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Metabolic brain networks associated with cognitive function in Parkinson's disease

Chaorui Huang^{a,b}, Paul Mattis^{a,c}, Chengke Tang^{a,b}, Kenneth Perrine^c, Maren Carbon^{a,b}, and David Eidelberg^{a,b,*}

^aCenter for Neurosciences, The Feinstein Institute for Medical Research, North Shore-Long Island Jewish Health System, New York, NY 11030, USA

^bDepartment of Neurology and Medicine, North Shore University Hospital and New York University School of Medicine, New York NY, USA

^cDepartment of Psychiatry, North Shore-Long Island Jewish Health System, Manhasset, NY 11030, USA

Abstract

The motor manifestations of Parkinson's disease (PD) have been linked to an abnormal spatial covariance pattern involving basal ganglia thalamocortical pathways. By contrast, little is known about the functional networks that underlie cognitive dysfunction in this disorder. To identify such patterns, we studied 15 non-demented PD patients using FDG PET and a voxel-based network modeling approach. We detected a significant covariance pattern that correlated ($p < 0.01$) with performance on tests of memory and executive functioning. This PD-related cognitive pattern (PDCP) was characterized by metabolic reductions in frontal and parietal association areas and relative increases in the cerebellar vermis and dentate nuclei. To validate this pattern, we analyzed data from 32 subsequent PD patients of similar age, disease duration and severity. Prospective measurements of PDCP activity predicted memory performance ($p < 0.005$), visuospatial function ($p < 0.01$), and perceptual motor speed ($p < 0.005$) in this validation sample. PDCP scores additionally exhibited an excellent degree of test–retest reliability (intraclass correlation coefficient, ICC=0.89) in patients undergoing repeat FDG PET at an 8-week interval. Unlike the PD-related motor pattern, PDCP expression was not significantly altered by antiparkinsonian treatment with either intravenous levodopa or deep brain stimulation (DBS). These findings substantiate the PDCP as a reproducible imaging marker of cognitive function in PD. Because PDCP expression is not altered by routine antiparkinsonian treatment, this measure of network activity may prove useful in clinical trials targeting the progression of non-motor manifestations of this disorder.

Keywords

Cognitive function; PD; FDG PET; Network analysis

Introduction

Parkinson's disease (PD) is a progressive degenerative neurological disorder characterized clinically by its motor manifestations. However, cognitive deficits and behavioral abnormalities are also well documented as part of the illness, with a prevalence of dementia ranging from 24% to 31% (Aasland et al., 2005). The dementia of PD typically includes difficulties in executive and visuospatial functions, as well as memory and language deficits (Bosboom et al., 2004). By contrast, more circumscribed executive deficits, as well as secondary disturbances of memory and visuospatial function, have been described in non-demented PD patients (Green et al., 2002; cf., Zgaljardic et al., 2003; Bosboom et al., 2004 for reviews). Such subtle behavioral/cognitive deficits may have a major impact on the quality of life of PD patients (Schrag et al., 2000).

The best recognized pathological change in PD is the loss of dopaminergic cells of the substantia nigra pars compacta, directly altering the activity of motor cortico-striatopallido-thalamocortical (CSPTC) pathways (Wichmann and DeLong, 2003). The depletion of striatal dopamine has also been suggested as a cause for the cognitive deficits of PD (Green et al., 2002). The direct dopaminergic connections between the ventral tegmental area and the prefrontal cortex may also influence changes in cognition in this disease (e.g., Mattay et al., 2002; cf., Cools, 2006 for review). Nonetheless, the modulation of dopamine systems cannot fully explain the cognitive deficits in PD, and other neurotransmitter systems may be influential (Emre, 2003; Pillon et al., 2003; Bosboom et al., 2004). Moreover, recent postmortem studies in PD suggest a correlation between dementia and cortical Lewy body formation as well as coincident Alzheimer's disease-associated neurofibrillary pathology (Braak et al., 2003, 2005; Kovari et al., 2003).

Positron emission tomography (PET) has been useful in the investigation of cognitive functioning in PD. Functional imaging studies have generally focused upon activation experiments to detect abnormal patterns of neural activity in PD patients during task performance (e.g., Dagher et al., 1999; Nakamura et al., 2001; Owen, 2004). Relevant information has also been obtained through imaging studies conducted in the rest state. For instance, PET imaging has been used to examine the relationship between neuropsychological test performance and the integrity of nigrostriatal dopaminergic projections (e.g., Marié et al., 1999; Brück et al., 2004; 2005; Cheesman et al., 2005). Recently, PET has also been utilized to contrast dopaminergic and cholinergic projection systems in PD patients with and without dementia (Hilker et al., 2005).

PET imaging in the rest state can also provide inferences regarding the status of neural pathways in PD patients. In this regard, ^{18}F -fluorodeoxyglucose (FDG) PET is particularly relevant as a measure of local synaptic activity and the biochemical maintenance processes that dominate the rest state (cf., Jueptner and Weiller, 1995; Eidelberg et al., 1997). Indeed, the effects of pathology on these local cellular functions appear to be greater than other factors that influence the variation in regional brain function that is observed in the resting condition (Ma et al., in press). Moreover, neuropathological processes, even if highly localized, can alter functional connectivity across the entire brain in a disease-specific manner (Eidelberg, 1998; Eckert and Eidelberg, 2005).

