Functional Neuroimaging in Parkinson's Disease

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The use of functional imaging in neurodegenerative diseases has increased in recent years, with applications in research into the underlying pathophysiology, aiding in diagnosis, or evaluating new treatments. In Parkinson's disease (PD), these imaging methods have expanded our understanding of the disease beyond dopaminergic deficits. Moreover, functional imaging methods have described alterations in functional networks relating not only to the motor symptoms, but also to many nonmotor features of PD, such as cognitive dysfunction. From a clinical viewpoint, functional imaging methods can assist in monitoring disease progression, such as in the context of clinical trials, and holds the potential to aid in early diagnosis of PD and differentiation from other parkinsonian disorders.

Structural and functional neuroimaging has long been used in the study of neurological disorders to elucidate disease mechanisms, to aid in diagnosis, and to assess potential new therapies. Clinical and research applications of functional neuroimaging to Parkinson's disease (PD) and other parkinsonian disorders have advanced over the past decade, leading to novel diagnostic methods and contributing to the development of new therapies. This article will review how such imaging has been applied to the study of PD.

The defining pathologic characteristic of PD is the progressive loss of nigrostriatal dopaminergic function, leading to downstream changes in basal ganglia circuitry. Although direct imaging of the dopaminergic system with positron emission tomography (PET) or single-photon emission computed tomography (SPECT) can be valuable for assessing PD, there has also been great interest in understanding the functional consequences of dopaminergic pathology.

Moreover, the symptoms of PD extend beyond the cardinal features of tremor, bradykinesia, and rigidity to other domains, including nonmotor symptoms. These manifestations of the disease cannot be attributed to simple dysfunction of the basal ganglia, but rather to widespread functional abnormalities involving a number of neuronal circuits (DeLong and Wichmann 2007). Accordingly, functional imaging with MRI (fMRI), PET, and SPECT has increasingly been used to assess neuronal connectivity, rather than focusing on single neurotransmitter systems. Moreover, functional imaging is not only able to study the processes underlying PD symptoms, but also can be applied to detecting subclinical and early disease and monitoring disease progression.

In this work we will briefly describe the principles behind PET, SPECT, and fMRI imaging and discuss the role of such imaging in assessing both motor and nonmotor features of

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PD. To date, the use of functional imaging in parkinsonian disorders has been largely restricted to research applications, which will be the focus of the article. We acknowledge that increasing efforts have been made to use these techniques in clinical practice (Poston 2011), but will not describe these in detail. Clinical applications include monitoring of preclinical disease (Tang et al. 2010a), studying at-risk populations (Piccini et al. 1999; Albin et al. 2000; Eisensehr et al. 2000; Ponsen et al. 2004; Sommer et al. 2004; Adams et al. 2005; Stiasny-Kolster et al. 2005), and using imaging as an adjunct method in diagnosis (Tang et al. 2010b). Last, functional imaging has been used in a number of clinical trials relating to PD (see Niethammer and Feigin 2011 for more information).

AN OVERVIEW OF FUNCTIONAL IMAGING TECHNIQUES

Radiotracer Imaging

PET and SPECT imaging use a number of radiotracers for in vivo assessment of normal and abnormal brain function. These techniques have been extensively used to study the dopamine system in parkinsonian disorders, but other neurochemical systems (e.g., cholinergic, serotonergic) can also be investigated. Cerebral blood flow and glucose utilization can be mapped with radio-labeled water or glucose (Dhawan and Eidelberg 2006).

In general, SPECT imaging is less expensive and more widely available than PET imaging. Routine SPECT can be performed in most nuclear medicine departments, and many radiopharmaceuticals are commercially available, obviating the need for an on-site cyclotron. However, PET has superior spatial resolution and higher sensitivity than SPECT. In regard to parkinsonian disorders, the resolution in SPECT limits the separation of caudate and putamen. The higher sensitivity of PET allows for shorter imaging times with less patient motion artifacts. Last, the short half-life radiotracers used in PET imaging make it feasible to perform multiple studies on the same subject on a single day.

In parkinsonian disorders, abnormalities of the storage and release of dopamine in the striatum occur as a consequence of dysfunction and cell loss in the substantia nigra. Dopaminergic imaging, therefore, can have utility in assessing severity of disease. The mechanisms by which these tracers function can be understood by examining the pathways of dopamine production, release, and reuptake.

The first step of dopamine synthesis in nigrostriatal neurons involves the conversion of tyrosine to L-3,4-dihydroxyphenylalanine (L-dopa), which is further converted to dopamine (DA) by aromatic amino acid decarboxylase (AADC). Levodopa given exogenously as part of dopaminergic therapy is actively taken up before its conversion to dopamine. Dopamine is then packaged into synaptic vesicles by the vesicular monoamine transporter type 2 (VMAT2). After release into the synaptic cleft, DA interacts with post- and presynaptic dopamine receptors, and is then either metabolized or recycled and taken back into the presynaptic terminal by the membrane dopamine transporter (DAT). Multiple radiotracers have been developed that can evaluate pre- or postsynaptic dopaminergic function (see Table 1 in Niethammer and Eidelberg 2012). Given the prominent nigrostriatal pathology, radioligand imaging of the dopaminergic system has been the most widely studied in PD. However, many other neurochemical systems such as serotonergic, adrenergic, or cholinergic can also be imaged using PET and SPECT (Brooks 2005).

[^{18}F]-fluorodeoxyglucose (FDG) PET provides a means for imaging cerebral glucose metabolism, reflecting regional synaptic activity. In parkinsonian disorders, spatial covariance methods have allowed for the detection of symptom-specific or disease-specific patterns that can be used to evaluate disease progression, diagnosis, or treatment effects. Because regional blood flow and cerebral metabolism tend to be largely linked in many neurodegenerative disorders, such pattern analysis can be applied to PET and SPECT imaging of cerebral perfusion as well (e.g., [^{15}O]-water PET or [$^{99\text{m}}\text{Tc}$]-technetium-ethylene cysteinyl dimer SPECT) (Feigin et al. 2002; Hirano et al. 2010).

