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Dissociating sequence learning performance in Parkinson's disease: Visuomotor sequence acquisition and pattern judgment on a serial reaction time task

Jared G Smith[1,*] and John McDowall[2]

[1]Division of Population Health Sciences and Education, St George's, University of London, London, United Kingdom, *Email: jasmith@sgul.ac.uk; [2]School of Psychology, Victoria University of Wellington, Wellington, New Zealand

In this study, the sequence learning performance of 16 non-demented patients with Parkinson's disease (PD) was compared with 18 age-matched healthy controls on a verbal version of the serial reaction time (SRT) task intended to encapsulate both visuomotor- and judgment-linked learning processes. Visuomotor sequence performance in PD patients was closely related to baseline response speed, with robust learning demonstrated by patients who responded with comparable speed to controls but severely impaired performance in patients who responded slowly. In contrast, both fast- and slow-responding PD patients were able to successfully categorise patterns according to their sequential status, a performance that was linked to declarative memory for the sequence. The findings highlight the important role of event timing in SRT performance and are in accord with the hypothesis that, despite the important role played by the basal ganglia in motor sequence learning, basal ganglionic dysfunction may not substantially impair sequence order learning so much as the translation of sequence knowledge into rapid motor performance for some PD patients. Intact pattern judgment on the SRT experiment suggests that the integrity of the neostriatum is not essential for learning judgment-linked categorical information about sequences of temporal stimulus movement.

Key words: basal ganglia, serial reaction time, sequence learning, Parkinson's disease, procedural learning

INTRODUCTION

A wide variety of real world skills crucially depend on the ability to detect patterns and organise individual events into complex visuomotor sequences. While people are frequently aware of these structures and can describe them readily, many of the sequential behaviours that people learn appear to be learned in a procedural manner without explicit awareness of the sequential regularities that underlie behavioural performance. This type of learning has often been described as "implicit learning" (Dienes and Berry 1997). Implicit learning is typically construed under the banner of nondeclarative memory, which encompasses a variety of heterogeneous tasks that are not subserved by a single brain region but is widely thought to be mediated by neuroanatomically and functionally distinct systems from those underlying explicit (declarative) memory (Squire and Zola 1996).

Much of the evidence on the neural mechanisms of implicit sequence learning comes from the serial reaction time (SRT) task (Nissen and Bullemer 1987). In the standard version of the SRT task, participants respond as quickly as possible to the presentation of a visual stimulus appearing at one of several different spatial locations on a computer monitor. Participants are required to respond by pressing a key which corresponds to the position of the stimulus. Importantly, unbeknown to participants, the location of the stimulus follows a sequence which is cyclically repeated over a number of trials. Sequence learning is typically inferred from decreased response times (RTs) across successive sequenced trials and, more specifically, participants' faster RTs for sequenced trials than for trials in which the positions of the stimuli appear in a random order. In the absence of explicit knowledge about the under-

Correspondence should be addressed to J.G. Smith
Email: jasmith@sgul.ac.uk

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lying visuomotor sequence, differences in RT between responses to sequential and random stimuli are assumed to reveal behavioural improvements that reflect implicit knowledge. This argument is supported by studies with amnesic patients who have sustained damage to the hippocampus and related medial temporal lobe (MTL) and midline diencephalic brain structures and exhibit declarative memory impairments, which have observed normal SRT sequence acquisition strongly suggesting that structures other than the MTL (explicit memory) system can support learning on visuomotor sequence learning tasks (Reber and Squire 1994). Rather, converging evidence from animal research and human brain-imaging studies implicates an important role of cortico-striatal circuitry in nondeclarative memory acquisition (for a review, see Packard and Knowlton 2002), including visuomotor sequence learning on the SRT (Rauch et al. 1997, Peigneux et al. 2000, Destrebecqz et al. 2005, Karabanov et al. 2010, Rieckmann et al. 2010). Yet specifying the necessity of neostriatal involvement in SRT sequence learning through studies of patients with disturbed neostriatal circuitry, such as Parkinson's disease, has proved more difficult.