Spatial covariance analysis has proven useful as a means of identifying the network abnormalities that are associated with neurological disease (Alexander and Moeller, 1994). Using this network-modeling approach, we have found that PD patients express an abnormal metabolic pattern characterized by increased pallido-thalamic and pontine activity associated with relative reductions in cortical motor regions (Eidelberg et al., 1994, 1997; cf., Carbon et al., 2003a). To date, this PD-related pattern (PDRP) has been detected in eight independent patient populations (Moeller et al., 1999; Feigin et al., 2002; Lozza et al., 2004; Asanuma et al., 2005; Eckert et al., in press) and its expression has been found to be highly reproducible in individual subjects (Ma et al., in press). In addition to accurately discriminating between PD patients and controls (Asanuma et al., 2005; Ma et al., in press), PDRP expression has been found to correlate consistently with Unified Parkinson's Disease Rating Scale (UPDRS) motor scores (Eidelberg et al., 1995; Lozza et al., 2004; Asanuma et al., 2006) and with clinical responses to therapy (e.g., Trošt et al., 2006; Asanuma et al., 2006; cf., Carbon et al., 2003a; Eckert and Eidelberg, 2005).

Similar network approaches can be used to identify potential imaging biomarkers of cognitive functioning in PD (see Carbon and Marié, 2003 for review). Using a covariance mapping approach in the analysis of FDG PET and neuropsychological data, Mentis et al. (2002) identified discrete patterns of resting metabolic activity associated with cognitive and affective functions in non-demented PD patients. In a subsequent FDG PET study, Lozza et al. (2004) used the scaled subprofile model (SSM) and principal components analysis (PCA) (Alexander and Moeller, 1994; cf., Habeck et al., 2005) to characterize a specific metabolic pattern associated with executive functioning in less severely affected patients. Interestingly, their data showed that the patterns associated with motor and cognitive functioning were orthogonal, i.e., statistically independent. This finding supported the notion that the neural pathways mediating these aspects of PD are functionally segregated, at least in the rest state (Wichmann and DeLong, 2003).

In the current study, we utilized a voxel-based adaptation of this approach (Carbon et al., 2003b; cf., Scarmeas et al., 2004) to identify specific spatial covariance patterns relating to cognitive function in non-demented PD patients. To validate these networks as potential metabolic markers of cognitive decline in PD, we determined whether pattern expression predicted performance in a prospective patient cohort. We further explored the potential of these patterns as biomarkers in clinical trials of interventions to improve cognitive function in PD patients. To this end, we evaluated the reproducibility of pattern expression in individual subjects, as well as the effects of routine antiparkinsonian therapies on measurements of network activity.

Materials and methods

PD patients

Pattern identification—To identify cognitive-related spatial covariance patterns in PD (PDCPs), we studied 15 non-demented patients (9 men and 6 women; 14 right handers and 1 left hander; age 58.6 ± 9.5 years [mean $\pm$ SD]; disease duration 11.0 ± 4.6 years; off-state UPDRS motor ratings 34.3 ± 18.2 ; MMSE 28.3 ± 2.1) with FDG PET and neuropsychological evaluation. A diagnosis of PD was made if the patients had “pure” parkinsonism without a

history of known causative factors such as encephalitis or neuroleptic treatment, and did not have dementia, supranuclear gaze abnormalities, or ataxia. Limited clinical and metabolic data from these subjects have appeared previously (Mentis et al., 2002).

Validation—To validate the PDCP as a marker of cognitive impairment, we computed the expression of this pattern in 32 subsequent non-demented PD patients (22 men and 10 women; 29 right handers and 3 left handers; age 58.8 ± 7.9 years; disease duration 12.6 ± 5.7 years; off-state UPDRS motor ratings 31.8 ± 15.0 ; MMSE 28.1 ± 1.4) who also underwent FDG PET and neuropsychological evaluation. Computed measures of PDCP expression in these subjects were correlated with their test performance. Additionally, to assess the reproducibility of PDCP expression in individual subjects, we studied a separate group of 20 medicated non-demented right-handed PD patients (10 men and 10 women; age 65.9 ± 9.7 years; MMSE 27.2 ± 1.8) who were scanned twice with FDG PET over a 2-month period. Limited test–retest data on these subjects have appeared elsewhere (Ma et al., in press).