Radioligand imaging also has the potential to directly visualize pathology in neurodegenerative disorders, although to date applications have been limited in parkinsonian disorders. Specifically, in vivo imaging of Lewy bodies can be accomplished with α -synuclein ligands such as 2-(1-[6-[(2-[^{18}F]fluoroethyl)(methyl)amino]-2-naphthyl] ethylidene) malononitrile (FDDNP) (Smid et al. 2006), or [^{18}F]-BF22 (Fodero-Tavoletti et al. 2009). However, neither of these ligands are specific for α -synuclein. They also bind to β -amyloid, necessitating separate imaging and image subtraction with ligands specific for β -amyloid, such as [^{11}C] benzothiazole-aniline (Pittsburgh Compound B, PIB) (Gomperts et al. 2008; Maetzler et al. 2008; Burack et al. 2010).

Functional Magnetic Resonance Imaging (fMRI)

fMRI is widely available and does not require the injection of a radiotracer, thus not imposing a limit on the number of scans that can be performed. It has high spatial and temporal resolution, which is useful for measuring dynamic changes in neural activity. fMRI detects the presence of deoxygenated hemoglobin. Interaction of deoxyhemoglobin with water molecules surrounding blood vessels results in a change in the proton signal, the blood oxygenation level-dependent (BOLD) contrast. Increased local metabolic demand results in an increase in focal blood flow, which results in a relative decrease in deoxyhemoglobin and an increase in BOLD signal. Although this is thought to reflect local neuronal activity, unlike radiotracer imaging, fMRI does not measure an easily understood quantity and has a poor signal-to-noise ratio.

More recently, resting-state fMRI has emerged as a potential means of elucidating functional brain architecture (Fox and Raichle 2007; Margulies et al. 2010). This method measures spontaneous fluctuations in the BOLD signal. Regional correlations in these spontaneous fluctuations are then assumed to reflect anatomical and/or functional connectivity across those brain regions. In its simplest form, the BOLD

signal fluctuations from an a priori seed region of interest are correlated to all other brain voxels. In response to the limitation imposed by a single seed, other approaches such as hierarchical clustering, which creates a correlation matrix from multiple seeds (Achard et al. 2006; Fox and Raichle 2007), or independent component analysis (ICA) (van de Ven et al. 2004; Damoiseaux et al. 2006; Margulies et al. 2010) have been developed to analyze functional connectivity across brain regions. Other methods, such as regional homogeneity (Zang et al. 2004), make no assumption on connectivity, but rather measure local activity. To date, limited resting-state studies have been systematically applied to PD (e.g., Wu et al. 2009; Helmich et al. 2010).

FUNCTIONAL IMAGING OF MOTOR SYMPTOMS AND MOTOR PHYSIOLOGY

Dopaminergic Dysfunction and Motor Symptoms

Dopaminergic imaging can be used to directly study the integrity of the nigrostriatal system in PD. [^{18}F]-6-fluorodopa (FDOPA) PET measures the activity of AADC, thereby providing a means for quantifying the density of dopaminergic nerve terminals. Striatal FDOPA uptake is consistently and significantly reduced in patients with PD and other parkinsonian disorders (Brooks et al. 1990; Eidelberg et al. 1990; Vingerhoets et al. 1994; Thobois et al. 2004), and correlates with pathological measures (Snow et al. 1993). The reduction is not uniform throughout the striatum, with the smallest reduction in the caudate and an anterior-posterior gradient in the putamen (Morrish et al. 1996; Nurmi et al. 2001). Additionally, the reduction is asymmetrical, being more pronounced on the brain hemisphere contralateral to the more severe motor signs (Brooks et al. 1990; Eidelberg et al. 1990; Vingerhoets et al. 1997; Benamer et al. 2000; Pirker 2003; Filippi et al. 2005). Other radiotracers that provide measures of presynaptic dopaminergic function (e.g., DAT and vesicular monoamine transporter [VMAT] ligands), show similar findings, and all decline with dis-

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ease progression (Vingerhoets et al. 1994; Hirano et al. 2010).

The degree of FDOPA reduction does not reflect all motor symptoms equally, but appears most strongly correlated with bradykinesia and, to a lesser extent, rigidity (Brooks et al. 1990; Eidelberg et al. 1990). Putaminal rather than caudate FDOPA uptake appears more closely related to motor function (Muller et al. 2000; Rinne et al. 2000; Ribeiro et al. 2002). Similarly, imaging of the dopamine transporter system (DAT) correlates with measures of bradykinesia, rigidity, gait, and facial expression (Pirker 2003). Interestingly, tremor, which is not uniformly responsive to dopaminergic therapy, does not appear to be correlated with dopaminergic deficits (Eidelberg et al. 1995a; Benamer et al. 2003; Pirker 2003; Isaías et al. 2007; Mure et al. 2011). Gait dysfunction also may not relate directly to dopaminergic loss. Bohnen et al. reported that cortical and thalamic cholinergic hypofunction rather than dopaminergic denervation is associated with fall risk in PD, perhaps relating to thalamic innervation from the pedunculopontine nucleus (PPN) (Bohnen et al. 2009). At least one study suggests that extrastriatal monoaminergic function as measured by FDOPA PET declines independently of the nigrostriatal system, although correlation of this decline with motor or nonmotor symptoms has not been established (Pavese et al. 2011).

Metabolic Networks and the PD-Related Motor Patterns

FDG PET provides a means for mapping spatially distributed regional changes in cerebral glucose metabolism, and potentially relating these changes to specific diseases and symptoms. Spatial covariance analysis has been extensively used to detect network-level functional abnormalities in a variety of neurodegenerative disorders, including PD (Eidelberg et al. 1994; Eckert et al. 2007b), atypical parkinsonian syndromes such as multiple system atrophy (MSA) and progressive supranuclear palsy (PSP) (Eckert et al. 2008; Spetsieris et al. 2009), Huntington's disease (Feigin et al. 2007), and dementia (Huang et al. 2007a; Habeck et al. 2008). The details of this method

based on principal component analysis (PCA) have been reviewed elsewhere (Eidelberg 2009; Habeck and Stern 2010; Spetsieris and Eidelberg 2011). Briefly, the scaled subprofile model (SSM), a double-centered log-normalized PCA, is applied to multivoxel metabolic imaging data in a combined sample of scans from healthy subjects and patients. Once a pattern is identified that distinguishes one group from the other, its expression can be prospectively quantified on an individual basis (Spetsieris et al. 2006; Ma et al. 2007), and the resulting subject scores (i.e., the PCA scalars) can be correlated with clinical and physiological measures of interest.

