Learning Networks in Health and Parkinson's Disease: Reproducibility and Treatment Effects

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Abstract: In a previous $H_2{}^{15}O$/PET study of motor sequence learning, we used principal components analysis (PCA) of region of interest (ROI) data to identify performance-related activation patterns in normal subjects and patients with Parkinson's disease (PD). In the present study, we determined whether these patterns predicted learning performance in subsequent normal and untreated PD cohorts. Using a voxel-based PCA approach, we correlated the changes in network activity that occurred during antiparkinsonian treatment and their relationship to learning performance. We found that the previously identified ROI-based patterns correlated with learning performance in the prospective normal ($P < 0.01$) and untreated PD ($P < 0.05$) cohorts. Voxel analysis revealed that target retrieval was related to a network characterized by bilateral activation of the dorsolateral prefrontal, premotor and anterior cingulate cortex, the precuneus, and the occipital association areas as well as the right ventral prefrontal and inferior parietal regions. Target acquisition was associated with a different network involving activation of the caudate, putamen, and right dentate nucleus, as well as the left ventral prefrontal and inferior parietal areas. Antiparkinsonian therapy gave rise to changes in retrieval performance that correlated with network modulation ($P < 0.01$). Increases in network activation and learning performance occurred with internal pallidal deep brain stimulation (GPi DBS); decrements in these measures were present with levodopa. Our findings suggest that network analysis of activation data can provide stable descriptors of learning performance. Network quantification can provide an objective means of assessing the effects of therapy on cognitive functioning in neurodegenerative disorders. *Hum. Brain Mapping 11:197–211, 2003.* © 2003 Wiley-Liss, Inc.

Key words: sequence learning; brain networks; PET; Parkinson's disease; deep brain stimulation; levodopa

INTRODUCTION

Although Parkinson's disease (PD) primarily affects motor functioning, cognitive decline occurring early in the course of the disease can impair quality of living in this patient group [Brown and Marsden, 1990; Cooper et al., 1991; Schrag et al., 2000]. Mild cognitive deficits typically involve visuomotor processing, working memory, executive strategies, semantic flu-

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ency, as well as procedural learning [Cooper et al., 1991; Nakamura et al., 2001; Pillon et al., 1989; Taylor et al., 1990].

The effect of medical and surgical therapy on cognitive functioning may be independent of motor benefit [Cools et al., 2001; Fukuda et al., 2002; Mattay et al., 2002]. Changes in cognition during dopaminergic therapy are likely to be task-specific and dependent upon disease stage, perhaps relating to the extent and spatial distribution of dopaminergic denervation [Cools et al., 2001; Kulisevsky 2000; Muller et al., 2001; Owen et al., 1997]. The effects of deep brain stimulation (DBS) on cognitive functioning have also been inconsistent. While several studies have reported declines in verbal fluency during stimulation, improved psychomotor speed can also be a feature of this intervention [Ardouin et al., 1999; Dujardin et al., 2001; Jahanshahi et al., 2000; Pillon et al., 2000]. The underlying mechanisms by which antiparkinsonian therapy can affect cognitive functioning are not well understood. A reduction in noisy pallidal output has been suggested as a crucial mechanism of action for stereotaxic surgical interventions [Brown, 1999; Davis et al., 1997], perhaps promoting the efficiency of cognitive cortico-striato-pallidal-thalamocortical (CSPTC) pathways [Fukuda et al., 2002]. A direct effect on mesocortical dopaminergic pathways has been proposed for levodopa action [Mattay et al., 2002].

Most activation studies mapping the action of antiparkinsonian therapy on regional brain function have focused on basic motor execution paradigms [Ceballos-Baumann et al., 1999; Feigin et al., 2002; Fukuda et al., 2001a; Limousin et al., 1997; Playford et al., 1992]. To date, few studies have addressed the effects of treatment during cognitive processing. Oral levodopa reduces prefrontal activity in PD patients performing working memory or planning tasks [Cools et al., 2002; Mattay et al., 2002]. By contrast, GPi DBS during motor sequence learning increased activation responses in the left prefrontal and posterior parietal regions as well as in the premotor cortex bilaterally, and in the right occipital association area [Fukuda et al., 2002]. The relationship between modulation of activity in these regions and changes in task performance with therapy is not well understood.

The processing of complex behaviors such as the learning of sequential information requires the concerted interaction of cortico-cortical and cortico-subcortical functional pathways [Hikosaka et al., 1999; Koechlin et al., 1996]. Since standard univariate correlations between behavior and brain activity do not directly assess these regional interactions, alternative multivariate approaches are needed to quantify brain networks and their activity in different subject groups and conditions. In an earlier $H_2{}^{15}O$/PET study of eight normal volunteers (mean age 56), principal components analysis (PCA) was applied to region of interest (ROI) data to identify specific covariance patterns associated with different aspects of sequence learning [Nakamura et al., 2001]. In that study, we found that the acquisition of target order correlated with individual differences in the activity of a functional network involving the left dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex, and rostral supplementary motor area (pre-SMA), as well as the basal ganglia. By contrast, the retrieval of correctly learned targets correlated with a different network involving bilateral activation of the rostral premotor cortex (PMC), and the right posterior parietal cortex and precuneus. As part of that study, we also quantified the activity of each of these learning networks in 16 age-matched subjects with unmedicated early-stage Parkinson's disease (PD). The network associated with target retrieval in normal volunteers accurately predicted learning in PD patients. However, the acquisition network failed to predict performance in the disease group.

In the current study, we extended the prior work to determine whether the originally identified network-performance relationships were reproducible in subsequent cohorts of normal subjects and PD patients. Specifically, we tested the hypothesis that the normal learning networks are predictive of performance in young as well as in older healthy volunteers. We also examined the possibility that normal network topographies may not be predictive of learning performance in PD patients with more advanced motor signs. Lastly, we tested the notion that changes in learning performance during pharmacologic or surgical treatment for PD are associated with concurrent modulation of brain network activity.

SUBJECTS AND METHODS

Controls

We studied 18 right-handed healthy volunteer subjects (mean ± SD, 43 ± 16 years; range 22–75). This group was comprised of the eight normal volunteers (age 56 ± 11 years) reported previously [Nakamura et al., 2001], as well as 10 subsequently recruited younger subjects (age 33 ± 10 years). Exclusion criteria for volunteer participation were: (1) past history of neurological or psychiatric illness; (2) prior exposure to neuroleptic agents or drug use; (3) past medical history of hypertension, cardiovascular disease and dia-

betes mellitus; and (4) abnormal routine neurological examination and MRI.

