) through its interactions with the default mode and dorsal attention networks (Dosenbach 2006).

The pathophysiology of cognitive impairment in PD reflects a disruption of neuronal circuits between the striatum and cortical areas in the prefrontal and parietal lobes (Carbon and Marie 2003). Functional connectivity magnetic resonance imaging (fcMRI) techniques have been used to study intrinsic connectivity patterns between the basal ganglia and the cortex in non-demented PD patients and age-matched control participants. fcMRI studies have tracked reorganization of neural networks (Pawela et al. 2010), while electrophysiological examinations of effective connectivity have gone further and distinguished between pathogenic and compensatory processes among synchronous activity in rat models of PD (Moran et al. 2011). Studies of resting state functional connectivity in humans with PD using seed regions in the basal ganglia have found some evidence of compensatory remapping (Helmich et al. 2010), and others have simply shown diminished functional coherence within networks identified in healthy control participants (Kwak et al. 2010).

In PD, decreased connectivity has been reported within the default mode network, the degree to which correlated with severity of cognitive symptoms, though not with disease duration, motor impairment, or levodopa therapy (Tessitore et al. 2012).

An fMRI study by Tinaz and colleagues (2008) found reduced resting activation in areas of the default mode network, in PD relative to a control group, suggesting that regions in frontal–basal ganglia circuits are dysfunctional even at rest in mild PD. With respect to the cognitive control network, another study demonstrated that freezing of gait is particularly associated with reduced connectivity between the basal ganglia and cognitive control network (Shine et al. 2013). This group also reported that visual misperceptions in PD are related to reduced activation of regions of the dorsal attentional network (Shine et al. 2014).

DiMartino and colleagues (2008) mapped out cortico-striatal functional connectivity in healthy young adults using resting state fcMRI analysis to examine connectivity from six striatal seed regions (ventral inferior striatum, ventral superior striatum, dorsal caudate, dorsal caudal putamen, dorsal rostral putamen, and ventral rostral putamen). The investigators found that the superior ventral striatum was functionally connected with the superior and lateral orbitofrontal cortex, regions implicated in executive function and motor planning. By contrast, the inferior ventral striatum showed correlated activity with the medial orbitofrontal cortex, parahippocampal gyrus, and posterior cingulate cortex, regions implicated in emotional processing. The dorsal caudate was implicated in cognitive control, correlating with activity bilaterally in the dorsolateral prefrontal cortex, while putamen seed regions predicted activity in the primary and secondary cortical motor areas. These findings revealed subtler distinctions in cortical connectivity among striatal subregions than had previously been reported and provided evidence for distinct functional networks mapping onto specific cognitive, affective, and motor domains.

The intrinsic connectivity of these cortico-striatal networks becomes dysfunctional in PD compared to younger adults and healthy individuals age-matched to PD. One study compared intrinsic fluctuations between these groups focusing on three cortico-striatal loops involving the posterior putamen, the anterior putamen, and the caudate nucleus (Helmich et al. 2010). Differences in connectivity profiles between PD and an age-matched control group were observed specific to putamen seed regions, as in PD the posterior putamen exhibited decreased coupling with the inferior parietal cortex, while the anterior putamen demonstrated increased coupling with the same region. The authors proposed that focal dopamine depletion in the posterior putamen results in a functional disconnection with the cortex, whereas the relatively spared anterior putamen demonstrates functional compensation via hyperconnectivity with the cortex. This study provides some evidence for a possible compensatory phenomenon as a maladaptive consequence of striatal dopamine depletion in PD.

Large-scale functional network analysis exploring brain function across healthy adults and brain-disordered individuals has led to a conceptual framework referred to as the triple network model of pathology. This model highlights three distributed neural networks that are disrupted across many neuropsychiatric and neurological disorders (Menon 2011): the default mode network (DMN), the salience network (SN), and the central executive network (CEN) (Greicius et al. 2003; Menon and Uddin 2010). These three networks are considered core neurocognitive networks because they play critical roles across a wide range of cognitive tasks (Menon 2011;

Seeley et al. 2007). The CEN (including dorsolateral PFC and lateral posterior parietal cortex) refers to largely the same regions referred to in previous literature as the Cognitive Control Network, while the salience network (including anterior insula and dorsal anterior cingulate cortex) is now recognized as functional and structurally distinct from the dorsal attention network under which it had previously been conceptualized. Typically, the salience network and CEN increase activation during cognitive tasks in response to external stimuli (Dosenbach et al. 2006), whereas DMN activity is suppressed (Greicius et al. 2003; Raichle et al. 2001). The triple network model posits that during cognitively demanding tasks, allocation of attentional resources to external stimuli activates the CEN, and suppression of more internal, self-referential processes deactivates the DMN (Menon 2011), resulting in anti-correlated activity between the CEN and DMN (Fox et al. 2005). The salience network is responsible for detecting and filtering the relevant information for maintaining goal-directed behavior (Menon 2011; Seeley et al. 2007). Critically, the salience network activates the central executive network and deactivates the default mode network during cognitive tasks as well as during the resting state (Menon 2011; Seeley et al. 2007; Sridharan et al. 2008), thereby shifting attention between external and internal processes.

As the striatum is a primary target of PD pathology and becomes more dysfunctional as the disease progresses (Ravina et al. 2012), it is important to understand the structural and functional connections the striatum has with regions of the neocortex. Through reciprocal connections, striatal neurons are thought to coordinate activity in many cortical regions (Macdonald and Monchi 2011). In particular, striatal neurons are highly interconnected with neurons in the insular cortex (Chikama et al. 1997; Fudge et al. 2005), an important node of the salience network. Dopamine depletion occurs in parallel in the striatum and the insula (Christopher et al. 2014; Monchi et al. 2007; Shine et al. 2013). It has been hypothesized that the loss of dopamine receptor type 2 (D2) signaling in the insula disrupts the modulation of salience network activity, impairing its function in activating and deactivating other core neurocognitive networks (Menon and Uddin 2010). Altered cortico-striatal-thalamocortical neurocircuitry resulting from dysfunctional striatal dopaminergic function leads to aberrant assignment of salience (Kish et al. 1988; Monchi et al. 2007; Shine et al. 2013) and has important implications for understanding cognitive dysfunction. As striatal dysfunction is characteristic of PD and worsens with disease severity, functional coupling between the striatum and the salience network is likely to be disrupted as a function of disease progression.

