Metabolic correlates of subthalamic nucleus activity in Parkinson’s disease

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Overactivity of subthalamic nucleus (STN) neurons is a consistent feature of Parkinson’s disease (PD) and is a target of therapy for this disorder. However, the relationship of STN firing rate to regional brain function is not known. We scanned 17 PD patients with 18F-fluorodeoxyglucose (FDG) PET to measure resting glucose metabolism before the implantation of STN deep brain stimulation electrodes. Spontaneous STN firing rates were recorded during surgery and correlated with preoperative regional glucose metabolism on a voxel-by-voxel basis. We also examined the relationship between firing rate and the activity of metabolic brain networks associated with the motor and cognitive manifestations of the disease. Mean firing rates were 47.2 ± 6.1 and 48.7 ± 8.5 Hz for the left and right hemispheres, respectively. These measures correlated (P < 0.007) with glucose metabolism in the putamen and globus pallidus, which receive projections from this structure. Significant correlations (P < 0.0005) were also evident in the primary motor (BA4) and dorsolateral prefrontal (BA46/10) cortical areas. The activity of both the motor (P < 0.0001) and the cognitive (P < 0.006) PD-related metabolic networks was elevated in these patients. STN firing rates correlated with the activity of the former (P < 0.007) but not the latter network (P = 0.39). The findings suggest that the functional pathways associated with motor disability in PD are linked to the STN firing rate. These pathways are likely to mediate the clinical benefit that is seen following targeted STN interventions for this disease.

Keywords: subthalamic nucleus; Parkinson’s disease; brain metabolism

Abbreviations: CSPTC = cortico-striato-pallido-thalamocortical; DBS = deep brain stimulation; PCA = principal components analysis; PD = Parkinson’s disease; STN = subthalamic nucleus

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Introduction

The subthalamic nucleus (STN) plays a key role in the pathophysiology of Parkinson’s disease (PD) by modulating the activity of cortico-striato-pallido-thalamocortical (CSPTC) pathways (Parent and Hazrati, 1995b; Hamani et al., 2004). Classically, the STN belongs to a reciprocal loop that receives input from and projects to the external globus pallidus (GPe), and sends excitatory projections to the basal ganglia output nuclei, i.e. the internal globus pallidus (GPI) and the substantia nigra pars reticulata (SNr). The output of these nuclei tonically inhibits their target nuclei in the thalamus and the brainstem (Alexander et al., 1990; Parent and Hazrati, 1995a). According to this model, in PD, dopamine depletion in the substantia nigra pars compacta (SNc) leads to reduced GPe output and a concomitant increase in STN neuronal activity, which contributes in turn to excessive GPI inhibitory outflow to the thalamus (Wichmann and DeLong, 1998). Indeed, elevated spontaneous STN firing rates have been reported in primate models of parkinsonism and in PD patients undergoing intraoperative single unit recordings from this structure (Hutchison et al., 1998; Sterio et al., 2002; Wichmann and DeLong, 2003). Moreover, the pattern of discharge from the STN is altered in parkinsonism,
with neighbouring neurons shifting from spontaneous firing to synchronized oscillation (Gatev et al., 2006; Wichmann and DeLong, 2006). Dopaminergic therapy as well as high-frequency deep brain stimulation (DBS) of this structure have been found to reduce both the firing rate and synchronization of STN neurons in PD patients (Levy et al., 2001, 2002; Devos et al., 2004).

In addition to reducing the overactivity of STN neurons, these interventions modulate the activity of an abnormal PD-related metabolic pattern (PDRP) that has been associated with the motor features of the disease (Eckert et al., 2007). This particular pattern was originally identified using a network model of resting-state brain activity (Eidelberg et al., 1994). The analytical approach, based upon principal components analysis (PCA), extracts multiple spatial covariance patterns from the functional imaging data, which together account for the variability in the combined dataset of patients and controls (Alexander and Moeller, 1994; Moeller et al., 1999).

The PDRP is characterized by increased pallidothalamic, pontine and motor cortical metabolic activity, associated with reductions in premotor and parietal association regions (Ma et al., 2007). The activity of this network is linked to longitudinal changes in motor functioning in PD patients (Huang et al., 2007b). Significant reductions in PDRP activity have been described following STN stimulation and lesioning (Asanuma et al., 2006; Trost et al., 2006), as well as with gene therapy targeting this structure (Feigin et al., 2007). In contrast to the PDRP, STN interventions do not affect the activity of the PD-related cognitive pattern (PDCP), a distinct prefrontal-parietal cortical metabolic network associated with memory and executive functioning in non-demented PD patients (Huang et al., 2007a, b). The relationship between these abnormal metabolic networks and STN neuronal activity in PD patients is not known.