PD patients

We studied 14 right-handed non-demented PD patients (age 56 ± 10 years; range 32–72; off-state Hoehn and Yahr stage (H&Y) 2.6 ± 1.1) who underwent PET imaging in the untreated baseline condition and following acute antiparkinsonian intervention. These patients were different from the 16 early stage (H&Y 1) patients whom we reported previously [Nakamura et al., 2001]. The current PD group was comprised of seven patients (age 52 ± 12 years; H&Y 3.2 ± 1.0) who were treated with GPi DBS, and seven other patients (age 60 ± 6 years; H&Y 2.0 ± 0.9) who received intravenous levodopa infusion. Clinical data, DBS settings, and levodopa infusion parameters for these patients have been published previously [Feigin et al., 2001; Fukuda et al., 2002].

Study design

Normal volunteer subjects were studied on two subsequent days, with a pre-scanning task training session on the first day and a PET session on the second day [Nakamura et al., 2001]. PD patients in both treatment groups were studied over a 3-day treatment period as described previously [Feigin et al., 2002; Fukuda et al., 2001a, 2002]. For these patients, all antiparkinsonian medications were withheld for at least 12 hours before each day of testing. The first day was utilized for task training and for the selection of experimental parameters for the PET studies. Imaging was performed over the next 2 days, with treatment condition randomized to being ON one day and OFF the other. On the ON day, stimulation parameters (DBS cohort) and infusion rates (levodopa cohort) were adjusted to achieve maximal improvement in the motor portion of the Unified Parkinson's Disease Rating Scale (UPDRS items 19–31) [Fahn and Elton, 1987] without inducing dyskinesia. In the GPi DBS cohort, patients were in a stable ON condition without medication for at least 12 hours before scanning. In the levodopa infusion cohort, imaging in the ON condition commenced once a clinical steady state was demonstrated by ≤5% variation in UPDRS motor ratings performed every 30 min. The presence of a steady state was confirmed by the measurement of plasma levodopa levels at multiple time points during the infusion [Feigin et al., 2002, 2003]. On the OFF day, all medications and stimulation were discontinued for at least 12 hours before imaging.

Behavioral tasks

All subjects performed two kinematically matched reaching tasks during PET imaging. In these motor tasks, subjects moved a cursor on a digitizing tablet with their dominant right hand. Cursor and target positions were displayed on a computer screen as an array of radially arranged circular targets, which were highlighted in gray when participants were required to reach for the target. Movements were out and back from a central starting point to one of eight radial targets. Subjects were instructed to reach for the targets without corrections and with sharp reversal inside each target. In all tasks, targets appeared in synchrony with a tone. Between-tone intervals and target extent were fixed for each subject across tasks and treatment conditions [Feigin et al., 2002, 2003; Fukuda et al., 2001b, 2002; Nakamura et al., 2001].

The subjects learned to perform the motor tasks in training sessions conducted the day before the first imaging session. Different sequences of equal complexity were used in the training and scanning sessions to prevent long-term learning interference. Training was complete once performance reached a stable level of accuracy judged by the ability to perform the motor execution reference task with 95% of hits. In PD patients imaged while undergoing treatment, we used the training session to determine the shortest tone interval and maximum target extent at which each individual subject could perform the task at this level of accuracy [Feigin et al., 2002; Fukuda et al., 2001a].

During scanning all subjects performed two reaching tasks in which repeating cycles of eight radially displayed targets were presented in trial blocks of 90 sec. The characteristics of these tasks have been described elsewhere [Feigin et al., 2003; Fukuda et al., 2002; Nakamura et al., 2001] (demonstration video clip of these tasks available online at http://www.neuroscience-nslij.org). These kinematically matched motor tasks differed with respect to the predictability of the presented sequence and the instructions on movement initiation given to the subject. In the motor sequence learning task (RT*learn*), the eight targets were presented in a pseudo-randomized repeating sequence of eight elements. Subjects were instructed to learn the order of the sequence while reaching for the targets, to anticipate successive targets, and then to reach each target in synchrony with the tone; they reported the order of the sequence verbally at the end of the 90-sec trial block. In the motor execution reference task (M*pred*), the targets appeared in a predictable counterclockwise order. Subjects were instructed to reach the target in synchrony with the tone.

Additionally, a third task was performed outside the scanner to determine the reaction time distribution for each subject. During this task (RAN), targets were presented in a pseudo-randomized and unpredictable order. Subjects were required to reach the targets as soon as possible after the target appearance, thereby minimizing reaction time but avoiding target anticipation. Minimal reaction times in RAN were used to determine the number of anticipatory movements in the RT*learn* task [Nakamura et al., 2001].

The normal volunteers were tested with an intertone interval of 1 sec and a target extent of 3.2 cm [Nakamura et al., 2001]. The PD patients were tested at individually determined tone interval and target extent; these experimental parameters were held constant across treatment conditions [Feigin et al., 2002; Fukuda et al., 2001a]. In the GPi DBS group, tone interval varied between 1 and 1.7 sec (mean 1.5 ± 0.2 sec) and target extents varied between 0.4 and 4.8 cm (mean 1.5 ± 1.6 cm). In the levodopa group, the tone interval was 1.5 sec and the target extent was 1.0 cm for all patients.

Learning performance: behavioral measures

For each movement, we identified the location and time bins of movement onset, peak velocity, peak acceleration, and movement reversal [Ghilardi et al., 2000]. In RT*learn*, we computed the total number of correct anticipatory movements, reflecting overall learning during the 90-sec trial block [Nakamura et al., 2001]. Movements initiated prior to the lowest individual reaction time determined outside the scanner during RAN were considered to be anticipatory. These movements were assessed as learned if they were directed to the correct target, hitting it in synchrony with the presented tone. The sum of all correctly anticipated movements during one trial block was termed the global retrieval index. Additionally, in each cycle we identified correctly anticipated targets that *had not* been learned in the previous cycle. These movements were considered to reflect the successful acquisition of new targets [Nakamura et al., 2001]. The total number of these movements in the trial block was termed the global acquisition index. Because of differences in the rate of target presentation across groups and subjects, global learning indices were normalized by the number of cycles completed during the PET epoch [Fukuda et al., 2002].