Parkinson's disease (PD) is a common neurological disorder caused by marked degeneration and atrophy of the substantia nigra and a consequent major reduction of the dopaminergic projection to the striatum (Agid et al. 1987). The characteristic motor symptomatology includes bradykinesia (slowness), akinesia (difficulty initiating movements), tremors, rigidity, motor arrests, postural instability, gait disturbance, and dysarthria (Barbosa et al. 1997). A salient feature of basal ganglia anatomy is their participation in multiple loops with the cerebral cortex. Traditional models of basal ganglia-cortical physiology have posited five parallel but structurally and functionally separate circuits: "motor", "oculomotor", "dorsolateral prefrontal", "lateral orbitofrontal" and "anterior cingulated" (Alexander et al. 1990). Each circuit is assumed to engage separate regions of the basal ganglia and thalamus, and the output of each is centred on a different part of the frontal lobe. Therefore, although the pathology is predominantly subcortical, frontal cortical function also is disrupted in PD with an emergence of neuropsychological impairments in the form of executive deficits such as planning, goal-directed behaviour, response selection, and task switching (Owen et al. 1993, Cools et al. 2001).

A number of studies have observed impaired sequence acquisition using the SRT paradigm in patients with degenerative basal ganglia diseases such as PD (Jackson et al. 1995, Helmuth et al. 2000, Shin and Ivry 2003, Deroost et al. 2006, Muslimović et al. 2007, Wilkinson and Jahanshahi 2007) and Huntington's disease (HD; Kim et al. 2004). PD patients have also demonstrated SRT sequence learning deficits on SRT tasks designed to minimise the influence of the motor symptoms of PD, in which motor response demands were reduced (Vakil et al. 2000) or SRT performance required verbal responses to sequential stimuli (as opposed to manual button presses; Westwater et al. 1998, Smith and McDowall 2004, 2006), suggesting the failure of PD patients to develop normal sequence-specific learning in the SRT is not attributable to their general movement difficulties. Nevertheless, it is worth considering that other studies of patients with basal ganglia dysfunction have revealed only minor sequence-specific learning deficits (Pascual-Leone et al. 1993, Sommer et al. 1999, Seidler et al. 2007, Stephan et al. 2011) or reported preserved sequence-specific learning and only nonspecific impairments such as reduced RT improvements over sequential trials (Exner et al. 2002, Werheid et al. 2003). Furthermore, normal SRT performance has previously been observed in both patients with PD (Smith et al. 2001, Kelly et al. 2004) and patients with HD (Brown et al. 2001). Straightforward comparisons of these findings are difficult because such studies typically involved small samples of patients and tended to vary somewhat in their methodology (e.g., patient characteristics, the extent to which acquired explicit sequence knowledge was controlled for, the statistical structure of the learned sequences). However, the only published meta-analysis of SRT sequence learning studies with PD patients supported the notion that implicit sequence learning is impaired relative to healthy controls (Siegert et al. 2006). Nevertheless, the claim that visuomotor sequence learning on the SRT task involves the necessary recruitment of basal ganglionic structures remains, at least to some extent, controversial, and the precise functional role (if any) played by these structures is less clear.

One almost uniform feature of PD studies of SRT sequence learning is that motor sequencing was the ultimate means by which individuals demonstrated their learnt knowledge. That is, very little research has measured acquired sequence knowledge via a method

which completely eliminated (sequenced) overt motor responding. Interestingly, where attempts have been made to ascertain Parkinson's patients' sequence knowledge in SRT experiments using non-motoric methods, they have been done so predominantly in the context of gauging participants' level of explicit knowledge for SRT sequences, typically employing recall (or free sequence generation) measures and/or recognition ratings for 'old' and 'new' sequences after the sequence acquisition phase of the SRT experiment (Smith and McDowall 2004, 2006, Wilkinson and Jahanshahi 2007, Gawrys et al. 2008, Wilkinson et al. 2009). This has largely been a response to growing recognition that experimental tasks such as SRT pattern learning are never process-pure, and that explicit knowledge cannot be experimentally eliminated, but rather controlled for (Shanks and St John 1994, Shanks et al. 2003). However, in PD studies of SRT sequence learning, awareness of the presence of the repeating sequence is often low in experimental groups (e.g., Wilkinson and Jahanshahi 2007), particularly once those scoring high in recall/recognition are excluded from learning analyses (e.g., Smith and McDowall 2004, Gawrys et al. 2008). Floor effects render comparisons of non-motoric learning of SRT sequences in such studies difficult to interpret.