In addition to disruption of the salience network, decreased functional connectivity within the DMN has been observed in PD during the resting state (Tessitore et al. 2012) and during cognitively demanding tasks (van Eimeren et al. 2009). The striatum is also connected with cortical areas that comprise the CEN through reciprocal circuitry with the dorsolateral prefrontal cortex and posterior parietal cortex (Alexander and Crutcher 1990; Kish et al. 1988; Leh et al. 2008), which display abnormal activations in PD during cognitively demanding tasks (Carbon et al. 2010; Eidelberg 2009; Lewis et al. 2003b; Schendan et al. 2013; Tinaz et al. 2008). These findings suggest that PD-related striatal disruptions are associated with dysfunctional

connectivity within the DMN and CEN. Recent work from our group suggests reduced functional coupling between the CEN and SN (SN=Salience Network) and paradoxically increased coupling between the DMN and CEN, in non- demented PD compared to age-matched control participants (Putcha et al. 2015). Further emphasizing the importance of connectivity between the salience network and DMN, better performance across domains of executive functions, verbal memory, and psychomotor speed was found to be associated with anti-correlated functional connectivity between the salience network and DMN in healthy aging and Parkinson's disease (Putcha et al. 2016).

## 9.3 Cognition in Parkinson's Disease

The cognitive deficits in PD are heterogeneous. Impairments arising from frontal or fronto-striatal dysfunction manifesting as executive dysfunction (Dirnberger and Jahanshahi 2013; Foltynie et al. 2004; Siepel et al. 2014), reduced working memory (Lewis et al. 2003a), impaired attention and planning (Dujardin et al. 1999; Williams-Gray et al. 2007), and decreased speed of information processing (Uc et al. 2005) have historically received the most attention (Baddeley and Della Sala 1996), partly because it appears that more individuals with PD exhibit frontal-type than posterior-type cognitive deficits (Miller et al. 2013). Long-term memory (visual and verbal) is nonetheless also affected in some with PD, implicating the temporal lobes (Amick et al. 2006a; Ibarretxe-Bilbao et al. 2011). A relatively recent emphasis is on visuospatial cognition in PD with corresponding focus on parietal and occipital regions as well as their connections to other brain areas (Amick et al. 2006b; Cronin-Golomb 2010; Poletti et al. 2012; Schendan et al. 2009; Stepkina et al. 2010). The pathophysiological mechanisms underlying cognitive dysfunction in non-demented PD are not well-understood (Barone et al. 2011), but there is evidence that it may be independent of the prominent motor symptoms that are a cardinal feature of the disease (Cooper et al. 1991). PD is typically characterized by the loss of dopaminergic neurons in nigrostriatal pathways and decreasing dopamine levels in the striatum (Kish et al. 1988). These local disruptions in dopamine function negatively impact the functioning of the striato-thalamo-frontal loops, indicating that distributed neural networks beyond the striatum into the neocortex are affected by disease progression (Monchi et al. 2007; Moustafa and Poletti 2013).

In the remainder of this chapter, we focus on visuospatial cognition and perception, for two reasons. First, most of the work in this area is recent relative to consideration of frontally based impairments in PD, including understanding of the contribution of perceptual compromise on cognitive abilities. Second, because the lateralization of cognitive function is more obvious in the visuospatial domain than in many others, focus in this area allows us to introduce the important concept of subtypes of PD. PD is a heterogeneous disorder with a range of clinical presentations, including the side of initial onset, as PD motor onset is almost always unilateral.

Onset on the left side of the body (LPD) reflects predominant right-hemisphere dysfunction, and on the right side (RPD) reflects predominant left-hemisphere dysfunction (Cronin-Golomb 2010; Djaldetti et al. 2006; Gomez-Esteban et al. 2010; Uitti et al. 2005). There is evidence for more dopamine depletion as well as reduction in dopamine uptake in the hemisphere contralateral to the side of onset (Kim et al. 1999; Marek et al. 1996), with DA asymmetry seen in never-medicated patients as well as those with more advanced disease (Antonini et al. 1995; Laulumaa et al. 1993; Leenders et al. 1990). Of importance in the study of PD in general, considerable asymmetry is maintained long after the disease progresses from unilateral to bilateral; those with moderate to severe bilateral motor disability still show asymmetry in the putamen and caudate and less dopamine (DA) activity contralateral to the initial side of motor onset (Antonini et al. 1995; Booij et al. 1997), and the continuance of asymmetry has been reported even at autopsy, with 25 % fewer neurons in the substantia nigra contralateral to the side of the initial motor onset than in the ipsilateral substantia nigra (Kempster et al. 1989). As predicted by understanding the basic laterality of function, those with LPD often experience cognitive impairments mediated by the right hemisphere, such as in global visuospatial perception, mild unilateral neglect of left hemispace, and problems in nonverbal memory (Amick et al. 2006a; c; Ebersbach et al. 1996; Foster et al. 2008; Lee et al. 2001; Schendan et al. 2009). By contrast, those with RPD more often have difficulty on tasks mediated by the left hemisphere, such as verbal memory (Amick et al. 2006a). As an example, we examined hierarchical pattern perception with the hypothesis that LPD would show impaired global processing, which is dependent on the integrity of the right posterior temporal-parietal junction, whereas RPD would be impaired at local-level processing because of its dependence on the left posterior temporal–parietal junction. LPD demonstrated abnormal global level processing, and RPD showed abnormal local level processing mainly when attention was biased toward the local level (Schendan et al. 2009) (Fig. 9.1).