In this study, PD patients undergoing STN DBS electrode placement were scanned preoperatively with $^{18}$F-fluorodeoxyglucose (FDG) PET. To identify brain regions in which glucose metabolism was associated with STN activity, we performed voxel-by-voxel searches for significant correlations with measurements of spontaneous firing rate recorded intraoperatively from that structure. Likewise, the firing rates were separately correlated with measurements of the activity of PD-related motor and cognitive metabolic networks computed in the preoperative metabolic images.

### Materials and Methods

#### Patients and procedures

We studied 17 non-demented PD patients [11 men/6 women; age 59.0±6.5 years (mean±SD); disease duration 10.6±3.3 years; off-state Unified Parkinson’s Disease Rating Scale (UPDRS) (Fahn and Elton, 1987) motor ratings 32.6±16.1; MMSE >27] who were referred for bilateral STN DBS electrodes implantation for medically refractory motor symptoms. All subjects were on anti-parkinsonian therapy with levodopa/carbidopa; 10 of the patients were also on COMT inhibitors. Eleven of the patients were on a combination of levodopa/carbidopa and dopamine agonist drugs. Four subjects were on amantadine and two subjects on selegeline as triple therapy with levodopa/carbidopa and dopamine agonists.

All patients underwent preoperative FDG PET imaging at North Shore University Hospital (mean 34 days before surgery). The subjects fasted overnight before PET imaging; all anti-parkinsonian medications were discontinued at least 12 h before the procedure. PET imaging was performed using a GE Advance tomograph (General Electric Medical Systems, Milwaukee, WI) in 3D mode. The 18-ring bismuth germinate scanner provides 35 image planes with an axial field of view of 14.5 cm and an intrinsic resolution of 4.2 mm of full width at half maximum (FWHM) in all directions. The details of the procedure have been presented elsewhere (Asanuma et al., 2006). Ethical permission for these studies was obtained from the Institute Review Board of North Shore University Hospital, Manhasset, NY. Written consent was obtained from all subjects following a detailed explanation of the procedures.

Off-state UPDRS rating was evaluated immediately prior to surgery. Spontaneous single unit activity was recorded during surgery and analysed as described in detail elsewhere (Sterio et al., 2002). In all subjects recordings from both right and left STN targets were obtained in an awake, unmedicated state, similar to that of the preoperative PET studies. A protective cannula, fixed to the stereotaxic frame, guided the microelectrode through a twist drill hole along the distance to the point 15 mm above the target point. A microdrive was employed to provide micrometer-graded extrusion of the microelectrode tip from the cannula. Single unit activity was recorded extracellularly with specially designed tungsten-tip disposable microelectrodes (0.5–1.0 MΩ impedance at 1000 Hz). The guiding cannula was the reference electrode. Extracellular action potentials were amplified with an AC amplifier (DAM-80, WPI, Sarasota, FL) and simultaneously recorded using standard recording techniques. Investigators blinded to the preoperative PET measures analysed spontaneous spike activity acquired in each of the operated hemispheres and calculated firing rate, time and interspike/interburst interval histograms. Limited clinical and neurophysiologic data from these patients have been reported previously (Sterio et al., 2002). The imaging data reported in this paper have not been published previously.

### Data analysis

#### Regional metabolic correlations with firing rate

Image preprocessing and analysis were performed using SPM5 (Institute of Neurology, London, UK) implemented in MATLAB 6.5 (Mathworks, Natick, MA). The raw scans from each subject were spatially normalized to the standard anatomical space developed at the Montreal Neurological Institute (Collins et al., 1994), and smoothed with an isotropic Gaussian Kernel (FWHM 10 mm for all directions) to improve the signal-to-noise ratio.

Voxel-based searches were conducted to identify regions in which local metabolic rate correlated with intraoperative recordings of firing rates. The distribution of the right and left STN firing rates was separately tested for normality using
a Shapiro–Wilk test for each side. Mean differences and homogeneity of variances in firing rates between the two hemispheres were examined using a paired $t$-test and a variance ratio $F$-test. If no differences were found between hemispheres, left and right STN firing rates were averaged for each subject. This measure was used as a covariate in a whole brain SPM correlation analysis designed to identify brain regions associated with STN neuronal activity. To account for potential effects of disease severity in these correlations, we entered the motor UPDRS ratings and the disease duration for each subject as ‘nuisance variables’ in this analysis. This was achieved using a multiple regression model in SPM5, in which positive and negative contrasts were respectively defined as ‘1, 0, 0’ and ‘−1, 0, 0’ for STN firing rates, motor UPDRS ratings, and disease duration.

