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Early Parkinson's Disease: Longitudinal Changes in Brain Activity during Sequence Learning

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Abstract

Impairment of sequence learning is common in Parkinson's disease (PD), but the time course of this cognitive abnormality is not known. We assessed longitudinal changes in sequence learning performance and associated task-related cerebral blood flow in 13 early stage PD patients who underwent H₂¹⁵O PET at baseline and again two years later. Ten healthy volunteer subjects served as controls. A trend toward decline in learning performance ($p=0.08$) was evident over the two years of follow-up. During this interval, significant declines in learning-related activation were detected in parietal and temporo-occipital association areas and in the right dorsolateral prefrontal cortex. Learning-related activation in these regions was normal at baseline, but declined to subnormal levels ($p<0.01$) at two years. Significant hippocampal activation ($p<0.005$) was present in the subjects with high learning performance over time. The findings are consistent with a decline in learning-related neural activity in cortical areas with prominent Lewy body formation.

Keywords

Parkinson's disease; sequence learning; disease progression; positron emission tomography

Introduction

Cognitive deficits in non-demented Parkinson's disease (PD) are frequent (Levin and Katzen, 2005; Caballol et al., 2007) and can involve sequence processing early in the clinical course of the disease (Nakamura et al., 2001; Ghilardi et al., 2003). These deficits have been attributed to subcortical influences on prefrontal activity (Cools et al., 2002; Carbon and Eidelberg, 2002), local neurochemical changes (Francis and Perry, 2007), and histopathological changes in the cerebral cortex itself (Braak et al., 2005). While circumscribed cognitive deficits can be

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found at the early stages in PD, the scope and intensity of these changes can worsen with disease progression (Cooper et al., 1991; Muslimovic et al., 2005; Williams-Gray et al., 2007). Nonetheless, the time course for the development of cognitive dysfunction in PD is not precisely known (Williams-Gray et al., 2007; Muslimovic et al., 2007b).

Functional imaging studies have linked cognitive deficits in early PD to abnormal activation responses in the prefrontal cortex and related structures (Nakamura et al., 2001; Cools et al., 2002; Mattay et al., 2002; Williams-Gray et al., 2007). Additionally, in the resting state, covarying reductions in the metabolic activity of frontal and parietal cortex have been linked to cognitive decline (Huang et al., 2007a). Nonetheless, the latter changes reach significance only at moderately advanced disease stages (Huang et al., 2007b; 2008).

In health, explicit motor sequence learning involves the activation of distinct spatially distributed networks, with contributions from the basal ganglia and ventral prefrontal cortices during the initial learning period, and from prefrontal and parietal regions at later stages (Nakamura et al., 2001; Carbon et al., 2003; 2004; Doyon and Benali, 2005). We have found that motor sequence learning networks activated by non-demented PD patients are topographically similar to those deployed by healthy subjects (Nakamura et al., 2001; Carbon et al., 2003). However, to achieve a normal level of learning performance, PD patients tend to employ activation strategies used by normals at greater levels of task difficulty (Mentis et al., 2003b). This compensatory response in early PD involves bilateralization of prefronto-parietal and cerebellar activation (Mentis et al., 2003a).

Based on the results of these cross-sectional activation studies, we designed a longitudinal within-subject study to assess the time course of impaired sequence learning performance in early PD and to determine when compensatory brain activation mechanisms begin to fail.

Materials and methods

Study design

We used ^{15}O -labeled water (H_2^{15}O) and positron emission tomography (PET) to assess longitudinal changes in modality-independent explicit sequence learning-related activation in early stage PD patients scanned twice over a two-year period. To explore changes in sequence processing independent of motor involvement, the subjects performed a visual sequence learning task in addition to the previously described motor sequence learning paradigm (Carbon et al., 2003). Longitudinal changes in regional cerebral blood flow (rCBF) were also recorded in motor and visual non-learning reference conditions.

Subjects

We studied 13 right-handed early stage PD patients [age 57.8 ± 10.3 years (mean $\pm$ SD); disease duration 3.2 ± 2.6 years; off-medication Unified Parkinson's Disease Rating Scale (UPDRS) motor scores 8.5 ± 5.0 ; see Table 1]. The subjects underwent H_2^{15}O PET imaging at baseline and after two years (mean interval 2.0 ± 1.4 years). Initially, all patients had hemiparkinsonism (left: 6; right: 7). [Baseline imaging data from this cohort have been reported in part (Carbon et al., 2003; 2004). We have also published a separate study of longitudinal changes in motor activation responses (Carbon et al., 2007). Limited longitudinal sequence learning data from a subset of the current patient cohort has been presented previously as part of meeting proceedings (Carbon and Eidelberg, 2006).]