Positron emission tomography

All subjects fasted overnight prior to scanning. $H_2{}^{15}O$/PET imaging was performed using the GE Advance tomograph at North Shore University Hospital, Manhasset, New York, in 3-D mode [Dhawan et al., 1998]. Ethical permission for these studies was obtained from the Institutional Review Board of North Shore University Hospital. Written consent was obtained from each subject following detailed explanation of the procedures. The details of the imaging procedures have been presented elsewhere [Fukuda et al., 2002; Nakamura et al., 2001]. All subjects were scanned while performing each of the two reaching tasks (one scan per condition) in randomized order using the dominant right hand. The PD patients were scanned on consecutive days in the OFF and ON treatment conditions; antiparkinsonian medications were withheld for at least 12 hours before each PET session [Feigin et al., 2002; Fukuda et al., 2001a]. Relative regional cerebral blood flow (rCBF) in each task and condition was estimated using a modification of the slow bolus method [Silbersweig et al., 1993].

Image analysis

Scan preprocessing was performed using SPM 99 (Wellcome Department Cognitive Neurology, London, UK) implemented in Matlab (Mathworks, Sherborn, MA). All scans from each subject were realigned using the first scan as a reference. After realignment, all images were proportionally rescaled to a global CBF of 50 ml/min/dl and stereotaxically normalized into a standard anatomical space developed at the Montreal Neurological Institute [Collins et al., 1994]. The images were smoothed with an isotropic Gaussian kernel (FWHM 10 mm for all directions) to allow for interindividual gyral variation and to improve the signal-to-noise ratio. For regional analyses, we employed the 39 standardized regions of interest (ROIs) that we have described previously [Nakamura et al., 2001]. In this study, we used an automated routine to place these ROIs on each set of Talairach normalized brain slices. This allowed us to apply identical ROI volumes across tasks and treatment conditions in each subject [Feigin et al., 2001; Fukuda et al., 2002]. Coplanar MRI was used to confirm ROI positioning for every case.

Network analysis

To test the reproducibility of network-performance relationships, we computed the expression of the original ROI-based learning networks [Nakamura et al., 2001] in each of the 10 new normal subjects and in 14 PD patients. These prospective calculations were performed for each subject using a procedure known as topographic profile rating (TPR) [Eidelberg et al., 1995;

Moeller et al., 1996; Spetsieris et al., 2002]. This method utilizes ROI data to compute the magnitude of pattern expression (i.e., the subject score) for the whole brain.

We then utilized the larger cohort of normal scans to identify learning networks on a data-driven basis. Voxel-based SSM/PCA [Alexander et al., 1999] was performed on RT*learn*–M*pred* difference images from the entire group of 18 normal volunteers to delineate independent (i.e., orthogonal) topographies associated with target acquisition and retrieval. This allowed us to improve the spatial definition of the learning-related covariance patterns that were previously identified by the ROI based approach [Nakamura et al., 2001]. The magnitude of these voxel-based patterns was determined in PD patients OFF and ON treatment utilizing the TPR algorithm. The resulting subject scores were used to quantify changes in network activity induced by therapy and to evaluate their correlation with concurrent changes in learning performance.

All network computations were performed blind to subject, intervention (DBS, levodopa), treatment condition (ON, OFF), and behavioral response (retrieval index, acquisition index). In the voxel-based SSM/PCA procedures, the resulting principal component topographies were displayed using a single-subject stereotaxic MRI template. Covariance patterns, singly or in linear combination, were considered to be learning-related if the associated subject scores correlated with performance indices at $P < 0.05$ [Nakamura et al., 2001]. Positive region weights at the local maxima (i.e., RT*learn* > M*pred*) were *Z*-thresholded at 2.0. Values above this threshold were tested for significance by correlating changes in globally normalized rCBF at each locus with the subject scores. Significant correlations ($P < 0.01$) were considered to reflect meaningful local contributions to whole-brain network activity [Eidelberg et al., 1997; Nakamura et al., 2001]. In the prospective TPR calculations, the computed subject scores for each learning network were offset such that the mean value for the M*pred* condition (i.e., no explicit learning) was zero. All network calculations were performed on PCs running Windows NT, using software available online (http://www.neuroscience.-nslij.org). Post hoc comparisons and correlational analyses were performed using JMP software (SAS Institute, Cary, NC) for PC.

RESULTS

Task performance

The learning indices for each subject group are presented in Table I. The normalized global retrieval index was reduced in the unmedicated PD cohort as compared with the normal volunteer subjects ($P < 0.05$). By contrast, the normalized acquisition index was comparable for the two groups. In normals, subject age was marginally correlated with indices of retrieval ($R^2 = 0.20$, $P = 0.06$) and acquisition ($R^2 = 0.23$, $P = 0.04$). However, despite the difference in mean age between the two normal cohorts ($P < 0.001$), Group × Performance interactions did not reach significance (retrieval F = 0.10, $P = 0.7$; acquisition F = 0.36, $P = 0.6$). Significant correlations between acquisition and retrieval indices were noted in both normals ($R^2 = 0.44$, $P = 0.03$) and PD patients ($R^2 = 0.52$ and 0.50 for the OFF and ON conditions, respectively, $P < 0.005$).

TABLE I. Learning performance: target acquisition and retrieval

Group (n)	Global retrieval index[a]	Global acquisition index[b]
Normal (18)	3.7 ± 0.07	0.72 ± 0.43
Original (8)[c]	3.4 ± 1.11	0.66 ± 0.17
Prospective (10)	3.8 ± 0.91	0.76 ± 0.13
PD (14)	2.0 ± 0.25[d]	0.87 ± 0.10[d]
DBS (7)		
OFF	1.7 ± 0.43	0.90 ± 0.18
ON	3.7 ± 0.68	0.86 ± 0.16
L-Dopa (7)		
Off	2.3 ± 0.24	0.85 ± 0.09
On	1.9 ± 0.23	0.75 ± 0.08

[a,b] Correct anticipatory movements/cycle (mean ± SE). (See text.)
[c] Nakamura et al. (2001).
[d] Untreated baseline condition (OFF). (See text.)