We do not restrict our consideration of PD subgroups to side of onset, but also describe studies examining cognitive performance in subtypes according to initial motor symptom, meaning the primary motor symptom present at disease onset (Selikhova et al. 2009) or predominance of current motor symptoms (Alves et al. 2006). Relative to PD that begins with tremor, those with the non-tremor-dominant type (NTD: rigidity, akinesia, and disordered gait, posture, and balance) show greater Lewy body pathology, cognitive and functional impairment, and risk for dementia and have more perceptual difficulties (Alves et al. 2006; Lewis et al. 2005; Seichepine et al. 2011; Selikhova et al. 2009; Taylor et al. 2008). A number of studies have found a positive correlation between extent of non-tremor symptoms (bradykinesia and rigidity) and cognitive impairment, including dementia (Iwasaki et al. 1989; Marttila and Rinne 1976; Reid et al. 1989) and impact on activities of daily living and quality of life (Appleman et al. 2011; Seichepine et al. 2011). Non-tremor symptoms may be associated with more rapid disease progression (Gasparoli et al. 2002), and specifically those with postural instability/gait dysfunction (PIGD) perform more poorly than tremor-dominant PD on visuospatial tasks such as judgment of line orientation and visuoconstruction of intersecting pentagons (Sollinger et al. 2010).

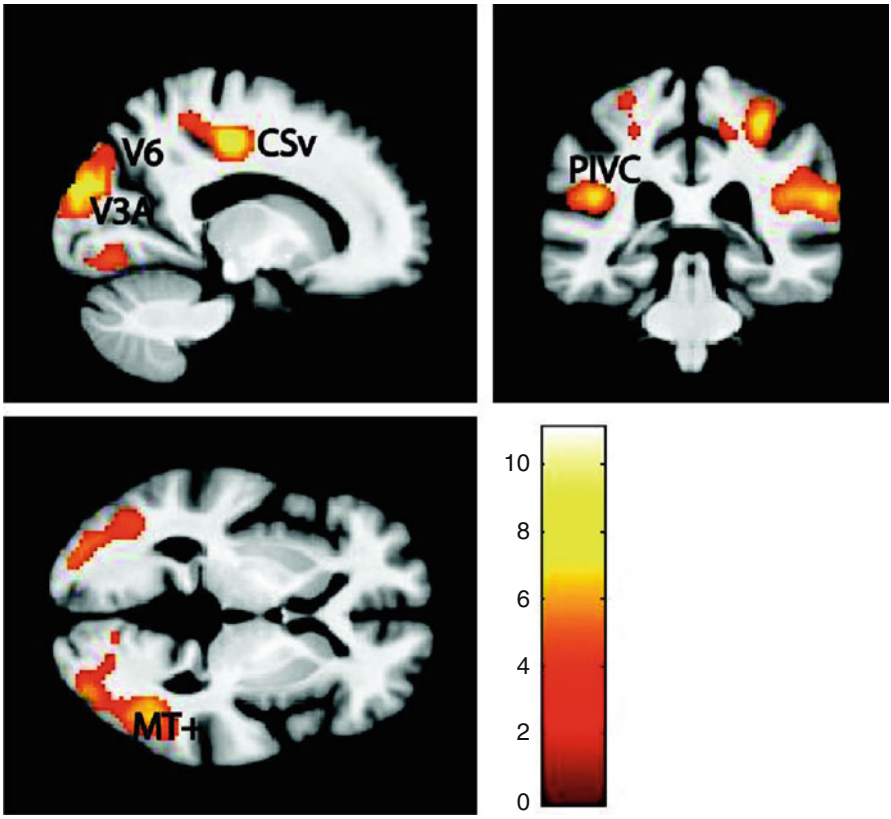


**Fig. 9.1** Optic flow network-group activation results. Whole group activation (control participants and PD together) in the optic flow network in response to a flow motion > random motion contrast. Optic flow network includes visual motion areas V6, V3A, and MT+, as well as visuo-vestibular areas parieto-insular vestibular cortex (PIVC) and cingulate sulcus visual area (CSv). The image shows significant activations at $p < 0.001$ cluster corrected with a 46 voxel extent threshold to $p < 0.01$ at MNI *xyz* [−17 −34 0]. Scale bar represents the *t* statistic. (From Putcha et al. 2014; *Frontiers in Integrative Neuroscience, 8 (57)*

Poor spatial vision, depth perception, peripheral vision, and visual processing speed in PD compared to control participants are more problematic to the non-tremor subtype in mild to moderate stages of PD (Seichepine et al. 2011), as is clock-drawing in regard to spatial arrangement of features (Seichepine et al. 2015).

We have known for over two decades that those with non-tremor dominant symptoms have more neural damage that those who are tremor-dominant (Paulus and Jellinger 1991). Emerging evidence focusing on more detailed pathological differences suggests substantially different neuropathological profiles in these groups. An FP-CIT (a isotopic ligand of dopamine reuptake sites) single photon emission computed tomography (SPECT) binding study revealed reduced dopaminergic projections to the dorsal putamen in non-tremor dominant patients and to the lateral

putamen and caudate nucleus in tremor-dominant patients (Eggers et al. 2011), implying differences in the progression of pathology. Some neuropsychological and animal studies have also suggested that non-tremor predominant symptoms are associated with the basal ganglia and cortico-striatal circuit dysfunction, whereas tremor may be associated with cerebellar, thalamic, and subthalamic nucleus abnormalities (Lewis et al. 2011; Mure et al. 2011; Weinberger et al. 2009).