The SPM correlations were considered significant at $P < 0.05$, corrected for multiple non-independent comparisons. Additionally, we reported findings at an uncorrected threshold of $P < 0.001$ at peak voxel, if related to prior hypotheses. The localization of each reported cluster was determined using the Talairach space utility (http://www.ihb.spb.ru/~pet_lab/TSU/TSUMain.html). We extracted metabolic values for each significant cluster using the volume-of-interest (VOI) function in SPM, with a sphere (radius = 4 mm) centred on each peak voxel. All metabolic correlations with firing rate were confirmed post hoc in the VOI data by computing Pearson product moment correlation coefficients. Correlations for each cluster were displayed graphically with linear regression lines. Consistent with the SPM analysis, left and right STN firing rate values were averaged for the post hoc analyses.

**Metabolic network correlations with firing rate**

We separately quantified the expression of the PDRP and PDCP spatial covariance patterns (Fig. 1) in each preoperative PET scan using a fully automated voxel-based algorithm (software available at http://feinsteinneuroscience.org/software) as described by us elsewhere (Huang et al., 2007b; Ma et al., 2007). For both patterns, network activity in the patient group was compared to values measured in a control group of 15 age-matched healthy volunteer subjects (8 men/7 women; age 56.7 ± 12.3 years) using Student’s $t$-tests.

We then determined whether network activity in individual patients correlated with intraoperative measurements of the STN firing rate. Multiple regression analysis was performed with whole brain PDRP or PDCP network values as the dependent variable and left–right averaged STN firing rates as the predictor variable. As in the SPM correlational analysis, UPDRS motor ratings and disease duration were entered as covariates in the multiple regression models. This allowed for assessment of the correlations between spontaneous STN activity and network expression after removing the potentially confounding effects of these variables. To illustrate these effects, we used partial regression leverage plots (Sall, 1990) that display the adjusted values for network expression and STN firing rate obtained in the regression models after accounting for individual differences in UPDRS scores and disease duration.

All statistical analyses were performed in JMP (SAS Institute, Inc. Cary, NC) and considered significant for $P < 0.05$.

**Results**

Frequency histograms of the STN firing rate data from the two hemispheres are shown in Fig. 2. The mean STN firing...
rate was 47.2 ± 6.4 Hz (mean ± SD) in the left hemisphere (range: 36–58 Hz) and 48.7 ± 8.5 Hz in the right hemisphere (range: 34–64 Hz). The STN firing rates were normally distributed on both hemispheres (left: P = 0.47; right: P = 0.89; Shapiro–Wilk test). No differences in mean values (P = 0.51; paired Student’s t-test) or variances (P = 0.27; F-test) of firing rates were found between the two hemispheres, suggesting consistent intrasubject STN firing rates between hemispheres. The left and right STN firing rates were therefore averaged for each subject; these average values also exhibited a normal distribution across subjects (P = 0.26; Shapiro–Wilk test; mean: 47.9 ± 5.9 Hz; range: 39–58 Hz). The average STN firing rate did not correlate with UPDRS motor ratings (P = 0.51; paired Student’s t-test) or disease duration (P = 0.22).

Regions with significant metabolic correlations with intraoperative measurements of spontaneous STN firing rate are presented in Table 1. Significant positive correlations (r > 0.62, P < 0.007) were identified in the putamen bilaterally, in the right globus pallidus and ventral thalamus, and in the left dorsolateral prefrontal cortex (DLPFC, BA 46/10) and sensorimotor cortex (SMC, BA 4) (Fig. 3, top and middle). In the right hemisphere, the cluster centered on the posterior putamen extended into the adjacent GPe, GPi and ventrolateral (VL) thalamic nucleus. In the left hemisphere, the cluster centered on the posterior putamen extended into the ipsilateral GPe. A significant negative correlation between regional metabolism and STN firing rate (r = −0.79, P < 0.0003) was found in the right inferior parietal lobule (BA 39/40) (Fig. 3, bottom).