Applying this method to resting-state FDG PET scans from PD patients has consistently revealed an abnormal disease-related spatial covariance pattern involving elements of the CSPTC circuitry (Eidelberg et al. 1994; Moeller et al. 1999; Eidelberg 2009). This Parkinson's disease-related pattern (PDRP) is characterized by increased pallido-thalamic and pontine metabolic activity and relative reductions in pre-motor cortex, supplemental motor area, and parietal association regions (Fig. 1A). PDRP expression does not simply discriminate patients with PD from healthy subjects, but also distinguishes between PD and atypical parkinsonian syndromes (see below). The PDRP topography has been identified in several independent patient populations (Moeller et al. 1999; Eckert et al. 2007a). Subject scores denoting pattern expression in individual patients have been found to show excellent within-subject reproducibility on test–retest evaluation (Ma et al. 2007). Because metabolism and cerebral blood flow are coupled, at least in the absence of dopaminergic medication (Ma et al. 2007; Hirano et al. 2008), PDRP expression can also be measured in scans of resting cerebral perfusion obtained with [^{15}O]H $_2$ O PET (Ma and Eidelberg 2007; Ma et al. 2007), $^{99\text{m}}\text{Tc}$ -ethylcysteinate dimer (ECD) SPECT (Feigin et al. 2002; Eckert et al. 2007b), or with arterial spin labeling MRI methods (Huang et al. 2007a; Melzer et al. 2011).

Individual subject PDRP expression values reproducibly correlate with Unified Parkinson's Disease Rating Scale (UPDRS) motor ratings (Eidelberg et al. 1994, 1995b; Feigin et al. 2002;

Figure 1. Abnormal metabolic networks in Parkinson's disease. (A) Parkinson's disease-related pattern (PDRP). This motor-related metabolic spatial covariance pattern is characterized by hypermetabolism in the thalamus, globus pallidus (GP), pons, and primary motor cortex, associated with relative metabolic reductions in the lateral premotor (PMC) and posterior parietal areas (Ma et al. 2007). (In the representative slices, relative metabolic increases are displayed in red; relative metabolic decreases are displayed in blue. Slices were overlaid on a standard MRI brain template.) (From Eidelberg 2009; reprinted, with permission, from Elsevier © 2009.) (B) PD tremor-related metabolic pattern (PDTP) identified using a within-subject network analysis of FDG PET scans from nine tremor-dominant PD patients scanned at baseline and during ventral-intermediate (Vim) thalamic deep brain stimulation (DBS) (Mure et al. 2011). This pattern is characterized by covarying increases in the metabolic activity of the sensorimotor cortex (SMC), cerebellum, pons, and the putamen. (From Mure et al. 2011; reprinted, with permission, from Elsevier © 2011.)

Lozza et al. 2004; Asanuma et al. 2006; Eidelberg 2009). Like dopaminergic imaging, abnormally elevated PDRP subject scores correlate mainly with bradykinesia and rigidity, rather than tremor (Antonini et al. 1998; Isaías et al. 2010; Mure et al. 2011). Moreover, these observations relate the abnormal PDRP functional topography to degeneration of nigrostriatal dopaminergic pathways (Eidelberg et al. 1990; Tang et al. 2010a). Of note, a similar pattern has recently been described in a 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) primate model of parkinsonian bradykinesia and rigidity (Peng et al. 2010; Ma et al. 2011).

PDRP expression increases continuously over time, in association with deterioration in motor function as well as putaminal dopaminergic function. The PDRP can be quantified separately in each hemisphere, and similar to dopaminergic imaging, PDRP expression is asymmetric, being worse on the side contralateral to the more affected body side (Eidelberg et al. 1995a; Tang et al. 2010a). Progression over time is similar in both hemispheres, preserving the initial

asymmetry (Tang et al. 2010a). In addition, PDRP expression in individual subjects (i.e., the "subject scores") has been found to correlate consistently with UPDRS motor ratings in multiple PD patient populations (Eidelberg et al. 1994, 1995b; Feigin et al. 2002; Lozza et al. 2004; Asanuma et al. 2006; see Eidelberg 2009). Nevertheless, correlations between longitudinal declines in presynaptic dopaminergic function, clinical deterioration, and increases in PDRP expression with advancing disease are modest ($R^2 \sim 30\%–40\%$), suggesting that these progression indices are not interchangeable (Eckert et al. 2007a; Huang et al. 2007a). Indeed, PDRP spatial topography conforms to the large-scale changes in regional synaptic activity predicted by experimental models of CSPTC circuitry (DeLong and Wichmann 2007). The biological relevance of PDRP is underscored by its relation to surgical treatments (Asanuma et al. 2006). For example, intraoperative recordings of subthalamic firing rates correlate closely with preoperative measurements of PDRP expression (Lin et al. 2008). Subthalamic lesioning and deep

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brain stimulation (DBS) both result in PDRP reductions of similar magnitude to those seen with levodopa treatment (Asanuma et al. 2006; Trost et al. 2006; Pourfar et al. 2009; Mattis et al. 2011).