Nevertheless, some SRT studies have suggested that sequence learning difficulties in patients with basal ganglia dysfunction extend beyond impaired acquisition for visuomotor response patterns. For example, post-experimental recall knowledge of SRT sequences has been found to be reduced in PD groups in two studies in which patients also demonstrated visuomotor sequence learning deficits (Pascual-Leone et al. 1993, Helmuth et al. 2000). More recently, Wilkinson and Jahanshahi (2007) reported that compared to PD subjects tested off medication, control participants were better able to discriminate between 'old' and 'new' test sequences in a recognition test administered after a number of SRT training blocks consisting of a probabilistic sequence in which targets appeared predictably on only 85% of trials throughout each block. In this study, PD patients did not recognise SRT sequences better than chance (unlike controls), indicating that patients failed to acquire categorical knowledge for sequences, a deficit that emerged despite the group's significant (albeit attenuated) learning for visuomotor response patterns in the same study. Therefore, there is preliminary evidence from SRT research that basal ganglia dysfunction in PD may also interfere with the acquisition of non-motoric (cognitive) representations of complex sequences presented in learning phases of the SRT.

On the other hand, it is worth considering that although PD patients have often exhibited visuomotor sequence learning deficits, across studies, they have performed normally on some cognitive (non-motor) pattern learning tasks assumed to rely on nondeclarative memory. These include artificial grammar (AG) acquisition and prototype dot pattern learning, tests that also require subjects to detect invariance in the stimulus environment across many trials and are novel in the sense that participants enter the experimental situation with no pre-existing knowledge, but do not necessitate a sequenced motoric response from participants (Reber and Squire 1999, Smith et al. 2001, Witt et al. 2002). This indicates that the incremental acquisition of complex patterned (judgment-based) information does not necessarily rely on the intact function of the basal ganglia or the nigrostriatal dopaminergic systems.

The nature of the dependent measure in implicit learning paradigms is likely to be especially important in determining precisely what is learnt and the specific brain structures recruited. Seger (1994, 1997) has distinguished between visuomotor-linked learning which uses efficiency measures, such as those that assess learning *via* increased speed and/or accuracy in performing actions contingent upon the stimuli, and judgment-linked learning, which employs conceptual fluency measures that tap participants' ability to rate or classify items. Using a modified version of the SRT task, Seger (1997) presented evidence indicating that in healthy controls, judgment-linked learning (pattern judgment) and visuomotor-linked (SRT) measures may access independent *implicit* pattern learning mechanisms, and suggested the two were also likely to be neurally dissociable. From this view, dissociations (across studies) between PD performance on SRT sequence learning tasks and pattern judgment tasks such as the AG and prototype learning paradigms may arise because the former is intimately linked to visuomotor learning, which relies on the basal ganglia, while the latter is a measure of judgment-linked learning, which does not.

Sequence learning on the SRT and learning on tasks like the AG and prototype dot pattern paradigms differ in many ways other than the dependent variable

used to measure performance, many of which are likely to be relevant, including the nature of the stimuli, responses in the acquisition phase, and perhaps most importantly, the nature of the underlying structure or pattern being learnt. A comparison of visuomotor- and judgment-linked learning in a single sequence learning paradigm that keeps the factors outlined above constant would be beneficial in determining whether efficiency and conceptual fluency measures rely on neurally independent learning mechanisms or related mechanisms with the same underlying neural substrates, and, more specifically, whether it is the requirement of acquiring patterns of visuomotor responses that determines the necessary recruitment of cortico-striatal systems in different non-declarative tasks. Such a paradigm may also help establish whether, as well as being independent of visuomotor pattern learning, judgment-linked learning mechanisms in the SRT task are independent of explicit sequence learning as was suggested by the findings of Seger (1997).

The design of the present study followed that of Seger's experiment (1997), in which participants performed a version of the SRT task which was extended to allow examination of both visuomotor- and judgment-linked learning, by comparing PD patients' performance on visuomotor sequence learning measures with their ability to judge sequential patterns subsequent to the SRT task. However, in this case, so as to ease the motor response demands on PD patients, a version of the SRT experiment requiring verbal rather than manual response was adopted. Additionally, the format of the SRT task departed from the standard block arrangement of separate random and sequence blocks employed in the majority of past studies investigating SRT learning in people with PD and instead included several blocks in which cycles of random and sequence trials were intermixed (see Curran 1997a,b, Werheid et al. 2003). As noted by other researchers (Curran 1997a, Shanks et al. 2003, Wilkinson and Jahanshahi 2007), this procedure carries with it several advantages with respect to assessing SRT learning, including unconfounding the learning of sequential regularities from effects related to general RT improvement and obscuring the presence of the sequence, so the acquisition of explicit knowledge about the sequence and its structure is less probable. The contribution of explicit knowledge to SRT performance was controlled for via the administration of confidence-rating measures designed to ascertain levels of explicit sequential knowledge (Perruchet and Amorim 1992, Willingham et al. 1993, Curran 1997a). These measures are based on the premise that a lack of relationship between confidence and task fluency does imply that at least some sequential knowledge is implicit, and so remain a preferable criterion for measuring explicit knowledge on tasks of implicit learning (Curran 1997a,b, for a review see Dienes and Perner 1999). A first-order conditional (FOC; Reed and Johnson 1994, Curran 1997a) sequence which included predictive pairwise information was employed in the modified SRT task as it enabled the opportunity for participants to (implicitly) learn both predictive pairwise information and higher-order associations. Several studies indicate that FOC sequences are sensitive to assess impaired sequence learning in PD (Kelly et al. 2004, Smith and McDowall 2004, Deroost et al. 2006) and thus an appropriate choice for measuring sequence leaning in the present study.