With respect to neuroanatomical integrity, there are few and conflicting results focusing on non-demented PD patients as a whole, likely due to the cognitive variation of the subtypes of patients studied and the analysis methods used (Ibarretxe-Bilbao et al. 2009). Decreased cortical thickness in PD relative to a control group has been reported in the left superior frontal gyrus, left lateral occipital cortex, bilateral middle temporal gyrus, right isthmus of the cingulate cortex, right inferior parietal lobule (Pagonabarraga et al. 2013), ventrolateral prefrontal cortex, parieto-occipital sulcus (Tinaz et al. 2011), and left lateral orbitofrontal cortex (Ibarretxe-Bilbao et al. 2009). There is also some evidence of subcortical atrophy in the left hippocampus (Bruck et al. 2004). There is not yet a consensus on how focal cortical thinning and subcortical atrophy relate to motor symptom type-dominance in mild to moderate stages of PD, and it is not known how cognitive dysfunction maps onto specific patterns of structural changes in the brain.

## 9.4 Visual Perception in Parkinson's Disease

As described above, it is now well-known that even at early stages of the disease, PD leads to changes in multiple non-motor functions, including cognition and sensory function (Chaudhuri and Schapira 2009; Cronin-Golomb 2010). Because normal cognition depends upon the integrity of the sensory and perceptual systems, it is important to consider to what extent the sensory–perceptual domains are impacted by PD. Many studies demonstrate changes in visual perception in this disorder. For example, contrast sensitivity is reduced (Amick et al. 2003; Kupersmith et al. 1982; Pieri et al. 2000) for both temporally and spatially modulated sinusoidal gratings (Price et al. 1992). Some studies have indicated diminished contrast sensitivity across a range of spatial frequencies (Price et al. 1992), whereas others have demonstrated a loss of contrast sensitivity specifically at middle and high spatial frequencies (Bodis-Wollner et al. 1987; Mestre et al. 1990). Dysfunction in the visual system in PD is not limited to contrast sensitivity, but encompasses a wide range of perceptual abilities, including decreased color perception and discrimination, altered visual motion and optic flow perception, increased visual dependence, double vision, and visual misperceptions, illusions, and hallucinations (Armstrong 2008; Bodis-Wollner 2003; Davidsdottir et al. 2005, 2008; Putcha et al. 2014; Uc et al. 2005). Recent findings from our group also demonstrate that PD impairs the ability to perceive human motion (biological motion; Jaywant, Shiffrar et al. 2016; Jaywant, Wasserman et al. 2016c). Eye movement abnormalities in some individuals include hypometric saccades that undershoot targets, reduced saccade speed,

difficulty planning saccades, and slowed smooth pursuit movements, with the main difficulty being with antisaccades (shifting the eyes in the direction opposite the cue) rather than with prosaccades (reflexive shift in the direction of the cue) (Chan et al. 2005; White et al. 1983).

Such changes in visual perception have significant functional consequences for individuals living with PD. For example, reduced contrast sensitivity is associated with poorer spatial orientation, visuoconstructional ability, visuospatial learning and memory, and visual hallucinations (Davidsdottir et al. 2005; Uc et al. 2005). Saccadic abnormalities may prevent normal foveation and hence lead to problems in visuospatial attention (Bodis-Wollner et al. 2013). Visual hallucinations and feelings of presence and passage are, in and of themselves, distressing to individuals with PD and are also strongly associated with cognitive decline and dementia (Archibald et al. 2011). Additional functional consequences of impaired visual perception in PD include bumping into objects and doorways, difficulty reading, difficulty estimating spatial relations, navigational veering, and an impaired ability to carry out visually based activities of daily living (Davidsdottir et al. 2005, 2008; Seichepine et al. 2011; Young et al. 2010).

There has been extensive debate in the literature regarding the neural mechanisms of altered visual perception in PD, with evidence implicating changes in the retina, cerebral cortex, and subcortical regions of the brain. The presumed role of the retina follows from the observation of dopaminergic amacrine cells in the inner plexiform layer of the retina in healthy adults (Balasubramanian and Gan 2014). Amacrine cells are thought to coordinate bipolar cell to ganglion cell neurotransmission and parkinsonian alterations in their functioning cause an "inappropriately dark-adapted state, resulting in larger retinal ganglion cell receptive fields and affecting contrast sensitivity, color perception, and visual acuity" (Archibald et al. 2009). Evidence for the contribution of the retina to visual dysfunction in PD comes from studies demonstrating increased latencies of visual-evoked potentials to spatial-frequency-modulated gratings (Archibald et al. 2009; Kupersmith et al. 1982) as well as electrophysiological changes in the retina measured by electroretinograms (Gottlob et al. 1987). Furthermore, contrast sensitivity is enhanced at peak (middle) spatial frequencies in the "ON" vs. "OFF" medication state (Bodis-Wollner et al. 1987) and after levodopa administration (Bulens et al. 2004), suggesting that changes in dopamine may directly affect contrast sensitivity.

Despite the possible involvement of the retina and dopaminergic retinal pathways in visual dysfunction in PD, an explanation based solely on the retina is insufficient to explain PD-related impairments. For example, Trick et al. (1994) demonstrated that adults with PD have a deficit in discriminating the orientation of high spatial frequency gratings, which suggests a cortical mechanism because orientation is known to be processed in visual cortex. Individuals with PD also have reduced metabolic activity in the occipital cortex that is correlated with nigrostriatal dysfunction and not retinal impairment (Bohnen et al. 1999) as well as cortical thinning in occipital cortex that is associated with increased disease duration (Jubault et al. 2011). Further, cortical pathology (Lewy bodies, cortical thinning) has been reported for occipito-parietal areas, including unimodal visual cortex (Tinaz et al. 2011).

Studies on altered visual motion perception (as described in the next section) have demonstrated selective impairments in processing higher-order motion mediated by the dorsal visual stream (Castello-Branco et al. 2009; Ezzati et al. 2010). In addition to cortically mediated perceptual impairments, subcortical neural changes contribute to vision difficulties in PD. Saccade abnormalities in PD are thought to arise from excessive inhibition of the superior colliculus by the basal ganglia (substantia nigra pars reticulate), resulting in disrupted connectivity between the superior colliculus and frontal eye fields, which is normally crucial for preparing and initiating saccades (Diederich et al. 2014; Hikosaka et al. 2000; White et al. 1983). The ability to modulate the perception of bistable figures appears to depend on multiple brain regions, as well as being subject to neurotransmitter modulation (Díaz-Santos, Cao, Mauro et al. 2015a; Díaz-Santos, Cao, Yazdanbakhsh et al. 2015b). Together, these findings implicate cortical and subcortical abnormalities in additional to retinal dopamine in the visual perceptual changes in PD.