Parkinsonian tremor has been linked to its own discrete spatial covariance pattern. A PD tremor-related pattern (PDTP) was identified using ordinal trends/canonical variates analysis (OrT/CVA) (Habeck et al. 2005), a within-subject network mapping algorithm based on supervised (i.e., guided) PCA methods. FDG PET scans were acquired in tremor-predominant PD patients at baseline (tremor present) and during high-frequency stimulation (tremor suppressed) of the ventral-intermediate (Vim) thalamic nucleus (Mure et al. 2011) (Fig. 1B). This reproducible pattern is characterized by increased metabolic activity in the cerebellum and dorsal pons, primary motor cortex, and in the caudate and putamen. PDTP expression correlates with accelerometric tremor measurements and UPDRS tremor subscale ratings, but not with UPDRS akinesia-rigidity subscale ratings.

Resting Studies of Motor Symptoms and Altered Motor Circuit Connectivity

In recent years, resting-state imaging has been more extensively used in the investigation of brain disorders. Scanning PD patients at baseline, Helmich et al. (2010) found reduced functional connectivity in pathways linking the posterior putamen and in the inferior parietal cortex in PD patients, whereas connectivity between the anterior putamen and the pre-MSA, and between the caudate nucleus and the dorsal prefrontal cortex did not differ from normal. Other studies have not found reductions in functional connectivity in untreated PD. Rather, the data revealed normalization of baseline increases in cortico-striatal functional connectivity by dopaminergic treatment (Kwak et al. 2010). In addition to the pathways constituting the classical cortico-striato-pallido-thalamocortical (CSPTC) circuit model of motor pathways, recent attention has focused on the role the so-called “hyperdirect” pathway between motor cortex and STN plays in the motor physiology of PD (Brown et al. 2001; Priori et al.

2004; Bronte-Stewart et al. 2009). PD patients have been found to have increased resting-state functional connectivity between the STN and cortical motor regions (Baudrexel et al. 2011). Subgroup analysis revealed differences between PD patients with and without tremor: Compared to controls, tremor patients showed increased STN connectivity with the hand area of the primary motor cortex and the primary sensory cortex, whereas nontremor patients also had increased connectivity between the STN and midline cortical motor areas (Baudrexel et al. 2011). In this vein, tremor in PD has been related to transient increases in functional connectivity between the basal ganglia and motor cortex (Helmich et al. 2010). In PD patients with tremor, activity within the cerebellar pathways co fluctuates with tremor amplitude, whereas the globus pallidus (GPi and GPe), and putamen are transiently activated at the onset of tremor episodes. These data suggest that tremor in PD results from abnormal interactions between the basal ganglia and the cerebellothalamocortical circuit (Helmich et al. 2010).

Motor Complications of Therapy—Dyskinesias

Treatment of PD with levodopa is highly effective, but prolonged treatment will lead to motor and nonmotor complications in the majority of patients. Among these, levodopa-induced dyskinesias (LID) occur in up to 90% of PD patients after 9 yr of treatment (Ahlskog and Muentner 2001; Rajput et al. 2002). The risk of developing LID is associated with earlier age of onset, longer disease duration, as well as duration and dose of levodopa treatment (Fabbrini et al. 2007). A major feature of LID appears to be overactivity of the direct striatal pathway, but the pathophysiology of LID is complex, likely involving both pre- and post-synaptic alterations in the nigrostriatal system (Cenci and Lundblad 2006; Cenci and Lindgren 2007). Presynaptic dopaminergic denervation is presumed to be necessary for the development of LID, illustrated by the fact that healthy subjects with an intact presynaptic dopaminergic system do not develop LID (Constantinescu

et al. 2007). Moreover, the development of LID presumably relates to an interaction between the endogenous dopaminergic denervation and application of levodopa, an exogenous dopamine precursor (Cenci and Lundblad 2006). Indeed, rodent and other animal models of LID have shown that abnormal presynaptic handling of levodopa as well as hyperactive postsynaptic dopamine responses play a role in LID (Cenci and Lindgren 2007). Pulsatile levodopa administration with rapid increase in synaptic dopamine concentrations appears to increase the risk of LID in animal models and PD patients (Smith et al. 2003; Pavese et al. 2006; Lindgren et al. 2010), and once established, there is a higher propensity for them to return even after prolonged interruption of treatment (Cenci and Lundblad 2006). Because peak-dose LID can be reliably triggered in many patients by levodopa administration, functional imaging has been able to add further insights into this complication of therapy.

On the presynaptic side, reduced FDOPA uptake (presumably reflecting greater disease severity) is associated with increased dyskinesia severity (Linazasoro et al. 2004). That study also suggested involvement of postsynaptic dopamine D₂ receptor availability as measured with [¹¹C]-raclopride PET (Linazasoro et al. 2004). Similarly, in a longitudinal study of levodopa versus ropinirole, patients treated with the agonist had less reduction in putaminal FDOPA uptake, with a lower incidence of LID (Whone et al. 2003). However, striatal dopaminergic denervation is not sufficient for the development of LID. Comparing patients with LID on low-dose levodopa with patients without LID on high-dose levodopa, Linazasoro et al. (2009) found equally reduced striatal DAT binding. Dopamine turnover may play a role in this regard. Early in the disease, synaptic dopamine turnover has been found to be increased when estimated by kinetic modeling of FDOPA time-activity curves (TACs) over prolonged scanning epochs (Sossi et al. 2002, 2004). The relative increase in dopamine turnover observed in early-stage disease was even more pronounced in younger patients, possibly contributing to larger swings in dopamine levels, which explains the

greater susceptibility to motor complications seen in those patients (Sossi et al. 2006). Higher synaptic dopamine levels in patients with LID were also shown using [¹¹C]-raclopride PET, and the size of the levodopa-mediated change in radioligand binding affinity correlates with dyskinesia severity (de la Fuente-Fernandez et al. 2004; Pavese et al. 2006). Of note, a multi-tracer study of VMAT and DAT binding revealed relative down-regulation of dopamine reuptake compared to nerve terminal loss (Troiano et al. 2009). This adaptation may help with symptoms early in the disease course, but can give rise to oscillatory synaptic dopamine and concomitant motor complications as the disease progresses. Animal studies have suggested an increase of D₁ receptor numbers in response to long-term levodopa treatment (Rioux et al. 1997). However, consistent changes in striatal D₁ and D₂ neuroreceptor binding have not been shown in human PD patients (Turjanski et al. 1997; Dentresangle et al. 1999).