Treatment effects—To evaluate the effects of antiparkinsonian treatment on PDCP activity, we compared pattern expression measured during therapy with baseline values in PD patients undergoing either intravenous levodopa infusion or subthalamic nucleus (STN) deep brain stimulation (DBS). The levodopa group was comprised of nine right-handed PD patients (6 men and 3 women; age 60.0 ± 9.3 years; off-state UPDRS motor ratings 28.9 ± 7.0). The STN DBS group was comprised of nine other right-handed PD patients (2 men and 7 women; age 61.7 ± 11.1 years; off-state UPDRS motor ratings 33.3 ± 12.1). In addition to being matched for age and baseline motor UPDRS ratings ($p=0.7$ and 0.9 , respectively; Student's t test), the two treatment groups were matched for clinical response to therapy (change in UPDRS motor ratings -38.3% and -39.17% for the levodopa and DBS treatment groups, respectively; $p=0.7$). Clinical and neuropsychological data for these subjects as well as the effects of treatment on PDRP expression have been presented elsewhere (Asanuma et al., 2006).

Neuropsychological tests

All patients in the initial and validation samples underwent neuropsychological testing while on their routine medications. This battery was constructed to be sensitive to cognitive dysfunction in PD patients as compared with other neurodegenerative conditions such as Alzheimer's disease. Cognitive function was assessed in five domains. Attention and executive function were assessed utilizing Stroop Tests (Goldon, 1978), Wisconsin Card Sorting Test (WCST) (Heaton et al., 1993), Symbol Digit Modality Test (SDMT) (Smith, 1982) and Trail Making Test (Batterly, 1944). Visuospatial function was assessed utilizing Hooper Visual Organization Test (HVOT) (Hooper, 1983). Language was assessed utilizing Boston Naming Test (BNT) (Kaplan et al., 1978) and memory by the California Verbal Learning Test (CVLT) (Delis et al., 1987). General cognitive function was assessed utilizing a Mini-Mental State Examination (MMSE) (Folstein et al., 1975). Affective status was evaluated utilizing Beck Depression Inventory (Beck, 1987).

Positron emission tomography

All subjects were scanned with FDG PET within 3 months of neuropsychological evaluation. The subjects fasted overnight before imaging; all antiparkinsonian medications were discontinued at least 12 h before PET was conducted. PET imaging was performed in 3D mode using a GE Advance tomograph (General Electric; Milwaukee, WI, USA). The 18-ring bismuth germanate scanner provides 35 image planes with an axial field of view of 14.5 cm and an intrinsic resolution of 4.2 mm full width at half maximum (FWHM) in all directions. All the subjects were set in a dimly lit room with minimal auditory stimulation with eyes open. Patients were positioned in the scanner using a stereoadapter with three-dimensional laser alignment with reference to the orbitomeatal line. Images were constructed into a 128×128×35 matrix with a voxel size of 2×2×4, and a 6 mm Hanning filter. This gave an effective 3D image resolution of 8 mm FWHM.

Ethical permission for this study was obtained from the Institutional Review Board of North Shore University Hospital. Written consent was obtained from each subject with detailed explanation of the procedures.

Imaging processing

FDG image preprocessing was performed using SPM99 (Wellcome Department of Cognitive Neurology, University College, London) running on Matlab 6.0 (mathworks Inc., Natick, MA). Scans were spatially normalized to a Talairach-based PET FDG template using a 12-parameter affine transformation, non-linear transformation, and trilinear interpolation. The normalized scans were then smoothed using a Gaussian kernel at FWHM=10 mm.

Network analysis

Pattern identification—To identify and characterize a significant PDCP topography, we used a voxel-based network modeling approach as described previously (see e.g., Carbon et al., 2003b; Scarmeas et al., 2004). This method is based on principal components analysis (PCA) and can be used to detect spatial covariance patterns that correlate with behavioral, physiological, or other subject descriptors acquired in the resting state or during brain activation (e.g., Moeller et al., 1996; Eidelberg et al., 1997; Nakamura et al., 2001). In this study, we used an automated software package available at our website (<http://www.neuroscience-nslj.org>) to rapidly perform PCA on groups of brain images transformed into a common anatomical space. To delineate topographies associated with cognitive function in the PD group, we limited the analysis to the set of principal components (PCs) that accounted for the top 50% of subject × voxel variability in the data and for which each individual PC contributed at least 10% to the total variance. PCs, singly or in linear combination, were considered to be cognition-related if the associated subject scores correlated with neuropsychological test performance at a threshold of $p=0.01$ (multiple linear regression). Voxel weights at the local maxima were Z-thresholded at 2.44, corresponding to significant ($p < 0.01$) contributions to whole brain network activity at peak voxel, and further tested for reliability using a bootstrap resampling procedure (Efron and Tibshirani, 1994). Coordinates were reported in the standard anatomical space developed at the Montreal Neurological Institute. The cytoarchitectonic localization of each reported

network-related region was confirmed using the Talairach space utility available at http://www.ihb.spb.ru/~pet_lab/TSU/TSUMain.html.

Reference values for PDCP expression were computed in a group of 15 healthy volunteer subjects (8 men and 7 women; age 56.7 ± 12.3 years). These calculations were performed on a prospective single case basis using a voxel-based automated algorithm as described elsewhere (Ma et al., in press; Spetsieris et al., 2006). Subject scores for the entire cohort (PD patients and normal subjects) were *z*-transformed and offset so that the control mean was zero.