Diederich and colleagues (2014) recently proposed an innovative theory to unify these seemingly diverse visual symptoms in PD. They suggested that in PD, the primary visual pathway (geniculo-striate) connecting the retina to the lateral geniculate nucleus of the thalamus and primary visual cortex, and responsible for conscious vision, is intact. By contrast, two pathways responsible for non-conscious vision (the retino-colliculo-thalamo-amygdala pathway, which is the tecto-pulvinar pathway extended to the amygdala, and the retino-geniculo-extrastriate pathway, which is a structurally and functionally distinct pathway through lateral geniculate nucleus directly to extrastriate cortex) are dysfunctional and serve as the underlying neurobiological mechanism for altered visual perception in PD. Diederich et al. suggested that dysfunctional signaling in the retino-geniculo-extrastriate pathway could lead to the erroneous perception of static or moving beings and inappropriate guessing of stimuli in the periphery, resulting in hallucinatory experiences. A deficit in the retino-colliculo-thalamo-amygdala pathway may contribute to impaired emotional face recognition, particularly for negatively valenced emotional faces, which is commonly observed in PD (Alonso-Recio et al. 2014; Clark et al. 2008; Kan et al. 2002; Saenz et al. 2013).

## 9.5 Relation of Visual Perception to Cognition in Parkinson Disease

Some of the visuospatial cognitive impairments seen in PD may be related to changes in basic visual abilities. First, how egocentric visual motion, or optic flow, information is processed may affect spatial cognition. Optic flow displays can mimic flow field motion as it is experienced in everyday life and include visual information about our own movement (ego-motion) as well as the environment we are moving in Dukelow et al. (2001) and Durant and Zanker (2012). Functional MRI and psychophysical experiments have identified human cortical areas that are

selective to visual motion processing, including the MT complex, MT+ (Duffy 2009; Tootell et al. 1997). Area V6, located in the dorsal parieto-occipital sulcus, has been described as selectively responding to expanding egocentric flow field visual motion information in young adult humans (Cardin and Smith 2010; Pitzalis et al. 2006, 2010).

In addition to MT+ and V6, several other regions responsive to egocentric coherent motion in the parietal lobes have been identified. These include the cingulate sulcus visual area (CSv) (Cardin and Smith 2010; Fischer et al. 2012; Wall and Smith 2008) and vestibular regions thought to process visual input, such as the parieto-insular vestibular cortex (PIVC) and putative area 2v (p2v) (Cardin and Smith 2010). Areas of the parietal lobe and parieto-occipital sulcus are affected by PD pathology (Levin et al. 1991; Vaugoyeau and Azulay 2010), and behaviorally, individuals with PD have shown optic flow perceptual deficits that were associated with veering and navigation error (Davidsdottir et al. 2008; Young et al. 2010). Recently, we established that individuals with PD showed diminished activity compared to age-matched control participants, particularly within visual motion area MT+ and the visuo-vestibular region CSv, and that activation in CSv was associated inversely with disease severity (Putcha et al. 2014) (Fig. 9.2). These findings suggest that impairments in optic flow perception and visuospatial performance, as documented by behavioral testing, may result from abnormal neural processing within visual motion and visuo-vestibular regions in PD.

It is noteworthy that our behavioral testing of optic flow perception (Davidsdottir et al. 2008) indicated side-of-onset effects: LPD tended to perceive speed of flow in the left visual field as slower than in the right visual field, whereas RPD and healthy age-matched control participants perceived speed asymmetry in the opposite direction. The task was to adjust flow speed in one hemifield until the observer perceived that it matched that of the speed-constant hemifield—the point of subjective equality across hemifields (Fig. 9.3). The same LPD individuals perceived their egocentric midline to be right of center, which is reminiscent of what is experienced in unilateral hemispatial neglect, in which the perceived midline is shifted towards the ipsilesional hemispace (e.g., Chokron and Bartolomeo 1997; Karnath 1997; Karnath et al. 1991; Richard et al. 2004). Data from our imaging study of optic flow perception in PD described above came from a smaller sample and hence we were unable to examine brain activation patterns for LPD and RPD subtypes.

Of possible relevance to interpretation of perceptual effects in PD was our finding, with the same research participants, that both LPD and RPD were more visually dependent that healthy adults. That is, they were less able to disregard visual environmental information (when attempting to set a tilted line to horizontal). LPD were more visually dependent than RPD. Those who were more visually dependent showed a trend toward more bumping into doorways, by subjective report, and for the RPD group, the more visually dependent demonstrated more leftward lateral drift (veering when walking). These findings accord with longstanding evidence that PD patients rely on visual guidance when walking and for performing tasks with significant perceptual demands. They are also supported by our recent