Other neurotransmitter systems have been implicated in the development of LID based on animal or postmortem studies. These include the opioid system, which acts as a modulator of dopamine and a cotransmitter within GABAergic neurons (Fox et al. 2006; Hallett and Brotchie 2007), the adenosine system (Calon et al. 2004), the serotonergic system (Carta et al. 2007; Carlsson et al. 2009), and the α₂ adrenergic system (Fox et al. 2001; Rascol et al. 2001). Piccini et al. (1997) found reduced binding of [¹¹C]diphenorphine (a nonselective marker of opioid receptors) in the striatum, thalamus, and anterior cingulate of PD patients with LID compared to without. LID severity was associated with reduced putaminal binding, possibly indicating increased opioid receptor occupancy by endogenous ligands in patients with LID.

Both dopamine agonists and levodopa trigger localized increases in cerebral blood flow (Tuor et al. 1986; Beck et al. 1988). Functional imaging studies utilizing Xenon-133 have found similar increases in PD patients and normal subjects in response to dopaminergic treatment (Montastruc et al. 1987; Kobari et al. 1995). Increased blood flow in the striatum, globus pal-

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lidus, and thalamus has been associated with adverse reactions to levodopa in PD patients, whereas those without adverse reactions show decreased blood flow (Henriksen and Boas 1985). In a motor activation study, patients with LID showed significant overactivation in the SMA and bilateral primary motor cortex measured with Xenon-133 compared to those without LID (Rascol et al. 1998). $H_2^{15}O$ PET has also been used to evaluate changes in blood flow after levodopa administration. Hershey et al. (1998) found that patients with LID showed increased perfusion in the ventrolateral thalamus even at levodopa doses insufficient to trigger LID (Hershey et al. 1998). In general, the blood flow changes have been attributed to direct effects of dopamine on local microvasculature (Iadecola 1998; Edvinsson and Krause 2002).

The changes in blood flow in response to levodopa contrast with changes in regional metabolism. Untreated PD patients show increased glucose metabolism in the putamen, globus pallidus, ventral thalamus, and dorsal pons (Fukuda et al. 2001a,b; Huang et al. 2007b). These regional abnormalities have been associated with disease-related changes in local synaptic activity at salient nodes of the PDRP metabolic network (Eidelberg 2009). In the rest state, tight correlations have been shown between regional cerebral metabolic rate (CMR) and blood flow (CBF), consistent with the notion that both measures reflect local synaptic activity (Ma and Eidelberg 2007). Thus, PDRP expression measured from FDG PET scans, H_2O PET scans, and perfusion-weighted MRI scans in the same subjects are significantly correlated (Ma et al. 2007, 2010). However, dopaminergic treatment has been found to dissociate (“uncouple”) these effects (Hirano et al. 2008). Effective treatment with levodopa reduces abnormally elevated metabolic activity (Feigin et al. 2001; Asanuma et al. 2006), but increases basal ganglia CBF (Kobari et al. 1995; Hershey et al. 2003). Indeed, PDRP network modulation is dissociated between CBF and CMR in PD patients undergoing levodopa treatment but not during STN stimulation of comparable clinical efficacy. The phenomenon of flow-metabolism dissociation observed at the network level was localized regionally to

the putamen and dorsal pons. In these areas, the increases in rCBF with levodopa treatment are greater in patients with LID, compatible with an exaggeration of microvascular responsiveness to monoamines in these individuals (Hirano et al. 2008). In animal models, levodopa treatment induces endothelial proliferation and angiogenesis, which may provide a possible basis for this observation (Westin et al. 2006; Lindgren et al. 2010).

FUNCTIONAL IMAGING OF NONMOTOR SYMPTOMS

The clinical diagnosis and definition of PD is based on motor signs and symptoms. Nevertheless, nonmotor symptoms may be prominent, and can precede motor symptoms (Tolosa et al. 2009; Lang 2011), and they can encompass a variety of categories, such as neuropsychiatric, sleep, or autonomic dysfunction (Lim and Lang 2010). Among the premotor symptoms, hypsomia and idiopathic rapid eye movement (REM) sleep behavior disorder both confer a higher risk of developing PD, and dopaminergic imaging may be abnormal in such patients as will be discussed further below. In this section we will focus on imaging applications relating to cognitive dysfunction.

Cognitive functioning can be substantially impaired in PD, playing a major role in clinical disability and in overall treatment outcome. The point prevalence of dementia in PD may be as high as 31%, with substantially higher cumulative prevalence (Aarsland et al. 2005; Aarsland and Kurz 2010). Even without dementia, cognitive difficulties can be present in early PD, with features similar but less severe to those seen in PD patients with dementia (PDD) (Green et al. 2002; Huang et al. 2007b).

Functional imaging studies have implicated multiple mechanisms for cognitive dysfunction and dementia in PD, including dopaminergic depletion, cholinergic dysfunction, as well as protein aggregation and cortical pathology (i.e., Lewy body formation). As with motor function, functional imaging in the resting state as well as activation paradigms has been applied to the study of cognitive dysfunction in PD.

Resting Metabolism

FDG PET has consistently shown cortical hypometabolism in PD. Even patients without apparent cognitive impairment show hypometabolism in the frontal and occipital cortices (Hosokai et al. 2009). This hypometabolism appears more widespread in PD patients with mild cognitive impairment (MCI), encompassing prefrontal and lateral parietal cortices (Mentis et al. 2002; Huang et al. 2007a, 2008) and may include occipital and medial frontal regions (Hosokai et al. 2009; Borghammer et al. 2010). Indeed, comparisons of patients with and without MCI, or patients with single- and multiple-domain MCI suggest that the degree and topography of hypometabolism reflects the extent of cognitive dysfunction (Peppard et al. 1990; Yong et al. 2007; Huang et al. 2008; Hosokai et al. 2009).