Validation—To validate the PDCP as a cognition marker, we computed its expression in each of the 32 subsequent PD patients who underwent FDG PET and neuropsychological testing. These prospectively computed PDCP scores were correlated with performance on the neuropsychological tests by calculating Pearson Product Moment Correlation Coefficients. Correlations were considered significant for $p < 0.01$.

To determine the test–retest reliability of prospectively computed PDCP scores, we quantified this measure in the group of 20 PD patients who underwent repeat FDG PET imaging 2 months following baseline imaging. Within-subject reproducibility of PDCP expression was assessed by computing the intraclass correlation coefficient (ICC) as described elsewhere (Ma et al., in press; cf., Bland and Altman, 1996).

Treatment effect—To evaluate the effects of antiparkinsonian therapy on PDCP expression, we quantified PDCP expression in FDG PET images obtained at baseline (OFF) and during treatment (ON). All PDCP computations were performed blind to intervention (STN DBS or levodopa infusion), treatment condition (OFF or ON), and clinical status (UPDRS motor ratings). As part of this analysis, we also quantified PDCP expression in 14 PD patients (8 men and 6 women; age 63.5 ± 7.7 years) who were scanned twice with FDG PET without undergoing an acute intervention. These subjects, an age-matched subset of the 20 test–retest subjects mentioned above, served as controls in our prior study of the effects of treatment on PDRP expression (Asanuma et al., 2006). PDCP scores for this test–retest group were compared with analogous values from the two treatment groups.

To determine group differences in treatment response, we performed a two-way repeated measures analysis of variance (ANOVA) on the PDCP scores from the three groups with the treatment condition as the repeated measure. By examining the Group**Treatment* interaction effect, this analysis allowed us to assess the change of PDCP expression following treatment in each intervention group relative to the change in network activity in the test–retest reference group. Post hoc Bonferroni pairwise comparisons were used to assess the change of PDCP expression within each group. The same procedure was applied to the PDRP scores of these subjects as previously described (Asanuma et al., 2006). Network computations were conducted on PCs running Windows 2000; ANOVA and correlation analyses were performed on these PCs using SPSS software (SPSS Inc., Chicago, IL).

Results

Neuropsychology and behavior

The results of neuropsychological evaluation and behavioral assessment are presented in Table 1. All the means are within two standard deviation of their respective normative mean, except for two executive tests: Trail Making Test B (identification and validation samples, and the combined sample) and Wisconsin Card Sorting Test: Categories Achieved (identification sample and the combined sample).

Network analysis

Pattern identification—Spatial covariance analysis was performed on the FDG PET scans of the original PD group ($n=15$). The first three principal components (PCs) accounted for 54.8% of the subject $\times$ voxel variance, with PC1, PC2, and PC3 accounting for 24.0%, 19.1%, and 11.7%, respectively. These three patterns were selected for further analysis. We found that of the three, only PC2 was associated with significant ($p<0.01$) correlations with neuropsychological test performance (see below). This PD-related cognitive pattern (PDCP; see Fig. 1 and Table 2) was characterized by covarying bilateral metabolic reductions in the rostral supplementary motor area (pre-SMA) and precuneus, the dorsal premotor cortex, and the inferior parietal lobule, as well as in the left prefrontal region. This pattern also included relative metabolic increases in the cerebellar vermis and dentate nuclei. Voxel weights for this pattern were found to be stable ($p<0.05$) by bootstrap estimation. Comparison with prospectively computed PDCP scores for the healthy volunteer subjects revealed that network activity was elevated in the patients relative to the controls ($p<0.005$; Fig. 2A).

Correlations between PDCP expression and neuropsychological test scores for the identification cohort are summarized in Table 1 (left column). Pattern scores correlated significantly ($R^2>0.39$; $p=0.01$) with Trail Making Test B and with several components of the California Verbal Learning Test (CVLT). In all cases, worse performance was associated with greater pattern expression, i.e., with greater metabolic reductions in network-related regions of the cerebral cortex. Significant correlations were not present between PDCP expression and performance on the BNT, WCST, MMSE, Hooper VOT, and the Beck Depression Inventory. PDCP expression did not correlate with UPDRS motor ratings ($R^2=0.05$, $p=0.6$).

Validation

In the prospective validation cohort ($n=32$), PDCP expression was found to be elevated ($p<0.0001$) relative to control values (Fig. 2A). Correlations between PDCP expression and neuropsychological test scores for this group are summarized in Table 1 (middle column). Computed PDCP scores correlated significantly ($R^2=0.34$, $p<0.005$) with performance on the CVLT (Sum 1 to 5). The pattern scores also correlated with performance on the SDMT and the Hooper VOT ($R^2>0.21$, $p<0.01$), tests which were not significantly correlated with network expression in the original cohort.