At baseline, six subjects were medication-naïve and six subjects were chronically treated with levodopa/carbidopa, dopamine agonists, or both. The remaining subject was chronically treated with deprenyl. By the second time point, all but one were medicated. In all treated subjects, antiparkinsonian medications were discontinued 12 hours before behavioral assessments (see

below) and PET imaging. Ten healthy volunteer subjects (age 52.3 ± 12.5 years) served as controls for the learning experiments. There was no significant difference in age between the subjects and the PD patients ($p > 0.25$).

Behavioral tasks and performance measures

During $H_2^{15}O$ PET imaging, all subjects performed a motor sequence learning task (MSEQ), a motor reference task (CCW), a visual sequence learning task (VSEQ) and a visual reference task (S). Task performance was trained before scanning such that CCW performance was automated. The features of these tasks have been presented in detail previously (Nakamura et al., 2001; Carbon et al., 2003; Ghilardi et al., 2003).

Explicit sequence learning tasks

MSEQ: Eight targets were presented in a pseudo-randomized, but 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.

VSEQ: As in MSEQ, eight targets were presented in a pseudo-randomized repeating sequence of eight elements throughout the duration of the 90 s trial block. Subjects were asked to learn the sequence order by attending to the display without moving. They reported the order of the sequence verbally at the end of each trial block.

Reference tasks

CCW: Targets appeared in a predictable counterclockwise order. Subjects had to reach the target in synchrony with the tone.

S: Subjects remained immobile but experienced comparable sensory stimuli as during the activation tasks. Screen targets, cursor images and tones were presented to the subjects asynchronously and irregularly in equal numbers to those used in the learning tasks.

Task performance measures—To quantify learning performance during MSEQ we calculated the number of correctly anticipated movements (Nakamura et al., 2001). The sum of all correctly anticipated targets in each trial block was defined as the global retrieval index (RET_{MSEQ} ; range 0–56). For VSEQ, the number of total correct target locations verbally reported by each subject at the end of a trial block (from 0- unawareness of a repeating sequence to 8- complete correct sequence) represented the declarative score (DS_{VSEQ}), a descriptor of the explicit learning that was achieved in the trial block.

The learning measures were analyzed using Student's t-test and ANOVA. All results were considered significant for $p < 0.05$.

Positron emission tomography

The PD patients were scanned with $H_2^{15}O$ PET at baseline and follow-up; healthy control subjects underwent $H_2^{15}O$ PET at a single time point. All subjects fasted overnight prior to scanning. Antiparkinsonian medications were withheld for at least 12 hours before imaging. Scanning was performed using the GE Advance tomograph at North Shore University Hospital as described in detail elsewhere (Nakamura et al., 2001; Carbon and Eidelberg, 2002). During both PET sessions, each subject was scanned while performing the MSEQ, VSEQ, CCW, and S tasks repeatedly in randomized order with the dominant right arm. Different sequences were employed for each learning trial; psychophysical recording of learning performance was acquired for every run. 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.

Data analysis—Scan preprocessing was performed as described earlier (Argyelan et al., 2008) using SPM5 software (Institute of Neurology, Queen Square, London, UK) implemented in Matlab Version 6.5 (Mathworks, Sherborn, MA, USA). All analyses were performed in the flexible factorial model with baseline age as a covariate of no interest. To minimize the potential confounding effects of concurrent longitudinal changes in rCBF associated with the non-learning motor reference task (Carbon et al., 2007), longitudinal changes were sought within a specific sequence learning (MSEQ – CCW) mask (Supplementary Fig. 1) (Fukuda et al., 2002; Argyelan et al., 2008). The main effects of the sequence learning tasks and the equipperformance changes (see below) were assessed without the use of a mask.

To explore potential compensatory mechanisms in these subjects, we used the behavioral heterogeneity of the cohort to advantage by employing an equipperformance design (Mentis et al., 2003b; Carbon et al., 2008). This study design controlled for the potential confounding effects of differences in task performance over time. To this end, a patient subset was identified in which learning performance was maintained at a high level. In this study, the equipperformance subgroup (PD_{EQUI}) included Subjects # 2, 3, 6, 12, 13 who had excellent VSEQ learning performance at both time points (see Table 1). Learning-related activation in PD_{EQUI} was compared to that observed in the remaining patients (PD_{REM}) who exhibited deterioration in VSEQ performance over time.