Early studies using PET imaging and network analysis suggested separate patterns of metabolic dysfunction relating to cognitive, affective, and motor function (Mentis et al. 2002; Carbon et al. 2003; Lozza et al. 2004). Applying spatial covariance analysis to FDG PET data from a cohort of nondemented PD patients, Huang et al. (2007a) identified a significant covariance pattern that correlated with cognitive performance, particularly involving executive functioning. This pattern, termed the PD-related cognitive pattern (PDCP), is characterized by metabolic reductions in frontal and parietal association areas, and increases in the cerebellar vermis and dentate nuclei (Fig. 2A) (Huang et al. 2007a). PDCP expression increased with worsening of cognitive impairment (see Fig. 2B,C) (Huang et al. 2008; Eidelberg 2009). The PD-related metabolic patterns are functionally independent. Although PDCP and PDRP expression progress over time, only the changes in PDRP expression correlate with concurrent declines in striatal dopaminergic function (Huang et al. 2007b). On group analysis, PDCP expression, unlike PDRP, does not respond to treatment of parkinsonian motor signs with levodopa or DBS (Huang et al. 2007a). Nevertheless, levodopa does affect cognitive function in some patients, and levodopa-mediated changes in verbal learning correlate with baseline PDCP ex-

pression. Moreover, in patients with meaningful improvement on levodopa there is a concurrent reduction in PDCP expression (Mattis et al. 2011).

Both beneficial and detrimental effects of PD treatment on cognition might be influenced by dopamine levels in different parts of the striatum (which in turn are affected by disease severity, genetic factors, and treatment) (Cools 2006; Mattis et al. 2011). For example, in a series of studies of motor sequence learning, GPi and STN stimulation were associated with improved performance, whereas levodopa was not (Fukuda et al. 2002; Carbon et al. 2003; Feigin et al. 2003; Argyelan et al. 2008). However, patients with poor baseline performance actually benefited from levodopa whereas patients with good baseline performance declined (Fig. 3) (Argyelan et al. 2008). Specifically, levodopa suppressed the normal deactivation in the ventromedial prefrontal cortex (vmPFC) that occurs during motor sequence learning. In good learners, deactivation of vmPFC was normal, but became abnormally depressed with levodopa. Other studies with fMRI or H215O PET have also found levodopa-mediated normalization of prefrontal activations, suggesting potential beneficial effects of levodopa on mesocortical pathways (Cools et al. 2002; Mattay et al. 2002).

The Default Mode Network

Patients with PD commonly show impairments in executive tasks (van Eimeren et al. 2009). During the past decade there has been recognition that performance of many executive or attentional tasks may require deactivation of a baseline network. This network, termed the default mode network (DMN), identified with fMRI or PET imaging, includes the medial prefrontal cortex, posterior cingulate cortex, precuneus, and lateral parietal and temporal cortices (Raichle et al. 2001; Raichle and Snyder 2007). Impaired deactivation of the DMN may be seen in normal aging as well as in patients with dementia or neuropsychiatric illnesses (Lustig et al. 2003; Grady et al. 2006; Calhoun et al. 2008). Given that the loss of dopamine in PD leads to functional impairment of CSPTC path-

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Figure 2. Parkinson's disease-related cognitive pattern: validation and correlates. (A) Parkinson's disease-related cognitive pattern (PDCP). This cognition-related metabolic spatial covariance pattern is characterized by hypo-metabolism of dorsolateral prefrontal cortex (PMC), rostral supplementary motor area (preSMA), precuneus, and posterior parietal regions, associated with relative metabolic increases in the cerebellum (Huang et al. 2007a). (In the representative slices, relative metabolic increases are displayed in red; relative metabolic decreases are displayed in blue. Slices were overlaid on a standard MRI brain template.) (B) PDCP expression correlates with performance on neuropsychological tests of memory and executive functioning in nondemented PD patients. For the California Verbal Learning Test: Sum 1 to 5 (CVLT sum), this correlation was significant for the entire cohort ($n = 56$; $r = -0.67$, $p < 0.001$), as well as for the original group used for pattern derivation (circles, $n = 15$; $r = -0.71$, $p = 0.003$) and in two prospective validation groups (squares, $n = 25$; $r = -0.53$, $p = 0.007$; triangles, $n = 16$; $r = -0.80$, $p < 0.001$) (Huang et al. 2007a). (C) Bar graph of PDCP expression (mean $\pm$ SE) in PD patients with dementia (PDD), multiple-domain mild cognitive impairment (MCI[m]), single-domain mild cognitive impairment (MCI[s]), PD patients without mild cognitive impairment (MCI[-]), and in healthy control subjects. There was a significant difference in PDCP expression across the patient and control groups ($F_{(4,70)} = 8.87$, $p < 0.001$; one-way ANOVA) and among the PD groups ($F_{(3,56)} = 4.84$; $p < 0.005$), with higher expression in the PDD and MCI(m) cohorts compared to the MCI(-) cohort ($p < 0.03$; Tukey-Kramer HSD). For each PD group, PDCP expression was separately compared to healthy control values using Student's t -tests. The asterisks denote significant increases in network activity relative to controls ($*p < 0.05$, $**p < 0.005$, $***p < 0.0001$) in all PD categories including MCI(-). (From Eidelberg 2009; reprinted, with permission, from Elsevier © 2009.)

ways and modulation of frontal lobe activity, it is not surprising that deactivation of the DMN would be impaired in this disease.