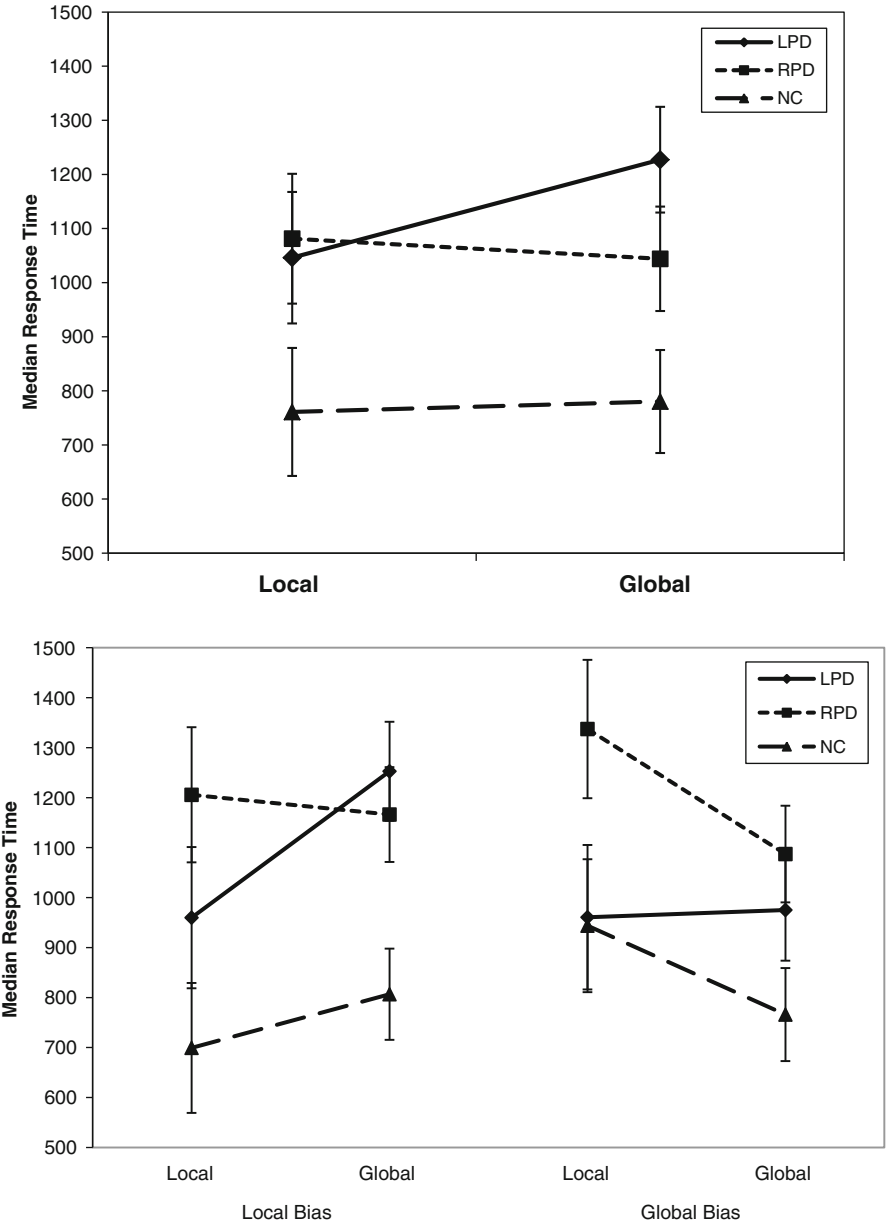


**Fig. 9.2** Hierarchical pattern perception results. (*Top*) Median RTs (ms) for the LPD, RPD, and control (NC) groups in the no-bias condition. (*Bottom*) Median RTs (ms) for the LPD, RPD, and NC groups in the biased-attention conditions. The left half of the graph represents median RTs to targets occurring at the global or local levels in the local-biased attention condition. The right half of the graph represents median RTs to targets occurring at the global or local levels in the global-biased attention condition. (From Schendan et al. 2009; *Behavioral Neuroscience, 123,* American Psychological Association)

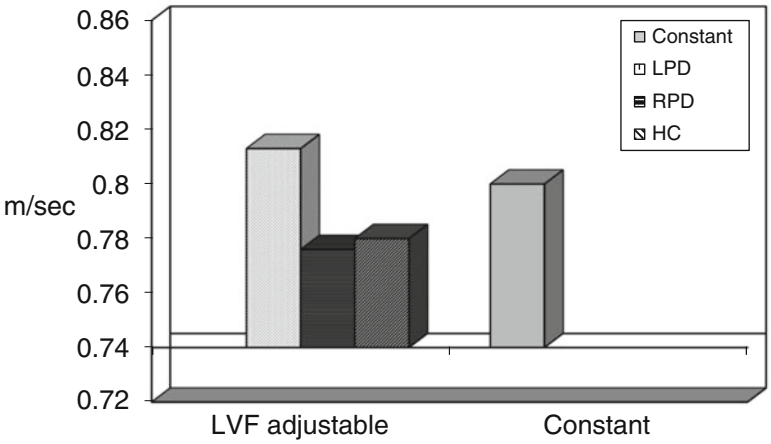


**Fig. 9.3** When optic flow speeds were equal in the two hemifields, RPD and HC (healthy control) perceived the speed of optic flow in the left visual field (LVF) to be faster than the speed of optic flow in the right visual field (RVF); that is, they thought the LVF flow speed should be slower in order to reach the point of subjective equality (PSE) with respect to constant flow speed in the RVF. By contrast, LPD tended to perceive the speed in the LVF as slower than the speed in the RVF; that is, they thought the LVF speed should be faster in order to attain the PSE with respect to the constant speed in the RVF. (From Cronin-Golomb 2010, *Neuropsychology Review, 20*, Springer)

report that those with PD are able to use appropriate low-level visual cues to enhance their ability to hold one percept of a bistable figure (Díaz-Santos, Cao, Mauro et al. 2015a).

Returning to egocentric midline perception, there have been a number of studies of hemifield biases relatively specific to LPD, including bisecting lines right of center (Lee et al. 2001), stimulus exploration that begins on the right rather than the left side (Ebersbach et al. 1996), and perception of objects on the left but not the right as smaller than their actual size (Harris et al. 2003). Our recent psychophysical investigation found no evidence of perceived spatial compression or reduced contrast discrimination (weakening of the visual signal) in the left visual field to explain rightward perceptual bias (Norton et al. 2015). In another study, we found no correlation of LPD line bisection bias with thinning of the retinal nerve fiber layer, as measured with optical coherence tomography, or with retinal function, as measured with frequency doubling technology (Laudate et al. 2013). In the latter study, eye movement recordings suggested that LPD explored the right side more than the left side of the line to be bisected (Fig. 9.4). Taken together, these results suggest that observed rightward perceptual bias in LPD presumably arises not from retinal or low-order cortical dysfunction, but rather from higher-order attentional difficulties. We have also found more fixations in the right visual field by PD patients (not LPD specifically) than a control group when categorizing the emotion of faces (fear) (Clark et al. 2010), suggesting that hemifield biases may not be restricted to LPD (as also discussed in Norton et al. 2015).