METHODS

Participants

Sixteen patients with idiopathic PD and 18 healthy control subjects matched for age and education participated in the experiment. The diagnosis of idiopathic PD was confirmed by senior staff neurologists at hospitals within the areas of Palmerston North and Wellington. None of the participants had a history of head injury within the preceding 10 years, or had a history of alcohol abuse, stroke, or epilepsy. All subjects had normal or corrected-to-normal vision. Ethical approval for experimental participation was given by the Wellington Hospital Ethics Committee. All participants gave their informed consent after a verbal and a written description of what their participation would involve and were paid $15 for their participation in the study.

Patients and controls were initially screened for dementia using the Mini-Mental State Examination (MMSE; Folstein et al. 1975) and for depression using the Beck Depression Inventory-II (BDI-II; Beck et al. 1996). All members of PD and control groups scored above the standard cut-off of 24 points on the MMSE, indicating an absence of abnormal cognitive decline. All control participants and 12 patients scored below the standard cut-off point of 14 on the BDI-II, indicat-

Table I

Demographic data and neuropsychological tests results for PD and control groups

	PD (*n*=15)	Control (*n*=18)		
Variable/Test	Mean (SD)	Mean (SD)	*F*	*P*
Age	62.73 (10.24) 57.95	61.06 (10.27)	0.22	0.643
Education	12.73 (2.81)	13.75 (3.46)	0.84	0.368
MMSE	28.80 (0.76)	28.78 (1.06)	0.01	0.947
BDI-II	9.93 (3.36)	4.00 (4.07)	14.39	<0.001
NART	117.85 (6.29)	120.27 (5.53)	1.34	0.256
COWAT	36.93 (11.79)	47.89 (13.37)	6.11	0.019
ANT	19.93 (6.56)	25.00 (8.35)	3.64	0.066
Spatial Span	14.40 (3.11)	13.39 (2.62)	1.03	0.318
LNS	9.13 (3.36)	10.59 (1.77)	2.44	0.129
WCST-64				
No. of categories	2.13 (1.41)	2.11 (1.45)	0.01	0.965
Total errors	23.80 (9.97)	24.11 (10.17)	0.01	0.930
Perseverative errors	10.67 (6.20)	14.78 (9.42)	2.10	0.158
TCC	16.27 (13.57)	18.28 (16.94)	0.14	0.713

Notes: MMSE - Mini Mental Status Examination, BDI-II - Beck Depression Inventory II, NART - National Adult Reading Test (expressed as a Wechsler Adult Intelligence Scale - Revised Full Scale equivalent), COWAT - Controlled Oral Word Association Test, ANT - Animal Naming Test, LNS - Letter-Number Sequencing, WCST-64 - short form of the Wisconsin Card Sorting Test; TCC - Trials to complete first category. Only 14 PD participants were administered the BDI-II. Only 14 PD participants performed the NART. Only 17 control participants performed the LNS test.

ing an absence of even mild depression. One patient scored 26, indicating moderate-to-severe depression and was excluded from all subsequent analyses. Two patients scores 18 and 19 respectively, indicating mild-to-moderate depression. Nevertheless, these patients were included in experimental analyses because they tended to have more severe PD symptomatology with scores higher for items describing somatic symptoms that may have arisen directly from the neurological effects of the disease. One patient was not administered the BDI-II due to scheduling complications but was also included in analyses.