Both interventions produced significant improvements in UPDRS motor ratings (Levodopa infusion: OFF = 25.7 ± 3.7, mean ± SE, ON = 16.6 ± 2.5; GPi DBS: OFF = 41.9 ± 6.5, ON = 25.3 ± 4.2; $p < 0.01$ for both interventions). However, levodopa infusion and GPi DBS differed in their effects on target retrieval (Table I). While GPi DBS improved the global retrieval index (+113%, $P < 0.01$), levodopa infusion tended to reduce this measure (−20.6%, $P = 0.2$). Neither of the interventions altered the acquisition index ($P > 0.5$).

Network reproducibility

We calculated the expression of the original ROI-based learning networks in each of the 10 prospective normal volunteers. Individually computed subject scores for the retrieval and acquisition patterns accurately predicted both aspects of learning performance in this cohort (retrieval: $R^2 = 0.57$; acquisition: R^2

= 0.65, $P < 0.01$), and in the combined cohort of all 18 controls ($R^2 = 0.65$ for both retrieval and acquisition, $P < 0.0001$). No significant Group × Subject score interaction was observed for either of the learning patterns (retrieval F = 0.28, $P = 0.6$; acquisition F = 0.20, $P = 0.7$).

Voxel-based mapping of learning networks

Given the similarities of ROI-based network-performance correlations in the two groups of normals, we combined the groups for purposes of network mapping on a voxel basis. In this SSM/PCA, we restricted the analysis to the first five principal components (PCs), accounting for 40% of the Subject × Voxel variance in the RT*learn–Mpred* difference scans. Subject scores for each of these topographies were correlated with the global learning indices. PC 1 scores correlated with retrieval ($R^2 = 0.60$, $P = 0.0002$); none of the remaining topographies correlated with this measure of learning ($P > 0.5$). By contrast, acquisition did not correlate with subject scores for any of the topographies, although trends were identified for PC 1 (R = 0.44, $P = 0.06$), PC 3 (R= −0.35, $P = 0.14$), and PC 5 (R = 0.43, $P = 0.07$). To identify independent patterns associated with each aspect of learning, we respectively mapped PC 1 for retrieval and a linear combination of PC 3 and PC 5 for acquisition.

Retrieval network

The first principal component (PC 1) of the SSM/PCA accounted for 9.2% of region × subject variance. Subject scores for this pattern ($R^2 = 0.60$, $P = 0.0002$; Fig. 1A) correlated with target retrieval. This network (Fig. 1B; Table II) was characterized by bilateral activation of the DLPFC (BA 46), the premotor cortex (BA 6), the anterior cingulate area (BA 24), the precuneus (BA 7), and occipital association regions (BA 18/19). The pattern also included activation of the right anterior cerebellum (lobule III), the lateral ventral prefrontal cortex (BA 47), and the inferior parietal cortex (BA 40), as well as the left pre-SMA (BA 6). A small contribution from the right caudate was also present. Subject scores for the voxel-based retrieval pattern correlated with analogous values computed using the original ROI-based retrieval pattern ($R^2 = 0.65$, $P = 0.0001$). Subject scores for this network were independent of age ($R^2 < 0.01$, $P > 0.9$).

Acquisition network

In analyzing the space orthogonal to PC 1, we found that subject scores for a linear combination of PC 3 and PC 5 (accounting, respectively, for 8.2 and 6.6% of Region × Subject variance) correlated with target acquisition ($R^2 = 0.31$, $P < 0.01$; Fig. 2A). This learning network (Fig. 2B; Table III), independent of the retrieval topography, was characterized by bilateral activation of caudate nuclei, the left posterior putamen, and the right dentate nucleus. These subcortical activations were associated with bilateral activation of ventral prefrontal cortex (left BA 11; right BA 25), as well as the left inferior parietal lobule (BA 40), and the inferior (BA 20) and superior temporal gyri (BA 22). Additionally, the network included a locus of activation within the right medial superior temporal gyrus, extending into the vicinity of the caudate tail and the parahippocampal gyrus. Subject scores for this voxel-based pattern correlated with the acquisition index and with analogous subject scores computed using the original ROI-based acquisition pattern ($R^2 = 0.23$, $P < 0.04$). These subject scores were marginally associated with age ($R^2 = 0.21$, $P = 0.05$).

Network activity in PD patients

Baseline measures

We prospectively computed the expression of the normal ROI- and voxel-based learning networks in each of 14 PD patients scanned in the untreated baseline condition (OFF). In these patients, target retrieval was predicted by the corresponding network whether obtained by the ROI ($R^2 = 0.37$, $P < 0.05$) or by the voxel approach ($R^2 = 0.36$, $P < 0.05$). By contrast, target acquisition was predicted by the corresponding normal ROI-based pattern ($R^2 = 0.30$, $P < 0.05$) but not by its voxel-based counterpart ($R^2 < 0.10$, $P > 0.1$).

Treatment effects

ON–OFF differences in computed subject scores for the normal voxel-based retrieval network correlated significantly with treatment-mediated changes in global retrieval ($R^2 = 0.40$; $P < 0.01$; Fig. 3). The effect of intervention on this network was different in the two treatment groups (Group × ON–OFF difference in network activity: F = 18.96, $P < 0.001$). DBS produced an increase in the expression of the retrieval network activity (OFF: 1,067.3 ± 353.2; ON: 1,889.4 ± 294.0, mean ± SE) while levodopa infusion produced a decline in this measure (OFF: 2,114.7 ± 372.2; ON: 1,069.9 ± 515.8). Changes in network activity with treatment did not correlate with reductions in UPDRS motor ratings or with changes in movement time measured during RT*learn* or M*pred*. No signifi-