For all analyses, activation differences across time points were considered significant at a false discovery rate (FDR)-corrected threshold of $p < 0.05$, with a cluster extent cutoff of $[k_e] > 70$ voxels. We also reported differences within the mask as hypothesis-testing at an uncorrected peak voxel threshold of $p < 0.005$ with the same cluster extent cutoff. Coordinates were reported in the standard anatomical space developed at the Montreal Neurological Institute. Posthoc analyses were used to (1) exclude the possibility that the longitudinal changes differed for the VSEQ and MSEQ conditions, (2) ascertain that these changes were not associated with concurrent longitudinal changes in the CCW and S reference conditions, and (3) contrast with task-specific activation in healthy subjects.

Paired student's t-tests and ANOVA were used as appropriate. All calculations and statistical analyses were performed on PCs running WindowsXP and JMP software (SAS Institute Inc, Cary, NC) for PC.

Results

Learning performance

There was substantial variability across the subjects with respect to changes in learning performance over time (Table 1). Motor sequence learning task performance (RET_{MSEQ}) tended to decline over time [T_1 : 20.4 ± 4.2 (mean $\pm$ SE); T_2 : 15.6 ± 3.7 ; $p = 0.08$]. Visual sequence learning performance (DS_{VSEQ}) did not change significantly over time (T_1 : 5.5 ± 1.1 ; T_2 : 4.8 ± 1.1 , $p = 0.15$). The two performance indices did not differ significantly from healthy control values (RET_{MSEQ}: 26.8 ± 6.6 ; DS_{VSEQ}: 6.56 ± 0.08) at either time point ($p > 0.13$).

Sequence learning-related activation

Main Effects—The main effect of the motor sequence learning task [(MSEQ_{T1} + MSEQ_{T2}) – (CCW_{T1} + CCW_{T2})] was associated with bilateral activation of the precuneus and parietal association cortex (PAC) (BA 7), DLPFC (BA 9), dorsal premotor cortex (PMC) (BA 6), pre-

supplementary motor area (SMA) and temporal association cortex (BA 37) as well activation of the left cerebellar hemisphere (Table 2A). The main effect of the visual sequence learning task in PD $[(VSEQ_{T1} + VSEQ_{T2}) - (S_{T1} + S_{T2})]$ was localized to a similar set of brain regions (Table 2B). The effect of sequence learning across both the VSEQ and MSEQ tasks (Supplementary Fig. 2) involved activation of the lateral and medial PAC (BA 40/7), DLPFC (BA 9/46; $L \gg R$), dorsal PMC (BA 6), pre-SMA (BA 6), and the anterior cingulate cortex (ACC) (BA 32; $L > R$), the cerebellar hemispheres bilaterally and the right temporo-occipital cortex (BA 37). Notably, this pattern was similar to that found experimentally for modality-independent sequence learning $[(MSEQ > CCW) + (VSEQ > S)]$ in the healthy control subjects (supplementary Table 1 A and B). Thus, in all the groups analyzed, learning-related activation was present within the pre-specified sequence learning mask determined in earlier independent subject populations (see Supplementary Fig. 1).

Longitudinal changes in sequence learning-related activation—We found that activation during sequence learning declined bilaterally in the precuneus and in the right PAC (BA 7/40), temporal-occipital cortex (BA 19/37), and DLPFC (BA 9/46) (Fig. 1A and B, *top*; Table 3). Over time, an increase in learning-related activation was observed in the right dorsal anterior cingulate cortex (dACC) (BA 32), extending into the adjacent pre-SMA (Fig. 1C, *top*; Table 3).

Posthoc analysis (Fig. 1, *bottom*) revealed that in PAC and DLPFC, rCBF during learning was normal at baseline, but declined to abnormal levels ($p < 0.001$ for PAC, $p < 0.01$ for DLPFC) at two years. By contrast, in the ACC (BA 32), rCBF during learning was lower than normal at baseline ($p = 0.01$), but not at follow-up. In these brain regions, there was no significant longitudinal change in rCBF recorded during the non-learning motor task.