Correlations between PDCP expression and neuropsychological test scores for the entire sample ($n=47$) are presented in Fig. 3 and Table 1 (right column). We noted highly

significant correlations ($R^2 > 0.25$, $p < 0.001$) between network activity and performance on Trails B (Fig. 3A) and several components of the CVLT (as illustrated by the CVLT Sum, Fig. 3B), as well as on the SDMT (Fig. 3C). Additional correlations of comparatively lower magnitude ($R^2 > 0.14$, $p < 0.01$) were present in the merged sample between PDCP expression and performance on the Stroop Word test and on the Hooper VOT (Fig. 3D). As a further validation step, we assessed the within-subject reproducibility of this measure of network expression. We found that computed PDCP scores were stable (ICC=0.89, 95% confidence interval 0.75 to 0.96) in the test–retest cohort ($n=20$) over an 8-week period (Fig. 2B).

Treatment effect

Prospective computation of PDCP expression in the FDG PET scans of PD subjects scanned ON and OFF treatment revealed no evidence of network modulation ($F(1,29)=0.25$, $p=0.8$) during either levodopa infusion ($p=0.7$) or STN DBS ($p=0.5$) (Fig. 4, left). By contrast, significant effects of both interventions on PDRP expression were observed for the same subjects (Fig. 4, right).

Discussion

In this study, we applied network analysis to FDG PET data from non-demented PD patients to identify a novel spatial covariance pattern associated with cognitive function in this disorder. Significant correlations between PDCP expression and performance on tests of memory and executive functioning were replicated in a larger group of patients. Additionally, test–retest studies demonstrated that measurements of PDCP activity in individual subjects were stable over an 8-week follow-up period. Finally, PET studies conducted during antiparkinsonian treatment failed to detect significant changes in PDCP expression despite concurrent improvement in motor ratings and reductions in abnormal PDRP activity. Overall, the results of these studies support the use of the PDCP as a biomarker of cognitive functioning in PD patients.

Neuropsychological correlates of PDCP activity

The neuropsychological instruments found to correlate with PDCP expression are representative of executive (Trails B and not Trails A), memory (CVLT), and visuospatial functioning (Hooper VOT), as well as perceptual motor speed (SDMT). These cognitive measures are known to be sensitive to PD [CVLT (Massman et al., 1990; Green et al., 2002); Trails B (Muslimovic et al., 2005); Hooper (Levin et al., 1991); SDMT (Muslimovic et al., 2005)]. Although PDCP scores correlated with test measures in which the subjects were deficient, pattern expression also correlated with those tasks that the subjects performed well. It is therefore unlikely that the relationship between PDCP activity and these particular performance measures is a simple artifact of test selection. We note, however, that network activity correlated with all aspects of the subcortical dementia syndrome, not just executive functioning. The close relationship between executive and non-executive deficits within this syndrome (Green et al., 2002) is likely to be the basis for the broad array of correlations between PDCP activity and cognitive function that were observed in our subjects.

The current study substantiates our earlier report in which a different covariance approach was used to link neuropsychological functioning to several discrete topographical profiles (Mentis et al., 2002). The two multivariate approaches led to somewhat different interpretations of the data. Whereas the original analysis sought to identify covariance patterns specifically associated with the CVLT (Sum 1 to 5) and the Hooper VOT, the current design was not restricted in this manner. Indeed, the method used in this study allowed for the detection and prospective validation of a metabolic network with a broader and more comprehensive relationship to cognitive functioning in PD patients. Nonetheless, despite these differences, the two methods revealed a similar metabolic basis for memory and visuospatial dysfunction in non-demented PD patients.

Pattern identification and validation

To examine the extent to which our original findings could be generalized to other patient samples, we quantified PDCP expression in a large prospective PD cohort. In this validation procedure, we found a continued relationship between PDCP scores and memory functioning (CVLT). Although the relationship with Trails B was no longer significant in the larger validation sample, network activity correlated with SDMT and Hooper VOT, which was the case in the original study wherein the latter test was used specifically as a covariate for pattern identification (cf., Mentis et al., 2002).

We further analyzed the stability of measured PDCP activity in a sample of patients scanned twice within 2 months. We found that the extent to which each individual expressed this pattern did not change appreciably over the follow-up period. Thus, like the PDRP, subject expression of the PDCP network is stable and not unduly influenced by state-dependent factors. Finally, we analyzed how this pattern is affected by treatments that target the motor symptoms of PD. Unlike the motor-related PDRP network, PDCP expression was not significantly altered by either levodopa or STN stimulation. These findings support the use of the PDCP as a potential imaging biomarker of cognitive status in non-demented PD patients.

Anatomical/Functional basis for the PDCP topography

The PDCP topography can be interpreted as a network of covarying metabolic reductions involving predominantly the medial frontal and parietal association areas, as well as interconnected neocortical regions situated on the lateral hemispheric surface. Of these, the pre-SMA and precuneus contributed most prominently to overall network activity. Regional contributions of comparatively lower magnitude were identified in the inferior parietal lobule, lateral prefrontal cortex, and in the medial prestriate area. We note that the representation of several of these regions in the PDCP was asymmetrical, with relatively greater involvement of one cerebral hemisphere or the other. This is likely attributed to the stringent threshold that was employed in the analysis. Indeed, the pattern became more symmetrical at a more liberal threshold for local contributions to network activity.