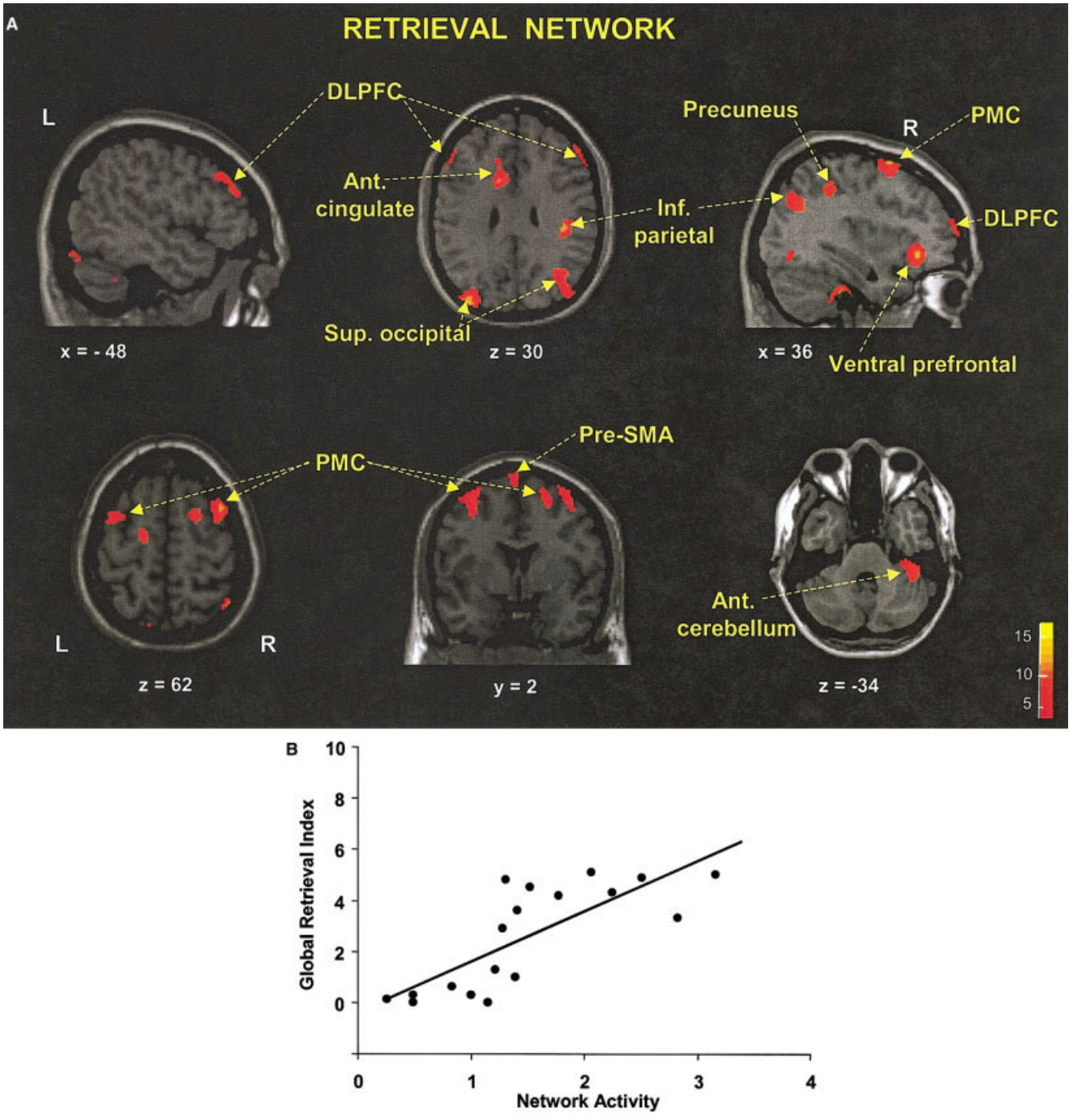

Figure 1.

Voxel-based network analysis of $H_2{}^{15}O$/PET data from 18 healthy controls scanned during motor sequence learning: retrieval pattern. **A:** In the normal cohort, subject scores for the first principal component (PC 1, accounting for 9.2% of the Subject × Voxel variance) correlated with target retrieval ($R^2 = 0.60$, $P < 0.001$). **B:** This network topography (Table II) was characterized by bilateral learning-related activations (RT*learn* > M*pred*) in the dorsolateral prefrontal cortex (DLPFC) and premotor cortex (PMC), and in the left anterior cingulate area and the right inferior parietal cortex. This learning pattern contained additional activations in the ventral prefrontal and occipital association areas, and in the lateral cerebellum. [Positive region weights (red-yellow) were thresholded at $Z = 2$ to display clusters contributing significantly ($P < 0.01$) to the network (see text)].

TABLE II. Regions contributing to the voxel-based retrieval network

Coordinates*			
x	*y*	*z*	Region
−51	34	18	Left middle frontal gyrus (BA 46)
42	60	3	Right middle frontal gyrus (BA 46)
35	30	−8	Right inferior frontal gyrus (BA 47)
−6	9	26	Left anterior cingulate (BA 24)
−4	4	70	Left Pre SMA (BA 6)
−39	7	57	Left middle frontal gyrus (BA 6)
46	−24	30	Right inferior parietal lobule (BA 40)
40	10	64	Right middle frontal gyrus (BA 6)
−4	−65	65	Left parietal lobe, precuneus (BA 7)
43	−55	59	Right superior parietal lobule (BA 7)
22	−75	55	Right parietal lobe, precuneus (BA 7)
−40	−83	30	Left superior occipital gyrus (BA 19)
−4	−95	−15	Left occipital lingual gyrus (BA 18)
47	−78	31	Right superior occipital gyrus (BA 19)
13	18	5	Right caudate (head)
2	−40	−8	Right anterior cerebellum, lobule III

* MNI standard space.

cant correlations were identified between changes in acquisition network activity and changes in learning performance.

DISCUSSION

Reproducibility of learning networks

In this study, we found that specific patterns of brain activation are correlated with learning performance in multiple cohorts of normal subjects and unmedicated PD patients. Moreover, these learning-related networks can be used to assess treatment effects on cognitive functioning. In our previous $H_2{}^{15}O$/PET study in which older normals performed the same pair of kinematically matched motor sequence learning and reference tasks, we used a native-space MRI guided ROI approach with SSM/PCA to identify independent (orthogonal) topographies relating to target acquisition and retrieval [Nakamura et al., 2001]. In the current study, these patterns were projected on a prospective basis into scan data from a new group of normal subjects. We found that subject scores for the original patterns accounted for over 50% of the variance in learning that was achieved during concurrent PET imaging. Similarly, in accordance with our previous study of early stage parkinsonism, these ROI-based patterns correlated with learning performance in more advanced unmedicated patients, albeit with less accuracy than for control subjects. We attributed this to the likelihood that the network architecture of PD is somewhat different than in controls [for discussion, see Nakamura et al., 2001], and may, in fact, change with disease progression. Nonetheless, the basic learning networks subserving target acquisition and retrieval in normals appear to be operative in moderately advanced PD.