Equipperformance comparison—The equipperformance subgroup (PD_{EQUI}) displayed a longitudinal increase in visual learning-related ($VSEQ - S$) activation, which was localized to the right hippocampus and the adjacent parahippocampal gyrus (BA 27, 28; $Z = 0.57$, cluster extent 319, $p < 0.05$ FDR-corrected) (Fig. 2, *top*). In the PD_{EQUI} group, hippocampal task-specific activation (i.e., $VSEQ > S$) was present at the second time point ($VSEQ$ vs S at T_2 ; $p = 0.02$) but not at baseline (Fig. 2, *bottom*). There was no evidence of learning-related activation in this region in the healthy subjects or in the remaining longitudinal PD patients (PD_{REM}) at either baseline or follow-up ($p > 0.5$). Further analysis revealed that this effect was attributable to longitudinal increases in neural activity recorded during learning ($VSEQ$: T_1 vs T_2 ; $p = 0.002$) as opposed to changes in rCBF in the control condition (S : T_1 vs T_2 ; $p = 0.10$). The $VSEQ$ change was referable to the second time point in which rCBF was greater in the equipperformance subgroup as compared to the remaining patients who deteriorated behaviorally over time (PD_{EQUI} vs PD_{REM} at T_2 ; $p = 0.03$). There was no between-subgroup difference in baseline rCBF recorded in either $VSEQ$ or S ($p > 0.5$). There were no areas with significant decline in task-specific activation over time.

Discussion

In this study, we demonstrate progressive changes in the neural responses that mediate sequence learning during the early clinical course of PD. Notably, learning-related activation declined in DLPFC and PAC, areas previously found to correlate with task performance (Nakamura et al., 2001; Carbon et al., 2003; Argyelan et al., 2008). By contrast, increasing activation over time was noted in the dACC, an area not consistently deployed to enhance learning performance (Polli et al., 2005).

Surprisingly, a clear decline in learning performance was found in only half of the cohort. Muslimovic and colleagues (2007a) have recently demonstrated that newly diagnosed drug-

naïve PD patients do not exhibit sequence learning deficits, while earlier studies have repeatedly shown sequence learning deficit early in the disease (Mahieux et al., 1998; Nakamura et al., 2001; Ghilardi et al., 2003; Siegert et al., 2006; Muslimovic et al., 2007b). The declines in visual task performance measures were relatively less pronounced than for the motor sequence learning task. Because dual tasking is not involved in VSEQ, this task was overall less challenging than MSEQ for patients and controls, with a higher percentage of subjects completing the learning of the target sequence in the former task. That said, the change in both learning descriptors over time was considerably smaller than the concurrent deterioration in motor functioning observed in the same patients (Carbon et al., 2007; Huang et al., 2007b).

As expected in both PD and healthy control subjects, learning-related activation in MSEQ and VSEQ was found in largely overlapping areas of the prefrontal, parietal and occipito-temporal regions. This observation confirms the results of previous studies in patients and controls scanned while performing the same (Nakamura et al., 2001; Fukuda et al., 2002; Carbon et al., 2003) or related sequence learning paradigms (Mentis et al., 2003b; Doyon and Benali, 2005). Additionally, the results indicate that prefronto-parietal activation during sequence learning is largely effector independent. Interestingly, although VSEQ did not involve explicit motor planning, this task was associated with significant activation of secondary motor cortices. Whether or not VSEQ involves features of motor imagery is not known. Nonetheless, by merging the MSEQ and VSEQ scans, we were able to characterize the effects of sequence learning in the longitudinal activation data while minimizing potential changes in motor activation response that may have concurrently occurred. That said, the intersubject variability of the performance indices and the associated changes in these measures over time was quite high. It is therefore likely that the study was underpowered for the detection of specific VSEQ and MSEQ differences.

As hypothesized, we detected a decline in DLPFC and parietal activation over time. Effective compensatory strategies in non-demented PD patients have been previously described in these brain regions, with increases in learning-related activation to achieve a normal level of performance (Mentis et al., 2003b). While these mechanisms were evident at early clinical stages, our data suggest that the ability to compensate through elevated task-specific activation diminishes with disease progression. In our cohort, decreasing activation was evident in the DLPFC and PAC, areas that also exhibit parallel declines in metabolic activity in the rest state (Huang et al., 2007b; 2008). Moreover, the observed declines in prefrontal and parietal activation during sequence learning are unlikely to be a consequence of the normal aging process. Longitudinal activation studies in a healthy aging cohort were not available for comparison with the PD progression group. However, a cross-sectional PET study of learning-related activation in normal subjects failed to reveal significant effects of aging on task performance or on associated neural responses in these brain regions (Carbon et al., 2003).