This spatial covariance topography is similar to the “default mode network”, a group of regions that are normally metabolically active in the waking rest state (see e.g., Gusnard and Raichle, 2001). It is tempting to relate elevated resting PDCP activity to abnormalities in the

function of this default network. In disease, metabolic reductions at one or more nodes of this system may interfere with the reallocation of neural resources to areas needed for normal task performance (cf., Binder et al., 1999; McKiernan et al., 2003). Thus, the behavioral effects of abnormal PDCP expression may not be limited to a specific cognitive domain. Rather, these would involve as in the current study, abnormalities in a variety of functions within the subcortical dementia syndrome. Indeed, several recent studies have used spatial covariance methods to identify similar resting state abnormalities in patients with Alzheimer's disease (AD) and with Mild Cognitive Impairment (MCI) (cf., Scarmeas et al., 2004; Rombouts et al., 2005; Huang et al., in press). These findings suggest that the PDCP topography is not necessarily disease-specific. Nonetheless, this class of covariance topographies may have relevance as a metabolic descriptor of prodromal cognitive dysfunction in patients with PD and other neurodegenerative diseases.

Apart from the localized metabolic reductions discussed above, the PDCP network also included covarying increases in the cerebellar vermis and dentate nuclei similar to those previously identified as part of the PDRP (cf., Trošt et al., 2006). The increases in cerebellar/dentate metabolism that were identified in both disease-related networks may represent compensatory responses to the loss of dopaminergic input to the striatum. The involvement of the cerebellum and dentate nuclei in both the PDRP and PDCP is compatible with the presence of distinct motor and non-motor efferent channels from the dentate nuclei to the striatum and cerebral cortex (cf., Dum et al., 2002; Hoshi et al., 2005). The latter may be particularly critical in the performance of complex tasks, as demonstrated by increased cerebellar–prefrontal activity in PD patients during trial-and-error sequence learning (Mentis et al., 2003). By contrast, the prominent increases in basal ganglia–thalamic activity that are characteristic of the PDRP (Moeller et al., 1999; cf., Carbon et al., 2003a) did not contribute to the PDCP spatial topography. We have found that metabolism in these regions is closely related to single unit activity in the motor pallidum (Eidelberg et al., 1997). It is therefore not surprising that these specific changes were not evident as part of the cognition-related network.

We note that the PDCP topography includes several cortical regions that also participate in the motor-related PDRP. In addition to the metabolic increases in the cerebellar vermis/dentate noted above, both disease-related patterns feature relative decreases in the pre-SMA and posterior parietal regions (cf., Trošt et al., 2006). Despite these qualitative similarities, the two networks are statistically independent, as is evident by the absence of a correlation between their region weights ($R^2=0.01$, $p=0.68$ for the ROI-based comparison of the two patterns). Thus, as in the earlier study of Lozza et al. (2004), the motor and cognitive disease-related topographies can be viewed as representing different spatially distributed neural systems.

Furthermore, the two PD-related topographies evolve differentially over time. In a recent longitudinal study (Huang et al., 2006a), we quantified PDRP and PDCP expression in FDG PET scans acquired at baseline and at two subsequent 24-month follow-up visits. While significant elevations in PDRP expression were already present at baseline, abnormalities in PDCP activity were discerned only at the final visit, 4 years later. This is consistent with the clinical observation that the time course of cognitive dysfunction in PD is slower than for

the motor manifestations of the illness. The current data indicate that this process is nonetheless progressive, with the development of substantial abnormalities in cognitive network expression by the end of the first decade following clinical onset.

Further evidence for the functional independence of the two PD-related metabolic patterns comes from the PET intervention studies. The data show that effective treatment of parkinsonian motor signs with either levodopa or STN stimulation fails to alter PDCP expression while substantially modulating the activity of the PDRP network. Thus, it is possible to dissociate the two networks experimentally by dopamine replacement or through the manipulation of basal ganglia outflow pathways (Trošt et al., 2006). Nonetheless, the minor qualitative reductions in PDCP activity that were observed with both interventions (Fig. 4, left) may have a behavioral concomitant in that these subjects exhibited improvements in several aspects of memory functioning during treatment (Asanuma et al., 2006). We note however, that the neuropsychological battery that was used in that study was different than that we employed to identify and validate the PDCP network. Further studies incorporating standardized cognitive testing instruments will be needed to fully assess the effects of therapy on the activity of the PDCP and related cognitive networks.

It is likely that therapeutic strategies to enhance cognitive function in PD will need to target one or more nodes of the PDCP network. One possibility is that elevated PDCP expression is a manifestation of reduced prefrontal activity mediated by mesocortical dopaminergic deafferentation (e.g., Cools et al., 2002; Mattay et al., 2002), loss of nigrocaudate input (e.g., Rinne et al., 2000; Brück et al., 2001; Carbon et al., 2004), or both. Nonetheless, the absence of significant changes in PDCP expression during levodopa treatment suggests that the influence of dopamine neurotransmission on the activity of this network, and on cognitive function in general, is not straightforward (cf., Cools, 2006).