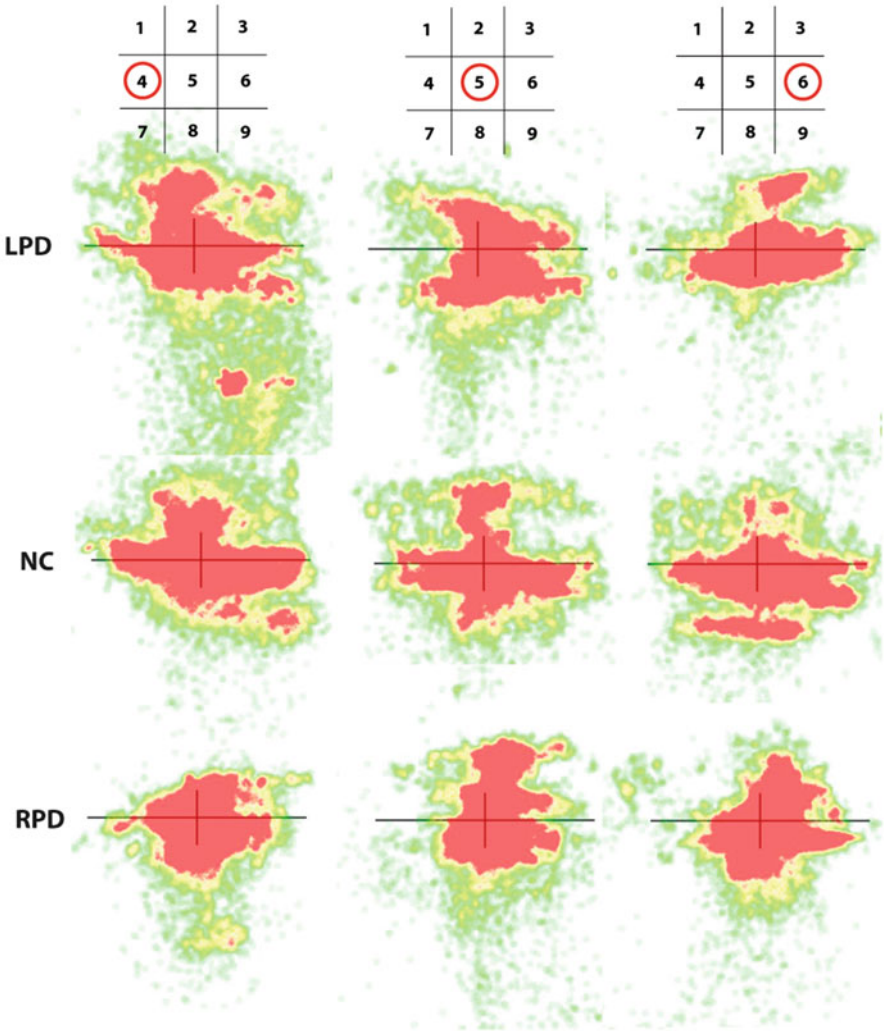


**Fig. 9.4** Eye tracking "heat map" representations for horizontal line bisection at left, center, and right visual field positions. See schematics at top of columns for positions, which is where participants looked while performing the line bisection task. Colors closer to the red end of the spectrum indicate the most time spent looking at those areas, and "cooler" colors indicate progressively less looking time. At center and right positions, LPD scanning appeared to be shifted rightward compared to the control group (NC). RPD exhibited compression of the scanning area along the line. *NC* normal control participants, *LPD* left body-onset Parkinson's disease, *RPD* right body-onset Parkinson's disease. (From Laudate et al. 2013, *Behavioral Neuroscience, 127, 151–163*, American Psychological Association)

## 9.6 Perception-Action Coupling in PD

As reviewed above, visual perception deficits are common in PD. The perception of human movements and actions in particular may be altered in PD because of the close association of motor function and visual perception, referred to as perception–action coupling. Researchers have investigated the role of the subthalamic nucleus (STN) in action observation in individuals with PD who underwent deep brain stimulation surgery. These studies revealed that oscillatory activity in the STN is modulated by action observation, and that observing and executing movements are associated with similar changes in STN electrical activity and coherence between the STN and neocortex (Alegre et al. 2010; Marceglia et al. 2009). These findings suggest a role for cortico-basal ganglia-thalamocortical loops in the perception of human actions.

It is reasonable to postulate that in individuals with PD with disrupted activity in the STN (i.e., who have not had deep brain stimulation surgery), action observation and understanding may be affected by altered synchronous neural activity. Indeed, behavioral evidence indicates dysfunction in perception–action coupling in PD. Healthy adults show motor facilitation when executing an action that is congruent with a previously observed action (visuomotor priming), as when viewing the motion of a hand (an index finger moving up or down) and then having to perform the same hand motion themselves; individuals with PD do not show this facilitation (Poliakoff et al. 2007). This lack of perception–action facilitation appears to be specific to movements that are no longer in the PD motor inventory. In one study, observers with PD viewed another person (who either did or did not have PD) grasping an object, and then had to grasp the object themselves. Grasping was improved only after the PD observers viewed the same action performed by an individual with PD, suggesting that visuomotor priming occurs only when the observed action is in the PD observers' motor repertoire (Castiello et al. 2009). The literature is not consistent in providing evidence for such a perception–action link in PD, however. Our group found that although biological motion perception was impaired in PD (Jaywant, Shiffrar et al. 2016 in regard to walking; Jaywant, Wasserman et al. 2016 in regard to social gestures), the deficit was not associated with PD motor symptoms, but was more likely related to difficulties in the integration of visual form and motion cues. In an intervention study, absence of visual–motor learning was suggested by the finding that perceptual training to discriminate normal from parkinsonian gait did not result in objective improvement in walking, though it did lead to self-reported increases in functional mobility (Jaywant, Ellis et al. 2016).