To date, few studies have addressed the DMN in PD. Using fMRI and a semantic event sequencing task, Tinaz et al. found that in contrast to controls, patients with PD did not show de-

creased activation of the DMN during task performance (Tinaz et al. 2008). Similarly, during a Montreal card sorting task, PD patients did not only show less deactivation of the parietal DMN nodes, but even showed decreased activation of these same areas during the control task (van Eimeren et al. 2009). This reverse pattern of activa-

Figure 3. Learning-related deactivation responses in the ventromedial prefrontal cortex (vmPFC) displayed as an inverted-U function. In addition to the influence of baseline phenotype on the cognitive response to dopaminergic therapy (Argyelan et al. 2008), we also found a significant influence of genotype. The observation that the effect of treatment on the vmPFC deactivation response varied according to COMT val¹⁵⁸met genotype suggests that this physiologic effect is linked to intrinsic differences in prefrontal dopamine pools. Specifically, in carriers of valine alleles (VAL, i.e., valine homozygotes and val/met heterozygotes), levodopa served to suppress learning-related deactivation in this region. In contrast, recovery of this response tended to occur in individuals without this allele (MET, i.e., methionine homozygotes). The individual data were found to conform to an inverted-U function. Bands of low and high dopamine at the edges of the curve (shaded areas) represent zones of optimal function in which local deactivation responses occur during task performance. (From Argyelan et al. 2008; reprinted, with permission, from the Society for Neuroscience © 2008.)

tion and deactivation differs from that seen in normal aging (Lustig et al. 2003) and may suggest PD-specific abnormalities relating to dopaminergic dysfunction. In healthy young subjects the complexity of a task correlates with the degree of DMN deactivation, a relationship that may be lost in healthy elderly subjects and PD patients (Nagano-Saito et al. 2009). Interestingly, in PD patients and healthy controls, apomorphine seems to restore this correlation (Nagano-Saito et al. 2009).

Imaging of Specific Neurotransmitters in PD Cognition

Reduced striatal dopaminergic function has been observed in PD patients with and without cognitive dysfunction (Ito et al. 2002; O'Brien et al. 2004; Bruck et al. 2005; Hilker et al. 2005).

That said, dopaminergic dysfunction in the caudate may contribute to the cognitive deficits of PD. Indeed, PD patients with dementia have been shown to have greater loss of tracer uptake in the caudate than those without dementia (Ito et al. 2002; O'Brien et al. 2004). Jokinen et al. (2009) found a significant correlation between verbal and visual memory functioning and caudate FDOPA uptake, although they also noted additional associations with hippocampal and prefrontal atrophy. Several other studies have shown relationships between reductions in caudate dopaminergic tracer uptake and impaired performance on tests of memory, executive, and frontal lobe function (Marie et al. 1999; Muller et al. 2000; Rinne et al. 2000; Bruck et al. 2001; van Beilen et al. 2008). During sequence learning, PD patients showed a correlation between correct acquisition of targets and caudate DAT

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binding (Carbon et al. 2004). Moreover, normal subjects showed close correlations between caudate DAT binding and learning-related activation in the dorsolateral and ventral prefrontal cortices, a relationship that was lost in PD patients (Carbon et al. 2004). Indeed, we have recently found that PDCP expression correlates with caudate but not putamen DAT binding (Tang et al. 2011).

Extrastriatal dopaminergic function may also be linked to cognitive performance. For example, FDOPA uptake in the dorsolateral frontal cortex may be increased in drug-naïve patients and is associated with worse performance on tests of sustained attention (Bruck et al. 2005). Conversely, increased FDOPA uptake in the medial frontal cortex and anterior cingulate is associated with improved performance on tests of suppressed attention. Although this may reflect compensatory changes of dopaminergic transmission in early PD, the same findings could also reflect increased AADC activity relating to other neurotransmitter systems (serotonergic and noradrenergic) in those regions (Rakshi et al. 1999; Bruck et al. 2005).

Postmortem examinations in patients with PD have consistently reported evidence of cholinergic dysfunction in thalamus, striatum, and cortical areas (Arendt et al. 1983; Whitehouse et al. 1983; 1988; Aubert et al. 1992; Pimlott et al. 2004; Schmaljohann et al. 2006), and Ruberg et al. (1986) reported greater reductions in the frontal cortex of demented PD patients compared to their counterparts. Unlike Alzheimer's disease (AD), there appears to be a loss of cholinergic function in the brain stem in PD (Jellinger 1988; Gai et al. 1991). Various radiotracers can be used for in vivo imaging of acetylcholinesterase (AChE), nicotinic and muscarinic acetylcholine receptors (nAChR and mAChR), and acetylcholine vesicular transporter (VACHT). Both [^{11}C]-methyl-4-piperidinyl propionate (PMP) and [^{11}C]-methyl-4-piperidyl acetate (MP4A) can be used to assess AChE function (Irie et al. 1996). Cortical AChE activity is reduced in patients with PD, PDD, and diffuse Lewy body disease (DLB). This reduction is more severe in PD patients with dementia (ranging from 17% to 29.7%) than in their nondemented

counterparts (10.2%–12.9%) (Shinotoh et al. 1999; Bohnen et al. 2003; 2009; Shimada et al. 2009). Moreover, cortical AChE deficits may be larger in PDD and DLB compared to AD (Herholz et al. 2000; Bohnen et al. 2003). This decline in cortical cholinergic function appears to begin early in the disease process, and worsens with the onset of dementia (Shimada et al. 2009). Cholinergic dysfunction is less correlated with disease duration and severity of motor symptoms than with tests of attention and cognitive function (Bohnen et al. 2006). Similarly, PD and PDD patients show reductions in striatal FDOPA uptake, although PDD patients have comparatively lower cortical MP4A binding (Hilker et al. 2005). Nevertheless, in PDD, reductions in cortical MP4A and striatal FDOPA binding are closely linked, suggesting that combined decline in the two neurotransmitter systems plays a role in these patients (Hilker et al. 2005).