Another possibility is that abnormal PDCP activity is a reflection of an evolving cholinergic deficit. Indeed, localized decreases in cortical cholinergic neurotransmission have recently been reported in demented and non-demented PD patients (Bohnen et al., 2003; Hilker et al., 2005). Interestingly, voxel-wise analysis revealed that the location of several regions with significantly reduced acetylcholinesterase activity in PD corresponded to key PDCP nodes in the inferior parietal lobule and medial occipital cortex. It is conceivable that neural activity in these areas may be enhanced by interventions like cholinesterase inhibition (e.g., Emre et al., 2004). It is however not yet known whether PDCP modulation is observed as a feature of this therapeutic approach for cognitive impairment in PD.

Lastly, the possibility exists that the increases in PDCP activity cannot be readily reversed by treatment. In other words, the network-related metabolic reductions observed in frontal and parietal association regions may be a reflection of histopathological changes in the neocortex itself (Braak et al., 2003, 2005). This possibility is supported by the gradual appearance of PDCP abnormalities in the period following the development of motor signs, and preferential involvement in the network of the cortical regions with the earliest histopathological involvement. While cortical Lewy body formation may underlie the PDCP topography, other histopathological changes may also contribute to regional abnormalities within this network. For instance, some of these regions may be directly or indirectly

involved by coincident Alzheimer-type pathology (Jellinger et al., 2002). Moreover, recent pathological studies have disclosed significant pyramidal cell loss in the pre-SMA, without intraneuronal inclusions (MacDonald and Halliday, 2002). Although aspects of this functional pathology are likely to be fixed, a degree of network modulation may be achievable, especially in PD patients with less advanced cognitive decline. PET studies incorporating quantitative measurements of PDGP activity may be helpful in determining the mechanism of response to treatment for the cognitive symptoms of this disorder.

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Fig. 1.

Parkinson's disease-related cognitive pattern (PDCP) identified by spatial covariance analysis of FDG PET scans from 15 PD patients (see text). This pattern was characterized by covarying metabolic reductions in the rostral supplementary motor area (pre-SMA) and precuneus (left), as well as in the dorsal premotor (PMC) and posterior parietal regions (middle), and in the left prefrontal cortex (right). Relative metabolic increases in the cerebellar vermis and dentate nuclei (DN) were also identified as part of this cognition-related topography. [The display represents regions that contributed significantly to the network at $Z > 2.44$ ($p < 0.01$) and were demonstrated to be reliable ($p < 0.05$) by bootstrap resampling (Efron and Tibshirani, 1994). Voxels with positive region weights (metabolic increases) are color-coded red, those with negative region weights (metabolic decreases) are color-coded blue].

Fig. 2.

(A) Plots of mean ($\pm$ SE) and individual values for PDCP expression in the original identification group (PD1, $n=15$; filled squares) and in the subsequent validation group (PD2, $n=32$; filled triangles). For reference, network scores were also computed on an individual case basis in an age-matched group of healthy control subjects (CN, $n=15$; open circles). PDCP activity was elevated in both patient groups (PD1: $p < 0.005$; PD2: $p < 0.0001$, Student's t test) relative to control values. There was no difference in PDCP expression between the two patient cohorts ($p=0.76$). (B) Correlation between measures of PDCP expression obtained in 20 PD patients scanned at baseline (test) and 8 weeks later (retest) ($R^2=0.82$, $p < 0.0001$). The fitted regression line had a slope of 1.09 (95% confidence interval (CI) 0.84 to 1.34), indicating no difference from the diagonal reference line (dots). These data are consistent with high within-subject reproducibility (see text).

Fig. 3.

Correlations between PDCP expression and neuropsychological test performance in the original identification group (PD1, $n=15$; filled squares) and in the prospective validation group (PD2, $n=32$; filled triangles). Significant linear relationships between network activity and performance ($p<0.01$) on the following tests are displayed for the whole sample (fitted regression lines and 95% confidence intervals): (A) Trails Making Test B (Trails B), (B) California Verbal Learning Test: Sum 1 to 5 (CVLT Sum), (C) Symbol Digit Modality Test (SDMT), and (D) the Hooper Visual Organization Test (Hooper VOT).

Fig. 4. Bar graph illustrating mean ($\pm$ SE) treatment-mediated changes in the expression of the PDCP (left) and PDRP (right) disease-related spatial covariance patterns (see text). ON–OFF differences in network activity with levodopa infusion (LD; black) and subthalamic nucleus deep brain stimulation (DBS; gray) compared with changes in network activity without intervention (CN; white). Significant treatment-mediated changes were observed only for the motor-related PDRP network (* p <0.05, ** p <0.01).