The prospective cohorts of normal volunteers and PD patients differed from those originally reported in several ways. Firstly, the new normal cohort was significantly younger than that utilized originally for pattern identification. Nonetheless, the expression of both ROI-based and voxel-based learning networks did not correlate significantly with subject age. Secondly, the original ROI-based analysis was conducted in native space with MRI coregistration. By contrast, regional data from the subsequent cohorts were analyzed using an automated template approach in standardized stereotaxic space [Feigin et al., 2001; Fukuda et al., 2001b]. The results demonstrated that formal PET-MRI coregistration is not required for prospective computation of network activity in individual subjects. These findings indicate that $H_2{}^{15}O$/PET activation data analyzed with SSM/PCA can be used to identify reproducible learning-related covariance patterns. Indeed, these networks can be used to predict performance in normal subjects irrespective of age, and in untreated PD patients with mild to moderate motor symptomatology. The stability of network-performance relationships in these groups suggests that the neural pathways subserving motor sequence learning are preserved in healthy aging and parkinsonism.

Voxel-based network topographies

In our original study, we attempted to utilize a voxel approach to identify learning-related brain networks [Nakamura et al., 2001]. Despite the success in

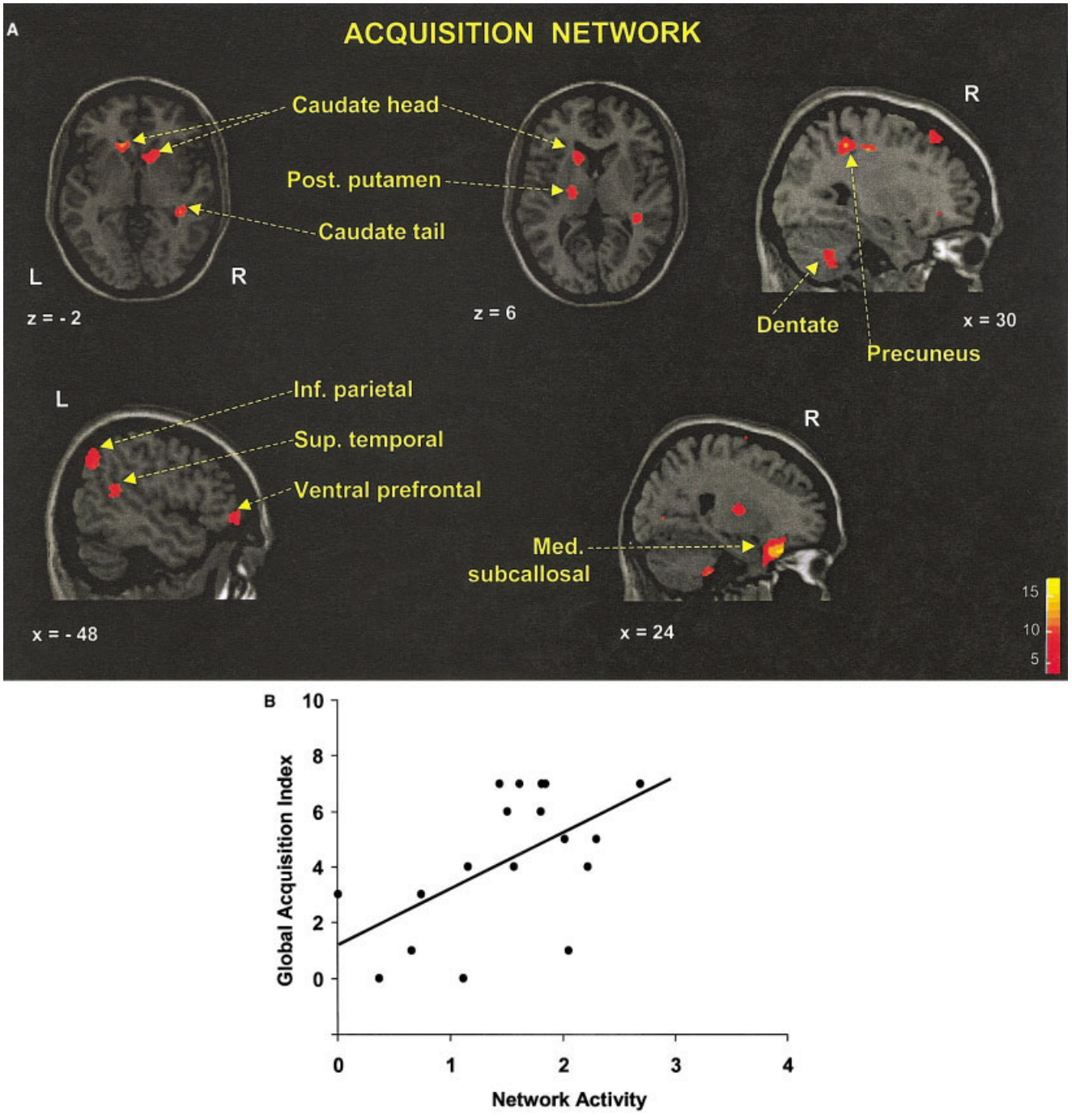

Figure 2.

Voxel-based network analysis of $H_2{}^{15}O$/PET data from 18 healthy controls scanned during motor sequence learning: acquisition pattern. **A:** In the normal cohort, subject scores for a linear combination of the third and fifth principal components (PC 3 and PC 5, accounting for 9.0% of the Subject × Voxel variance) correlated with target acquisition ($R^2 = 0.31$, $P < 0.01$). **B:** This network topography was characterized by learning-related activations (RT*learn* > M*pred*) in the caudate and ventral prefrontal cortex, as well as in the superior temporal gyrus and posterior parietal regions. [Positive region weights (red-yellow) were thresholded at $Z = 2$ to display clusters contributing significantly ($P < 0.01$) to the network (see text)].