Imaging of the VACHT system with [^{123}I]-iodobenzovesamicol (IBVM) has similarly revealed cortical reductions in nondemented PD patients, predominantly in the parietal and occipital cortices, with more widespread and severe reductions in PDD (Kuhl et al. 1996). Studies of nAChR in PD have shown a consistent reduction in subcortical tracer binding, with most also reporting reduced cortical receptors (Fujita et al. 2006; Oishi et al. 2007; Kas et al. 2009; Meyer et al. 2009). Although these studies were performed largely in nondemented PD patients, O'Brien et al. (2008) used [^{123}I]-5-I-A-85380 SPECT to evaluate nAChR activity in patients with DLB. They found reduced tracer binding in the striatum, frontal, temporal, and cingulate areas, with a relative increase in the occipital cortex, perhaps suggesting a link between cholinergic function and visual hallucinations in that area (O'Brien et al. 2008). In contrast to the nicotinic system, imaging studies of mAChR have reported increased frontal and occipital receptor activity in patients with PD and PDD (Asahina et al. 1995, 1998; Colloby et al. 2006). However, demented patients with PSP did not show this increase, perhaps implying that the muscarinic system is not directly linked to cognitive dysfunction (Asahina et al. 1998). Possibly the increase in occipital mAChR activity,

like the increase in occipital nAChR activity, underlies the visual disturbances seen in DLB and PDD (Colloby et al. 2006). Overall, cortical cholinergic dysfunction appears to be a feature of cognitive impairment in PD. These observations are consistent with the observed improvement in cognition in clinical trials of AchE inhibitors in demented PD patients (Giladi et al. 2003; Emre et al. 2004).

Protein Aggregation

As in other neurodegenerative diseases, the pathology of PD is associated with the accumulation of misfolded proteins, namely, Lewy bodies (Galvin et al. 2001). Lewy bodies, neuronal intracellular inclusions that contain α -synuclein, are more widespread in PDD and DLB. Additionally, β -amyloid deposition, i.e., Alzheimer pathology, is seen in both PDD and DLB, and may be associated with poor clinical outcome (Jellinger et al. 2002). The past few years have seen the development of radioligands for in vivo imaging of amyloid deposition. Of these, 2-(1-{6-[(2-[18 F]Fluoroethyl)(methyl)amino]-2-naphthyl}ethylidene)malononitrile (FDDNP) is relatively nonspecific, labeling senile plaques and neurofibrillary tangles in AD, prion plaques, amyloid deposits, and cortical Lewy bodies in vitro (Agdeppa et al. 2003; Smid et al. 2006). In contrast, [*N*-methyl-C-11]2-(4'-methylaminophenyl)-6-hydroxybenzothiazole (Klunk et al. 2004) (Pittsburgh Compound B, PIB) binds strongly to amyloid plaques in AD, but not significantly to Lewy bodies (Fodero-Tavoletti et al. 2007; Ye et al. 2008). Indeed, limited autopsy studies suggest that in PDD or DLB, in vivo PIB imaging does reflect β -amyloid rather than Lewy body pathology (Bacskaï et al. 2007; Burack et al. 2010). For instance, Burack et al. (2010) reported on three PDD cases that had PIB imaging within 15 months of their death. Two of the three had elevated PIB uptake. All three had abundant cortical Lewy bodies, but the two individuals with elevated PIB uptake were also found to have abundant diffuse A β plaques.

Several studies have used PIB to evaluate patients with synucleinopathies (PD, PDD, DLB) (Brooks 2009). Generally speaking, cognitively

normal PD patients do not have elevated PIB binding (Edison et al. 2008; Gomperts et al. 2008; Johansson et al. 2008; Maetzler et al. 2009). In contrast, patients with DLB show abnormally elevated cortical PIB binding, at levels comparable to patients with AD (Gomperts et al. 2008; Maetzler et al. 2009). PDD, which may be part of the same spectrum as DLB, or a separate disease more closely related to PD, is generally associated with normal cortical PIB binding. When PIB is elevated in PDD, it is generally lower than in DLB patients (Fig. 4A) (Edison et al. 2008; Gomperts et al. 2008; Brooks 2009), and amyloid load may not correlate with measures of dementia severity (Gomperts et al. 2008). Nevertheless, in the synucleinopathies, occipital PIB binding was higher compared to that observed in AD patients, and amyloid deposition in the parietal and posterior cingulate region was related to visuospatial impairment (Gomperts et al. 2008). In another recent study amyloid deposition was associated with lower MMSE scores in patients with dementia (DLB and PDD), but a majority of demented patients did not have elevated PIB binding (Maetzler et al. 2009), suggesting that other factors play a role in cognitive decline in Lewy body disease.

Although FDDNP and PIB imaging in combination might be useful for in vivo measurements of Lewy body pathology via a subtraction approach, to date there are no published studies formally evaluating this approach in PD. We have studied a 64-yr-old PD patient with FDG, PIB, and FDDNP PET imaging. This individual had elevated PDCP expression measured with FDG PET. We next used an automated region-of-interest approach to assess specific PIB and FDDNP binding relative to the cerebellum. In the majority of the regions, PIB and FDDNP uptake were closely matched, but in four areas there was significant discrepancy (Fig. 4B). For instance, in the anterior cingulate region, FDDNP binding was elevated whereas PIB binding was not. Furthermore, metabolic rates were reduced in areas of increased protein aggregation, suggesting that key nodes of the PDCP network show a relationship between reduced glucose utilization and increased protein aggregation. However, it remains to be seen if PIB and

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Figure 4. Protein aggregation in Parkinson's disease. (A) ^{11}C -PIB uptake in a healthy volunteer, PDD subject without significant amyloid, and two DLB patients with a significant amyloid load. (From Brooks 2009; reprinted, with permission, from John Wiley & Sons © 2009.) (B) Distribution of cortical protein aggregation in regions of interest (ROIs) computed using a standard brain atlas. Binding values for ^{11}C -PIB and ^{18}F -FDDNP were estimated from PET images acquired in PD patients by measuring the target-to-cerebellum ratio >60–90 min following radiotracer injection. The values presented on the Y-axis represent the difference in uptake of the two tracers in regions with metabolic reduction in the same subject.

FDDNP indeed can reflect regional differences in pathology in a large cohort of PD patients.

CONCLUSIONS

The past decade has seen many advances in the use of functional imaging in neurodegenerative disorders. Imaging has been used to both better understand disease processes and to assess new therapies. In PD, imaging studies have helped to elucidate the widespread consequences of nigrostriatal dopaminergic degeneration and are shedding light on the pathophysiology of non-dopaminergic systems. These insights will allow for improved methods of diagnosing PD and related disorders, and may ultimately aid in the development and assessment of new therapies.

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