The PD group considered for the SRT experiment comprised 11 males and 4 females, while in the control group, 11 were male and 7 were female. As assessed in an 'ON' state by a neurologist (who was blind to experimental results) on the Hoehn and Yahr (1967) degree of clinical disability scale, 3 of the patients were in Stage I, 8 were in Stage II, 2 were in Stage III, and 2 were in Stage IV. Time since diagnosis among the PD participants ranged from 18 months to 12 years, with an average time since diagnosis of 5.31 years (SD = 3.38). At the time of testing all patients with PD were receiving anti-Parkinsonian medication and were in an 'on' phase. Specifically, 5 of the patients were receiving dopamine precursor levodopa exclusively, while 2 patients were taking dopamine agonists (pergolide) exclusively. Three of the patients were taking both dopamine precursor levodopa and agonist medication, of which one was also receiving amantadine, and one a selective monoamine-oxidase-B inhibitor (MAO-B) inhibitor (selegiline). Four patients who were undergoing dopamine precursor levodopa treatment (but not agonist treatment) were receiving other medications as well; 2 taking a catechol-O-methyl tranferase (COMT) inhibitor (tolcapone), and 2 taking anticholinergic medication (orphenadrine), one of which was also receiving a MAO-B inhibitor (selegiline). Finally, one patient was receiving anticholinergic medication (procyclidine) exclusively. No patient had undergone surgery (e.g., unilateral pallidal surgery) for Parkinson's disease. Four patients were receiving SSRI antidepressant medication (paroxetine or fluoxetine).

Neuropsychological Assessment

All participants were administered a small battery of neuropsychological tests, which included the National Adult Reading Test (NART; Nelson and Willeson 1991) as well as measures of verbal fluency, specifically, the Controlled Oral Word Association Test (COWAT; Benton and Hamsher 1976) and the Animal Naming subtest from the Boston Diagnostic Aphasia Examination (ANT; Goodglass and Kaplan 1972). Participants also performed the short form of the Wisconsin Card Sorting Test (WCST-64; Axelrod et al. 1992), while assessments of short-term and working memory employed measures from Wechsler Memory Scales – III, namely the spatial span and the letter-number sequencing (LNS) test.

PD subjects performed neuropsychological tests and the SRT/pattern judgment task in a pseudorandom order (counterbalanced across subjects) over two experimental sessions that were separated by a maximum of 27 days (mean separation period = 11.33 days, SD = 7.21). Ten of the control subjects also participated in two experimental sessions (mean separation period = 10.80 days, SD = 6.09) that followed an identical procedure to that of PD participants, while eight control subjects performed all experimental tasks in one experimental session only. Scheduling limitations prevented one patient from completing the BDI-II while one control participant did not perform the LNS task. Finally, one PD patient was unwilling to perform the NART.

A summary of the group demographics and neuropsychological test results is displayed in Table I. One way ANOVAs showed no significant group differences on the MMSE and the NART. PD patients did, however, evidence a deficit on the COWAT and there was a trend for impaired performance on the ANT. While PD and control groups' performance on the spatial span (combined forwards and backwards) was almost indistinguishable, the control group performed better than patients on the LNS test, although the difference was nonsignificant. Despite PD patients experiencing difficulty when performing fluency tasks, indicative of mild executive dysfunction in the PD group, patients achieved an almost identical number of categories and made numerically fewer errors than the control group in the WCST-64. Finally, the PD group showed elevated scores on the BDI–II.

Materials and Procedure: SRT task

Each time participants performed the SRT, they completed three different tasks in the following order: the SRT task itself; a recognition task aimed at assessing declarative memory for the stimulus sequence; and a pattern judgment task (see Seger 1997). The SRT task used here was a verbal version of the classic SRT task (Hartman et al. 1989). A stimulus (an asterisk) appeared in one of four positions (designated as the letters A, B, C, and D from left to right) along the bottom of a computer monitor (approximately 2 cm above the screen bottom). The farthest left and right asterisk positions were located 1.5 cm from the side of the screen and each position was exactly 5.2 cm to the left

or right of the next. The computer was interfaced with a voice-response box. After participants had provided a verbal response (indicating the position of the stimulus), the stimulus disappeared, and the next stimulus appeared in one of the other locations. In this study, the response-stimulus interval (RSI) was 500 ms. The repeating sequence employed for this study was a 12-item first-order conditional (FOC) sequence. Two assignments of sequence position to screen location were used (A-D-A-C-D-B-C-B-A-C-D-B and C-B-C-A-B-D-A-D-C-A-B-D), and these were counterbalanced across subjects.