TABLE III. Regions contributing to the acquisition-specific network

Coordinates*			
x	*y*	*z*	Region
−9	16	4	Left caudate (head)
5	10	0	Right caudate (head)
30	−55	−21	Right dentate nucleus
−42	55	−12	Left medial frontal gyrus (BA 11)
10	5	−18	Right subcallosal gyrus (BA 25)
−48	−40	46	Left inferior parietal lobule (BA 40)
−22	−36	46	Left precuneus (BA 7)
40	−52	50	Right precuneus (BA 7)
−60	−42	16	Left superior temporal gyrus (BA 22)
−50	−20	−28	Left inferior temporal gyrus (BA 20)
41	−32	3	Right superior temporal gyrus/caudate (tail)

* MNI standard space.

extracting reproducible regional covariance patterns from ROI data, analogous voxel-based learning topographies were not identifiable. We attributed this to the small number of subjects analyzed. Inherently, ROI approaches involve a considerable degree of spatial editing: brain regions considered to be anatomically/functionally irrelevant on empiric or hypothetical grounds are excluded from analysis. This approach appears to be justified in the case of our motor sequence learning task, given the reproducibility of the ROI-based patterns across normal and PD cohorts. However, the availability of a larger combined cohort of normals in the current study provided an opportunity to map the learning networks on a voxel basis. As in the ROI-based analysis, the voxel approach generated discrete topographies relating to different aspects of the sequence learning process.

Retrieval networks

PC 1, representing the major source of Subject × Region variance, was associated with target retrieval. Despite the relatively lower eigenvalue (effect size) associated with the voxel-based retrieval pattern, it predicted performance in the healthy controls and in untreated PD patients to a degree that was nearly identical to its ROI-based analogue. Indeed, a high correlation (R^2 = 60%) existed between subject scores for the two retrieval patterns in both the normal and PD populations.

Despite these similarities, the voxel and ROI-based retrieval patterns are by no means topographically identical. The voxel-based retrieval network covered all areas previously found by the ROI technique, i.e., the DLPFC and precuneus bilaterally, and the right superior parietal lobule. The functional-anatomical role of these regions in motor sequence learning has been discussed previously (Nakamura et al., 2001). We note, however, that the voxel-based retrieval network included contributions from brain regions that were not identified with the ROI approach. Specifically, voxel mapping identified covariate activations in the occipital association cortices, lateral ventral prefrontal cortex, and the right anterior cerebellum. The activation clusters in the occipital lobe likely subserve visuomotor transformation processes [Frutiger et al., 2000; Honda et al., 1998; Miller 1987; Nishitani et al., 1999], and ought to be similar in magnitude to those occurring with the M*pred* reference task. Nonetheless, it is conceivable that the higher visuospatial demands of the learning task required greater regional activation

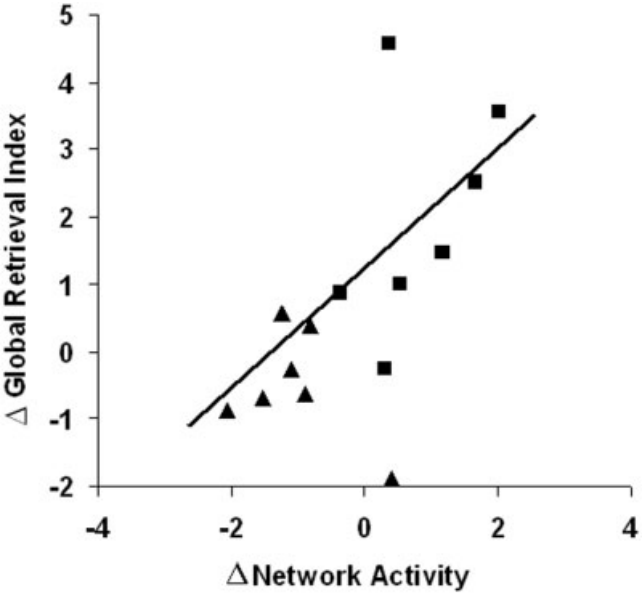

Figure 3.
Changes in learning performance and network activity during acute antiparkinsonian intervention with internal pallidal deep brain stimulation (squares) or levodopa infusion (triangles). Treatment-mediated (ON–OFF) changes in the subject scores for the normal retrieval network correlated significantly with concurrently measured changes in the global retrieval index (R^2 = 0.40, $P < 0.01$). Learning performance and network activity tended to increase during pallidal stimulation and to decline with levodopa infusion (see text).

at this locus. The precise role of the lateral ventral prefrontal cortex in sequence learning is currently unknown. Activations in this area in humans have been associated with category learning [Reber et al., 1998], the encoding and retrieval of pictures of objects [Ranganath et al., 2000], as well with the maintenance of working memory during encoding and retrieval [Wagner 1999].

The voxel-based retrieval network also included areas that have been previously associated with the ROI-based *acquisition* topography, i.e., the left DLPFC, pre-SMA, and anterior cingulate cortex [Nakamura et al., 2001]. The fact that the retrieval and acquisition performance indices are intercorrelated suggests that these aspects of learning may also overlap topographically. Our previous study emphasized the independence of acquisition and retrieval by computing the respective networks from orthogonal principal components. While useful as a starting point for network analysis, this assumption may not be completely valid. Indeed, the inclusion of subject scores for the voxel-based *retrieval* pattern (PC 1) in multiple linear regression enhanced the correlation with *acquisition* performance by approximately 20%. The notion that the two learning patterns share common features is compatible with electrophysiological and fMRI studies showing a gradual and individually variable transition from frontal to parietal processing during sequence learning consolidation [Hikosaka et al., 1999; Ranganath et al., 2000; Sakai et al., 1998].

Acquisition networks

Voxel-based network analysis delineated an acquisition-related pattern that included regions identified in the previous ROI-based analysis as well as additional clusters. Specifically, the acquisition pattern included bilateral activation of the caudate head, left posterior putamen, and right dentate nucleus, as well as the right medial subcallosal cortex (BA 25), the left lateral ventral prefrontal (BA 11) and inferior temporal (BA 20) areas, and the medial superior temporal gyrus. Several of these regions, e.g., BA 11 and 25, were not likely to have been adequately sampled with the ROI template. While these regions have traditionally been implicated in brain activation related to the emotional valence of cognitive tasks [Barbas 2000; Bechara et al., 2000; Blood et al., 2001; Small et al., 2001], they have also been associated with motor planning [Okuda et al., 1998]. Our study was not specifically designed for neutral emotional valence and subjects received continuous visual feedback. Thus, implicit rewarding may have contributed to the subcallosal and ventral prefrontal activity found with our paradigm.