We also quantified the expression of the PDRP and PDCP metabolic networks in each of the preoperative FDG PET scans. Prior to surgery, these subjects had significant elevations in network activity relative to healthy controls (PDRP: P < 0.0001; PDCP: P < 0.006). Following adjustment for individual differences in disease severity and duration, multiple regression analysis disclosed a dissociation between the two networks in their correlations with STN activity (Fig. 4). A significant correlation with firing rate was evident for the motor-related PDRP network (r = 0.76, P < 0.007) but not for the cognition-related PDCP network (r = 0.29, P = 0.39).

**Discussion**

**Regional metabolic correlations with STN neuronal activity**

We found that the spontaneous firing rate of STN neurons recorded in awake, unmedicated PD patients correlates with resting glucose utilization in regions that receive direct or indirect projections from this structure. We note that rather than indicating causal relationships, such correlations may instead be attributed to a set of parallel changes occurring in a multidimensional disease. With this caveat in mind, we will explore the potential relationship of our findings to models of altered functional connectivity in PD. For purposes of discussion, we defined regions receiving monosynaptic input from the STN as first-order structures.

### Table 1 Regions with significant metabolic correlations with STN firing rate

<table>
<thead>
<tr>
<th>Brain region</th>
<th>Coordinates</th>
<th>Cluster size</th>
<th>Zmax</th>
</tr>
</thead>
<tbody>
<tr>
<td>Putamen, left</td>
<td>−34, −2, 6</td>
<td>927</td>
<td>3.70</td>
</tr>
<tr>
<td>Putamen, right</td>
<td>−36, 4, 2</td>
<td>497</td>
<td>3.28</td>
</tr>
<tr>
<td>GP/Thalamus, right c</td>
<td>24, −14, 2</td>
<td>694</td>
<td>3.00</td>
</tr>
<tr>
<td>DLPFC (BA 46/10), left</td>
<td>−34, 38, 10</td>
<td>94</td>
<td>3.54</td>
</tr>
<tr>
<td>SMC (BA 4), left</td>
<td>−66, −4, 18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inferior Parietal lobe (BA 39/40), right</td>
<td>62, −60, 22</td>
<td>301</td>
<td>3.80</td>
</tr>
</tbody>
</table>

aMontreal Neurological Institute (MNI) standard space. bNumber of voxels in each cluster. cCluster submaximum.

*P < 0.05 (corrected for multiple non-independent comparisons); †P < 0.001 (uncorrected).

STN = subthalamic nucleus; GP = globus pallidus; DLPFC = dorsolateral prefrontal cortex; SMC = sensorimotor cortex; BA = Brodmann area.
Fig. 3  (A) Areas in which STN firing rates correlated significantly with regional glucose metabolism (see text). [The displays were superimposed on a single-subject MRI brain template and thresholded at $t = 3.0$, $P < 0.005$ (peak voxel, uncorrected).] (B) Scatterplots of the significant correlations between STN neuronal activity and globally normalized regional glucose metabolism (see text). [The coordinates refer to the Montreal Neurological Institute (MNI) standard space. DLPFC: dorsolateral prefrontal cortex; GP: globus pallidus; VL: ventrolateral thalamus; SMC: sensorimotor cortex. The left side (L) is labelled on the image].

Fig. 4  Partial regression leverage plots illustrating correlations between spontaneous STN firing rate and metabolic network activity after removing the effects of disease severity and duration. The activity of the motor-related PDRP network correlated significantly with STN firing rate ($P < 0.007$; left). In contrast, the activity of the cognition-related PDCP network did not correlate with this intraoperative measure ($P = 0.39$; right). [In the multiple regression models examining the correlations between PDRP/PDCP network activity and STN firing rate, UPDRS scores and disease duration were included as covariates to account for individual differences in these clinical features, and the resulting adjusted values of network expression (y-axis) and STN firing rate (x-axis) are displayed to illustrate these correlations (Sall, 1990).]
Regions separated from the STN by two synapses (e.g. the thalamus) were referred to as second-order structures and those separated from STN by three synapses (e.g. the motor cortex) as third-order structures. First-order areas with significant positive metabolic correlations with STN activity included the GPe, GPi and putamen. Interestingly, the SNr, another first-order region, was also included in this cluster if a more lenient correlation threshold ($P < 0.01$, uncorrected) was applied in the SPM analysis. The results are consistent with the subthalamic efferent pathway discerned from anterograde and retrograde labelling studies in primates (Parent and Smith, 1987; Smith et al., 1990b) and recently from magnetic resonance diffusion tractography in human subjects (Aravamuthan et al., 2007). Indeed, the first-order areas identified through correlational analysis with the STN firing rate data correspond closely to the sites of significant postoperative metabolic reduction observed following therapeutic lesioning of this structure (Su et al., 2001; Troit et al., 2003). We also note that in the squirrel monkey, projections from STN to putamen and globus pallidus were approximately 4 times more numerous than those to caudate and substantia nigra, while subthalamonic projections were 5 to 6 times more frequent than the projections from STN to pedunculopontine nucleus (PPN) (Parent and Smith, 1987). Therefore, it was not surprising that significant correlations were evident between STN neuronal activity and putaminal and pallidal glucose metabolism, but not SNr or PPN.