Table 1

Neuropsychological test performance and correlations with PDCP expression

Cognitive test	Pattern identification <i>n</i> =15		Pattern validation <i>n</i> =32		Total sample <i>n</i> =47	
	Mean±SD	<i>R</i> ² (<i>p</i> value)	Mean±SD	<i>R</i> ² (<i>p</i> value)	Mean±SD	<i>R</i> ² (<i>p</i> value)
<i>Stroop interference test</i>						
Word	100.0±12.9	0.17 (0.18)	98.6±15.3	0.19 (0.04)	99.1±14.3	0.18 (0.01)
Color	65.3±10.2	0.08 (0.37)	64.9±11.4 *	0.25 (0.02)	65.0±10.9 *	0.14 (0.02)
Color/Word	38.5±10.3	0.08 (0.37)	36.4±9.6	0.04 (0.33)	37.1±9.8	0.07 (0.12)
<i>Trail making test (seconds)</i>						
A	44.4±14.6	0.05 (0.42)	54.7±33.9 *	0.13 (0.05)	51.4±29.4 *	0.12 (0.02)
B	138.1±63.9 **	0.42 (0.01)	127.0±70.6 **	0.10 (0.12)	130.8±67.7 **	0.28 (<0.001)
SDMT	36.6±13.2	0.14 (0.18)	36.2±13.5	0.34 (<0.005)	36.3±13.3	0.34 (<0.0001)
WCST						
Categories	1.8±1.6 **	0.26 (0.09)	3.1±6.3 *	0.06 (0.22)	2.7±5.3 **	0.06 (0.14)
Perseverative responses	18.5±12.8	0.03 (0.61)	13.3±9.7	0.04 (0.33)	14.9±10.8	0.01 (0.67)
Failure maintain test	0.2±0.4	0.11 (0.31)	0.7±1.8	0.00 (0.69)	0.5±1.5	0.00 (0.75)
<i>BNT</i>	51.5±8.5	0.00 (0.89)	52.3±7.1	0.05 (0.22)	52.0±7.5	0.01 (0.64)
<i>HVOT</i>	19.2±4.5 *	0.00 (0.97)	19.3±5.7 *	0.21 (<0.01)	19.2±5.3 *	0.14 (0.01)
<i>CVLT</i>						
Sum 1 to 5	35.0±15.3	0.41 (<0.01)	39.4±9.5	0.34 (<0.005)	37.7±12.0	0.36 (<0.0001)
List B	4.8±2.2	0.28 (0.04)	5.2±1.9	0.07 (0.18)	5.0±2.0	0.15 (0.01)
Short-delay free recall	6.1±4.4	0.39 (0.01)	7.1±2.9	0.14 (0.06)	6.8±3.5	0.26 (<0.001)
Short-delay cued recall	6.9±4.0	0.54 (<0.005)	8.2±2.2	0.20 (0.02)	7.7±3.0	0.33 (<0.001)
Long-delay free recall	6.8±4.1	0.34 (0.02)	7.5±2.9	0.18 (0.03)	7.2±3.3	0.25 (<0.001)
Long-delay cued recall	7.6±3.7	0.56 (<0.005)	8.0±2.6	0.20 (0.03)	7.9±3.0	0.32 (<0.001)
Hits	13.5±2.7	0.51 (<0.005)	13.0±2.8	0.13 (0.08)	13.2±2.7	0.18 (<0.01)
False positives	4.9±3.9 *	0.09 (0.29)	3.7±4.0 *	0.04 (0.34)	4.2±3.9 *	0.07 (0.10)
<i>Beck depression inventory</i>	12.9±7.2	0.03 (0.51)	9.8±5.8	0.02 (0.48)	10.9±6.4	0.01 (0.56)

Bolded tests significant at 0.01 level in total sample.

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SD=standard deviation; SDMT=Symbol Digit Modality Test; WCST=Wisconsin Card Sorting Test; BNT=Boston Naming Test; HVOT=Hooper Visual Organization Test; CVLT=California Verbal Learning Test.

* 1.0 SD below reference value.
** 2.0 SD below reference value.

Table 2
Brain regions with significant contributions to the Parkinson’s disease-related cognitive pattern (PDCP)

Brain region	Coordinates ^a			Z _{max}	p-Value ^b
	x	y	z		
<i>Network-related decreases (negative voxel weights)</i>					
Superior frontal gyrus, BA 6/8	4	6	68	3.76	<0.001
Precuneus, BA 7	-2	-52	66	2.98	<0.005
Angular gyrus, BA 39	-36	-74	8	2.58	<0.01
Middle frontal gyrus, BA 8/9	38	6	28	2.56	<0.01
Inferior parietal lobule, BA 40	44	-56	54	2.49	<0.01
Lingual gyrus, BA 18	2	-88	-18	2.49	<0.01
Middle frontal gyrus, BA 10	-32	48	-2	2.46	<0.01
<i>Network-related increases (positive voxel weights)</i>					
Cerebellar vermis/dentate nucleus ^c	2	-52	-36	3.46	0.001
	8	-66	-46	2.94	<0.005

^aMontreal Neurological Institute (MNI) standard space. BA=Brodmann area.
^bIndicating significance of correlations between normalized metabolism at peak voxel and whole-brain PDCP activity (see text).
^cAccording to the atlas of Schmahmann et al. (2000).