It is possible that both the rest state and activation changes in these regions reflect evolving cortical pathology. Nevertheless, postmortem studies have reported neocortical Lewy Body (LB) inclusions only in patients with severe motor disability (Braak et al., 2003; 2005). By contrast, our *in vivo* study was limited to early stage non-demented PD patients. Therefore, the cortical activation changes observed in our cohort do not necessarily reflect local LB inclusions as is more likely the case at later disease stages. Rather, our data suggest that functional impairment may antecede the appearance of clear-cut degenerative changes in these neocortical areas.

Most of the observed longitudinal changes in learning-related brain activation point to the loss of efficient processing, cognitive reserve, or both. Despite a marginal decline in performance over time, there was no evidence of a significant compensatory response across the entire

cohort. Considering the heterogeneity of cognitive decline in PD, it would not be surprising if different compensatory mechanisms were deployed for different subpopulations of otherwise similar patients. To identify such processes, we analyzed the subgroup of individuals who maintained a high level of performance throughout the course of the study. We found that these subjects engaged the right parahippocampal gyrus to sustain a high degree of learning performance, despite progressive impairment of activation in the other cortical regions. Nonetheless, in accord with other studies of sequence processing (Doyon, 2008), prominent hippocampal activation during visual sequence learning was not present in our healthy control group. However, hippocampal activation is known to be involved in spatial location processing (Warburton et al., 2001; Burgess et al., 2002; Postma et al., 2008) and early phases of sequence learning in normals (Carbon et al., 2003). It has been argued that striatal and hippocampal activation are competing and dissociable processes during procedural learning (Poldrack et al., 2001; Myers et al., 2003). However, increasing evidence from experimental studies favors a model of integrated prefrontal-striatal and hippocampal functioning in spatial processing (cf. Mizumori et al., 2008; Doeller et al., 2008).

In this vein, increased hippocampal activation during motor planning has been reported previously in several independent PD cohorts (Dagher et al., 2001; Moody et al., 2004; Beauchamp et al., 2008). This suggests that hippocampal activation can substitute for deficient striatal and prefrontal activation under certain pathological conditions. So why then did only a high performing subgroup of PD patients exhibit this compensatory strategy in the face of declining striato-prefrontal processing? One possibility is that incipient hippocampal cell loss/atrophy contributed to the inconsistent engagement of this region. Indeed, volume loss in this region has been found to be associated with the subsequent development of dementia in these patients (Camicioli et al., 2003; Tam et al., 2005; Bouchard et al., 2008). In this light, the lack of a compensatory hippocampal activation response may be a specific functional indicator of incipient cognitive decline in non-demented PD patients at early disease stages.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1. Longitudinal changes in sequence learning related activity

Top: Brain regions in which learning-related activation changed significantly over time in early PD (see text). [SPM{t} maps were superimposed on a single-subject MRI T1 template. The color stripe represents T-values thresholded at 2.5, $p = 0.005$, uncorrected within the task-specific mask.]

Bottom: Bar diagrams of regional cerebral blood flow (rCBF) measured during sequence learning in the significant clusters identified on the voxel-based analysis (see above). Values (mean $\pm$ SE) at baseline (gray) and at two year follow-up (black) for the key regions are depicted for the PD patients; values for healthy controls (white) are presented for reference. Longitudinal reductions in rCBF recorded during task performance were present bilaterally in the parietal association cortex (PAC) and precuneus (A), and in the right dorsolateral prefrontal cortex (DLPFC) (B). An increase in learning-related rCBF over time was present in the dorsal anterior cingulate cortex (dACC) (C). This regional change was also present in the non-learning motor reference condition (see text).

Figure 2. Increased hippocampal activation in PD patients with sustained learning performance over time

Top: Longitudinal increases in hippocampal activation during visual sequence learning in a subgroup of PD patients (PD_{EQUI}) who maintained equivalently high learning performance at both time points (see text). [SPM{t}] map was superimposed on a single-subject MRI T1 template. The color stripe represents T-values thresholded at 3.6, $p = 0.05$, FDR-corrected].

Bottom: Regional cerebral blood flow (rCBF) in the right hippocampal cluster displayed above. rCBF in this region was measured posthoc during visual sequence learning (V) and in the non-learning sensory (S) reference condition (see text). Values ($\pm$ SE) are displayed for the healthy control subjects (white) and for the PD patients at baseline (light gray) and at two year follow-

up (dark gray). The patient cohort was divided into a subgroup with equivalently high learning performance (PD_{EQUI}) at the two time points (*middle*). The remaining patients comprised a second group (PD_{REM}) that was characterized by deteriorating learning performance over time (*right*). The data indicate an increase in learning-related activation in the PD_{EQUI} patients in whom learning performance was maintained despite concurrent decline in motor functioning. This compensatory response was not present in normal subjects or in the PD_{REM} patients.