Positive metabolic correlation with STN firing rate was also found in the ventrolateral thalamus, a second-order area directly receiving inhibitory projections from the GPi (Alexander et al., 1990; Parent and Hazrati, 1995a). We further detected significant correlations between STN firing rate and metabolic activity in third-order areas, including the primary motor area and the dorsolateral prefrontal cortex. Anatomical studies using anterograde and retrograde transneuronal labelling methods have shown that the dorsolateral region of the STN projects to the primary motor cortex via the pallidal–thalamic pathway, while receiving direct afferents from this cortical region in return (Kelly and Strick, 2004). Similarly, the ventromedial region of the STN projects to the DLPFC through the mediodorsal thalamus while receiving direct input from the DLPFC (Monakow et al., 1978; Aravamuthan et al., 2007). According to the classical model of basal ganglia connectivity (Alexander et al., 1990; Eidelberg et al., 1994), metabolism in these cortical regions would be predicted to have a negative correlation with STN neuronal activity, i.e. to decline with increasing STN firing rate and concomitant pallidothalamic inhibition. However, contrary to expectations, we detected positive correlations with STN firing rate in these regions. We note that STN activity may be modulated by direct cortical input to this structure from motor cortex (Nambu et al., 2002) and from prefrontal areas (Maurice et al., 1998; Chudasama et al., 2003; Aravamuthan et al., 2007). A hyperdirect loop, linking motor cortical input directly to STN activity has also been suggested in recent computational basal ganglia models (Leblois et al., 2006). In keeping with this notion, we have noted progressive increases in glucose consumption in both the STN and SMC of early stage PD patients (Huang et al., 2007b). Nonetheless, we cannot exclude the possibility that cortical adaptation during the chronic course of PD may lead to compensatory resting state increases in regions with reduced motor activation responses.

Significant correlations with STN firing rate were also identified in other third-order cortical areas. Unlike the primary motor cortex and DLPFC, the correlations with metabolism in the inferior parietal lobule were negative, i.e. higher STN activity was associated with lower rates of regional metabolism. Parietal hypometabolism is associated with cognitive impairment in PD (Huang et al., 2007a). It is therefore possible that this correlation is not causal, but simply reflects the likelihood of cognitive impairment in PD patients with more advanced disease.

The intersubject variability of the STN firing rates reported in this study resembled that reported previously in MPTP primates and PD patients (Hutchison et al., 1998; Sterio et al., 2002). Indeed, as confirmed in the post hoc VOI analyses, the regional correlations detected in voxel-based searches of the whole brain were not artifacts of irregularities in the distributions of the intraoperative measurements. Additionally, unbiased statistical interrogations of the imaging data revealed that these correlations corresponded consistently to the anatomical connectivity of this structure in primates and humans (Parent and Hazrati, 1995b; Aravamuthan et al., 2007). Nonetheless, the metabolic correlations with single unit activity that were observed could potentially have been confounded by between-subject variability in disease severity. Metabolic activity in several of the reported regions has been reported to correlate with motor disability ratings (Lozza et al., 2002). Thus, if higher STN firing rates were associated with greater motor disability, the observed metabolic correlations might in fact have been driven by the latter effect, and not necessarily by subject differences in spontaneous neural activity. Nonetheless, we did not find evidence of significant correlations between UPDRS motor ratings and STN firing rates. Furthermore, to reduce the influence of a correlation of this sort, the SPM searches were conducted with these ratings and the disease duration entered as ‘nuisance variables’. Thus, the correlations between the regional metabolic values and the STN firing rates were not affected by disease severity and duration in the patients, as confirmed on post hoc analysis.