A small area within the left temporal cortex, not captured by ROI analysis, also contributed to the voxel-based acquisition pattern. In other learning paradigms, activity of the left temporal cortex has been related to verbal processing, while visuospatial encoding and retrieval were related to homotypical regions in the right hemisphere [Bernard et al., 2001; Golby et al., 2001; Kohler et al., 2000]. Nonetheless, during object-centered spatial information processing, Honda et al. [1998] detected activations in the left medial temporal gyrus adjacent to the areas identified in our acquisition network. However, we note that these activations might also stem from a different source. In our paradigm, subjects may have used silent counting as a mnemonic strategy during sequence learning. Thus, activation in the left superior and middle temporal gyrus may reflect brain activation related to word generation [Price, 2001].

Additionally, the acquisition network included activation of the medial part of the right superior temporal gyrus spreading into the vicinity of the tail of the caudate nucleus, and the parahippocampal gyrus. The functional role of the caudate tail in humans is unknown. In primates, this region is a major projection site of the extrastriate visual cortex [Brown et al., 1995; Cheng et al., 1997] and has been proposed as a functional relay for visuomotor processing [Brown et al., 1995]. Involvement of the parahippocampal gyrus in target acquisition is consistent with the role of right hippocampus and neighboring structures in the early phases of spatial memory [Curtis et al., 2000; Maguire et al., 1996; Toni et al., 2001].

ROI techniques may similarly have undersampled highly localized network contributions from the cerebellum. Cerebellar activation was not detected in the early ROI-based analyses. By contrast, both voxel-based learning networks included cerebellar activation: the right dentate nucleus for acquisition and the right superior anterior cerebellum (lobule III) [Schmahmann et al., 1999] for retrieval. The cerebellum is thought to play a role in basic forms of motor learning, such as classical conditioning or motor skill acquisition [Doyon et al., 2002; Mauk 1997]. However, the specific involvement of the cerebellum in the learning of sequential information has been debated [Hikosaka et al., 1999; Ivry and Baldo, 1992; Jueptner and Weiller, 1998; Tanji 2001]. A cognitive role for the cerebellum has been proposed in sequence learning independent of motor execution [Levisohn et al., 2000], as well as in associative learning [Drepper et al., 1999; Schultz and Dickinson, 2000; Timmann et al.,

2002; Tucker et al., 1996]. The precise localization of these functions within the primate cerebellum is currently unknown.

Effects of age on learning networks

Target acquisition and retrieval indices were predicted by the activity of the respective learning networks, irrespective of subject age. Age correlated weakly ($R^2 \sim 0.20$) both with acquisition performance and with the activity of the corresponding network. This suggests that the age-related decline in target acquisition may be mediated by concomitant changes in the expression of this pattern. By contrast, although retrieval performance correlated with age ($R^2 = 0.20$), there was no association between retrieval network activity and subject age. Although the magnitude of correlation between these two variables is small, a subtle relationship cannot be excluded in the study in a relatively small sample of subjects. However, in a stepwise multiple regression analysis, we found that correlations between network activity and performance were unrelated to subject age, suggesting that the retrieval network is an age-independent topography. However, we emphasize that our analysis focused on the reproducibility of previously established brain activation-performance relationships in different age groups. The delineation of specific aging effects on brain activation responses is a topic of ongoing investigation.

Modulation of network activity by antiparkinsonian therapy

In this study, we found that the normal retrieval network also predicted learning performance in a cohort of moderately advanced PD patients scanned in the untreated state. By contrast, target acquisition was less reliably correlated with the expression of the corresponding brain network. These findings are compatible with those reported by us previously in early stage patients [Nakamura et al., 2001]. We additionally found that treatment-mediated changes in retrieval performance correlated significantly with concurrent modulation of learning network activity. To date, few imaging studies have addressed the cognitive effects of antiparkinsonian treatment. In a recent study, we used SPM to compare brain activation during motor sequence learning in PD patients on and off pallidal stimulation [Fukuda et al., 2002]. GPi DBS increased learning-related activation in the DLPFC, premotor cortex and posterior parietal regions while levodopa infusion produced only minimal increases in the premotor cortex, as well as decrements in the parieto-occipital association regions. In both interventions, the regional alterations identified with SPM did not correlate with changes in performance.

Treatment-mediated changes in behavior did however correlate significantly with modulation of the normal retrieval network. In the case of GPi DBS, improved sequence learning occurred concurrently with increased network activity. Indeed, network activity increased with stimulation in six of the seven GPi DBS patients, suggesting enhanced functioning of higher order CSPTC loops and related pathways [Fukuda et al., 2002; Wichmann and DeLong, 1996]. By contrast, six of the seven subjects undergoing levodopa infusion demonstrated reductions in network activity with treatment. As reported by Mattay et al. [2002], we found that changes in learning performance with levodopa are heterogeneous across subjects. Those investigators and others [Cools et al., 2002] detected a significant effect of drug on working memory performance. This was associated with a reduction in prefrontal activation responses, which was attributed to a direct effect of dopamine on the mesocortical pathways. Our sample of levodopa-treated patients is too small to assess between-subject differences in the cognitive effects of drug administration. Medication dose and disease stage, separately and in combination, may influence learning performance and brain activation responses during dopaminergic treatment.

The differing effects of levodopa and DBS on sequence learning, despite comparable motoric benefit (35–40% changes in UPDRS motor scores), are consistent with current notions of tonic and phasic dopaminergic action [Brooks, 2001]. Dopaminergic therapy may suffice to restore tonic striatal dopamine release, which is necessary to maintain the execution of motor programs. By contrast, it is possible that DBS mimics phasic striatal dopamine release, which is required for new learning. The modulation of network activity by antiparkinsonian therapy and its relationship to learning performance suggests that regional covariance analysis can be useful in the objective assessment of cognitive processing in PD and other neurodegenerative disorders.

CONCLUSIONS

Our findings indicate that the network topographies associated with motor sequence learning are reproducible across populations and that network-performance relationships are independent of subject age. New voxel-based network mapping approaches can be used to improve the spatial definition of these

learning-related topographies. The significant correlation between changes in network activity and concurrent treatment effects suggests that this imaging technique may be suitable to assess the impact of therapy on cognition in neurodegenerative disorders.

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