Table 1

Patient Data

Patient	Age/Gender	Baseline			24 Months		
		UPDRS ^a	MSEQ	VSEQ	UPDRS	MSEQ	VSEQ
1	57/M	5.0	10	3	16.0	9	2
2	57/M	4.5	43	8	8.0	34	8
3	49/M	10.0	19	8	13.0	23	8
4	32/M	12.0	34	8	40.0	21	4.5
5	60/M	9.0	21	2	20.0	4.5	1.5
6	52/M	8.0	20.5	8	7.0	29	8
7	52/M	6.0	46	8	12.0	41.5	4
8	58/F	3.0	20	1.5	11.0	2	1.5
9	67/F	15.0	4	2	17.0	4	3
10	70/M	2.0	4.5	2.5	8.0	6	1
11	70/M	19.0	0.5	--- ^b	22.0	0	--- ^b
12	65/F	11.5	9	7	12.0	13	8
13	62/M	5.0	35	8	15.0	16	8

^aUnified Parkinson's Disease Rating Scale motor ratings in the off-medication state.

^bData not available.

MSEQ = motor sequence learning task; VSEQ = visual sequence learning task

Table 2
Sequence learning-related activation responses in early PD: main effects of the motor and visual tasks

Brain region	MNI coordinates			Z-max	Cluster size
	x	y	z		
A. Motor Sequence Learning (MSEQ > CCW)^a					
R/L i/sPAC, precuneus [BA 7]	-32	-64	52	6.34	>2000 ^c
L PMC, SMA, DLPFC [BA 6/9]	-32	0	52	5.74	>2000
R PMC, SMA, [BA 6]	32	10	60	4.19	369
R DLPFC [BA 9]	32	38	38	4.19	131
R Orbitofrontal and frontopolar area [BA 11/10]	44	52	-10	3.20	90
L Insular/inferior prefrontal gyrus [BA 13/47]	-28	26	-4	3.45	75
L Middle occ.-temporal gyrus [BA 37/19]	-48	-64	-10	3.80	72
R Middle and inferior occ.-temporal gyrus [BA 37/20]	64	-58	-24	3.82	228
L Insular/inferior prefrontal gyrus [BA 13/47]	-28	26	-4	3.45	75
L Cerebellum posterior lobe	-36	-60	-40	4.33	262
B. Visual Sequence Learning (VSEQ > S)^b					
R sPAC, precuneus [BA 7]	18	-74	60	5.47	195
L sPAC, precuneus [BA 7]	-16	-72	44	5.45	398
L PMC, SMA [BA 6]	-56	-6	44	4.83	111
L Precuneus, cuneus, posterior cingulate [BA 18/30/31]	-6	-88	10	4.34	351

^aMain effect of motor sequence learning: (MSEQT1 + MSEQT2) - (CCWT1 + CCWT2)

^bMain effect of visual sequence learning: (VSEQT1 + VSEQT2) - (ST1 + ST2)

^cCluster size = number of significant voxels in each cluster (k_e)

MSEQ = motor sequence learning task; CCW = kinematically similar motor execution reference task; VSEQ = visual sequence learning task; S = sensory reference task (see Methods).
i/sPAC = inferior/superior parietal association cortex; PMC = pre-motor cortex; SMA = supplementary motor cortex; DLPFC = dorsolateral prefrontal cortex.

Table 3

Longitudinal changes in sequence learning-related activation

Brain region	MNI coordinates			Z-max	Cluster size
	x	y	z		
Decreased activation at 24 months ^a					
R i/sPAC [BA 40/7]	46	-56	52	5.56	196 ^c
R DLPFC [BA 9/46]	38	34	34	3.69	196
L Precuneus, sPAC [BA 7]	-20	-82	46	3.65	274
R Temporo-occipital gyrus [BA 19]	38	-84	36	3.11	120
L Temporo-occipital gyrus [BA 37/19]	-58	-66	-16	3.60	96
Increased activation at 24 months ^b					
R dorsal anterior cingulate cortex [BA 32]	10	4	50	3.81	148

^a(MSEQ/VSEQ)/T2 < (MSEQ/VSEQ)/T1

^b(MSEQ/VSEQ)/T2 > (MSEQ/VSEQ)/T1

^cCluster size = number of significant voxels in each cluster (k_e)

i/sPAC = inferior/superior parietal association cortex; DLPFC = dorsolateral prefrontal cortex