Network correlations with STN neuronal activity

We note that the regions with significant correlations with STN activity were key components of the PDRP, a validated metabolic brain network associated with the motor manifestations of the disease (Eckert et al., 2007; Huang et al., 2007b;
Ma et al., 2007). Indeed, PDRP expression was markedly elevated in our patients, consistent with their advanced motor symptoms. Moreover, the activity of this network correlated with STN firing rates, in keeping with its modulation by stereotaxic interventions targeting this structure (Asanuma et al., 2006; Trost et al., 2006; Feigin et al., 2007). In this regard, the findings resembled those previously reported using an older, region-of-interest (ROI)-based covariance mapping approach (Eidelberg et al., 1997). In that study, preoperative FDG PET scans were obtained in PD patients undergoing unilateral ventral pallidotomy for advanced motor symptoms of disease. ROI analysis revealed a significant correlation between GPi firing rates recorded intraoperatively and the expression of a regional covariance pattern that was topographically similar to the PDRP. In the current study, the correlations with network activity were performed using prespecified spatial covariance patterns that had been extensively validated prior to use (Eckert et al., 2007; Huang et al., 2007a, b; Ma et al., 2007). Moreover, we now employed a fully automated voxel-based network quantification algorithm to assess pattern expression blindly in individual subjects, as opposed to the more cumbersome ROI-based measurements that were used in the earlier study. Notably, re-analysis of the original GPi data (Eidelberg et al., 1997) using the current voxel-based method disclosed a correlation between pallidal firing rate and PDRP activity of greater magnitude than that previously reported ($r = 0.84$ and 0.65 for the voxel- and ROI-based techniques, respectively).

Overall, our findings indicate that in PD patients, the expression of this metabolic network is closely associated with the spontaneous activity of neurons mediating basal ganglia output. Given that many anti-parkinsonian interventions exert their effect by reducing overactive inhibitory outflow from this region (Asanuma et al., 2006), the assessment of changes in PDRP activity with treatment can provide an objective, non-invasive measure of therapeutic efficacy (Asanuma et al., 2006; Feigin et al., 2007).

In contrast, STN firing rates recorded during surgery did not correlate with the activity of the cognition-related metabolic network. This is consistent with the observed lack of association between PDCP expression and the motor features of the disease (Huang et al., 2007b), and the absence of change in this network during either STN stimulation or dopaminergic therapy (Huang et al., 2007a). Moreover, the topography of this pattern involves mainly metabolic reductions in prefrontal and medial parietal association regions, without major contributions from the basal ganglia and thalamus. The presence of significant correlations between PDCP activity and STN discharge firing rates would therefore be unlikely. Nonetheless, the possibility of such a relationship cannot be excluded without intraoperative recordings from the more ‘associative’ portions of this structure (Parent and Hazrati, 1995b). Indeed, additional studies in a larger patient cohort will be needed to validate the lack of association between STN activity and PDCP expression observed in the current dataset.

Caveats

Changes in the firing rate of basal ganglia structures have been associated with the development of motor symptoms in traditional models of PD pathophysiology (Wichmann and DeLong, 2003). However, the relevance of isolated alterations in firing rate has been challenged (Levy et al., 2000; Brown, 2003; Hutchinson et al., 2004). Indeed, recent studies have increasingly emphasized the role of changes in neuronal firing patterns, including burst discharges, synchrony and oscillatory activity (Gatev et al., 2006; Wichmann and DeLong, 2006). Nonetheless, our findings of significant network correlations with STN and GPi spontaneous firing rates (Eidelberg et al., 1997) suggest that these simple electrophysiological measures may be functionally meaningful.

We recognize that the interpretation of the current data relies on the notion that local FDG uptake reflects afferent synaptic activity in a given brain region (Jueptner and Weiller, 1995; Sokoloff, 1999). Although generally imaging signals have more complex relationships with cellular energetics (Attwell and Iadecola, 2002), this assumption may be valid when the time resolution of the imaging measurement and the recorded physiological covariate is comparatively long. Indeed, such conditions are likely to be met in the current study in which the PET signal reflected the summation of events during 20 min of radiotracer uptake, and in which intraoperative firing rates measures used for correlational analysis reflected a time average of recordings acquired over a similar period (Sterio et al., 2002). That said, this approach is likely to be insensitive to variations in patterns of neuronal firing that occur within a shorter time frame than that of the imaging measurement. The development of functional imaging approaches to capture these features of STN activity in PD patients may help clarify their connection with clinical manifestations of the disease.

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