Together, these studies suggest that changes in action observation in PD may be related to basal ganglia-mediated motor dysfunction, but may also arise from altered processing in cortical areas that support visual perception. Further understanding perception–action coupling as it relates to pathways supporting complex visual perception will be important in designing and refining targets for intervention.

## 9.7 Concluding Remarks

In this chapter, we have discussed neural network organization in PD, as well as changes in cognition and in the sensory and perceptual processes that affect cognitive abilities in PD. The ubiquity of some degree of cognitive impairment in PD underscores the urgency of the need to develop treatments. Not only does quality of life suffer as a result of direct cognitive problems, but these problems are also relevant to gait and falls in PD. The consequences of gait impairments are substantial and include increased disability, increased fall risk, and reduced quality of life (Shulman 2010). Gait abnormalities are exacerbated under dual-task conditions requiring the simultaneous performance of cognitive tasks (Fuller et al. 2013). Dual-task walking deficits in PD, including reduced gait speed, step length, alterations in cadence, and increased gait variability, have been associated with impairments in executive function, set-shifting, and attention (Lord et al. 2010; Plotnik et al. 2011; Rochester et al. 2004). This is particularly important in PD where there is a need for increased reliance on cognitive resources to control gait and posture due to the reduced movement automaticity associated with basal ganglia dysfunction (Kelly et al. 2012; Takakusaki et al. 2004). When two tasks are performed concurrently in persons with PD, competition for limited resources results in dual-task interference and deterioration in performance of one or both tasks (Power et al. 2012; Woollacott and Shumway-Cook 2002).

To date, interventions for cognitive deficits in PD include pharmacologic and, more recently, cognitive training. PD medications for motor symptoms largely do not reduce cognitive impairments, and although acetylcholinesterase inhibitors have shown some encouraging results (Seppi et al. 2011), none have proven effective for those with mild cognitive disturbance (Barone et al. 2011). They also have significant side effects (e.g., nausea, vomiting, and weight loss) and may be quite expensive to maintain over the duration of the disorder (Bond et al. 2012).

Cognitive training programs that aim to enhance specific cognitive processes through repeated practice are inexpensive and have no significant side effects. Additionally, they can be individually tailored, performed at home, and allow for remote supervision by a clinician/therapist. This approach may be particularly relevant in PD because cognitive training has been associated with increased dopamine release (Backman et al. 2011). Though only a handful of cognitive training studies have been performed in PD (reviewed in Calleo et al. 2012), the preliminary reports have been positive. For example, Sinforiani and colleagues (2004) had PD patients perform a 6-week program aimed at improving attention, abstract reasoning, and visuospatial ability. Participants showed improvement on some tasks, which remained stable for 6 months, but there was no control group, and training failed to enhance inhibition, set shifting, or working memory, key aspects of executive functioning deficient in PD. Paris and colleagues (2011) had individuals with PD perform a 4-week program targeting selective attention, working memory, processing speed, psychomotor speed, executive functioning, and visuospatial processing. Compared with the control group who performed speech therapy, the

experimental group improved on standard tests of attention, processing speed, memory, visuospatial processing, and executive functions, but not on self-reported cognitive difficulties in activities of daily living, and there was no follow-up to assess the longevity of the effects. Edwards and colleagues (2013) conducted 3 months of speed of processing training (SOPT) with 87 individuals with PD. Compared to a test–retest control group, SOPT improved PD performance on useful field of view (a measure of visuospatial processing and speed of processing). There was no alternative training or active-placebo condition to contrast with SOPT, and the improvements did not generalize to executive functions or everyday life (Chou and Cronin-Golomb 2013). In sum, although cognitive training programs show promise, there is a need for both additional interventions that target key PD cognitive impairments and better-designed studies such as those that include matched active control training conditions.

Greater attentional capacity and control with flexible allocation of attention between tasks could potentially improve performance in both cognitive and gait domains (Kelly et al. 2012). Because deficits in sustained attention (i.e., continuously engaging in attention-demanding tasks over a period of minutes and avoiding distraction) and inhibitory control (i.e., stopping an automatic behavior) are quite common in PD (Luque-Moreno et al. 2012; Obeso et al. 2011), and because these capacities may underlie higher aspects of attention, executive functioning, and cognitive ability in general (Sarter et al. 2001), these deficits may modulate many other PD cognitive impairments. For example, task switching (e.g., as measured by Wisconsin Card Sorting Task) may require the inhibition of competing stimulus-response links specified by the now inappropriate task (Rogers and Monsell 1995). Furthermore, decreased ability to sustain attention has been linked to deficits in visuospatial processing in healthy individuals (Matthias et al. 2009) as well as in individuals suffering from severe visuospatial deficits such as spatial neglect (Robertson et al. 1997). In a proof-of-concept study, we recently reported a case series of four individuals with PD who underwent training of sustained attention, which reduced spatial bias on a visual search task (DeGutis et al. 2016). Hence, enhancing inhibitory control and sustained attention in PD could improve several cognitive domains beyond these specific processes as well as tasks that require cognitive–motor integration.

Finally, the use of noninvasive brain stimulation techniques such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) have gained increasing traction as neuromodulatory approaches to enhance cognition in neurological disorders (Fregni and Pascual-Leone 2007). With respect to PD, one study used tDCS to increase cortical excitability over the dorsolateral PFC, while adults with PD completed an n-back working memory task, and found improved working memory performance following electrical stimulation as compared to a sham stimulation condition (Boggio et al. 2006). Another investigation found that tDCS over bilateral dorsolateral PFC led to a sustained 1-month improvement on the Trail Making Test part B (a measure of executive function, set shifting, and working memory) compared to sham stimulation (Doruk et al. 2014). The use of noninvasive brain stimulation coupled with the cognitive training interventions described above may hold particular promise for improving cognitive function in PD.

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