For this SRT experiment, all participants completed eight blocks of trials, each consisting of 120 trials and separated by a rest period of no less than 30 seconds. Each block of trials was composed of both random (R) and sequence (S) conditions, arranged as: RSSRSSRSSR. Each sequence condition consisted of one complete sequence cycle (i.e., one repetition of the 12-element sequence) that began in a random position within the sequence. Each random condition was made up of 12 trials in which the location of the stimulus was determined randomly, with the constraints that no two stimuli appeared consecutively in the same location and the four stimulus-locations appeared in the same proportion as in the repeating sequence (i.e., each stimulus-location appeared three times). This ensured that the learning of the sequence could not be attributable to unequal frequency or distribution of the four stimulus-locations.

All participants were asked to respond to the location of each stimulus by saying aloud the letter corresponding to its location. Participants were asked to respond as quickly as possible but to attempt to be accurate. The experimenter stood behind each participant and recorded any errors made. The target stimulus was advanced to the next spatial location whether or not a correct response was made. In this way, perceptual information about the sequence was available for every trial, even those in which verbal responses were in error. No feedback was provided regarding performance. Abnormally short or long RTs arising from technical difficulties were excluded from analyses. This resulted in the omission of 1.4% response trials in which the RT was below 100 ms and less than 0.4% of trials in which the RT was longer than 1 800 ms. Thirty practice trials were administered prior to performance of the SRT task.

SRT: Explicit awareness measures

At the conclusion of the task all, participants were asked to list any sequence or patterns they could recall from the SRT task. More sensitive measures of explicit knowledge for sequences were obtained using sequence recognition measures: the whole sequence test (Willingham et al. 1993) and the fragment recognition test (Perruchet and Amorim 1992). Immediately before administration of the recognition tests, participants were informed of the presence of a repeating sequence throughout the SRT task. In the whole sequence test, participants were presented with eight sequences listed on one sheet of paper, the experimental (target) sequence and seven distractor sequences, and asked to rank the likelihood that each sequence had been the sequence repeatedly presented in the SRT task; ratings were made on a scale ranging from certain it was not repeated (0) to certain it was repeated (100). A rating of 50 indicated complete uncertainty. The sequences were presented as the letters corresponding to locations used in the experiment (e.g., A-D-A-C-D-B-C-B-A-C-D-B) and were formed by taking the experimental FOC sequence and a second-order conditional sequence used in a previous experiment (SOC; A-B-A-D-B-C-D-A-C-B-D-C ; Smith and McDowall 2004) and making four varieties of each by assigning each location (1–4) to each letter (A–D). The position of the target sequence was counterbalanced. The fragment recognition test required participants to differentiate between (a) four-element subsequences (or fragments) from the SRT sequence and (b) four subsequences of the other assignment of sequence element to screen location. Four fragments were randomly selected from each of the screen location assignments and displayed in a random order that was counterbalanced across participants (however, for each participant, the same fragments were used). Participants were asked to rank the likelihood that each fragment had been a part of the sequence repeatedly presented in the SRT task on the 100-point scale used in the whole sequence test. For both recognition tests, there was no time limit for making each rating.

SRT: Pattern judgment task

The design of the pattern judgment test allowed for a measure of sequence learning which encapsulated both pairwise and higher-order knowledge and con-

trolled for stimulus frequency and stimulus distribution (Seger 1997). Specifically, participants made sequence judgments about 72 different subsequences. The task was divided into three parts according to subsequence length: 24 subsequences of length 5, 24 of length 6, and 24 of length 7. Of the subsequences in each part, 12 were made up of the possible subsequences from the sequence condition of the visuomotor response part of the SRT task (sequence items), and 12 were incorrect subsequences (nonsequence items) that were not part of the SRT sequence. Nonsequence items were formed by changing two of the elements from a sequence item of length 5 or length 6 and by changing three of the elements from a sequence item of length 7. Each sequence position was changed approximately equally often and sequence and nonsequence items were (as a whole) matched for stimulus frequency and stimulus distribution. Nonsequence items were of two types: one in which either two, three, or four of the pairwise associations were illegal (i.e., did not appear in the sequence in the SRT verbal response task; for example, given the SRT sequence A-D-A-C-D-B-C-B-A-C-D-B and the subsequence, C-B-A-C-D-B, the incorrect subsequence, C-B-A-B-D-C, has three illegal pairs, A-B, B-D, and D-C); and one in which all the pairwise associations in the item were legal (i.e., occurred in the sequence in the verbal response task), but the overall sequence itself was illegal (for example, given the SRT sequence A-D-A-C-D-B-C-B-A-C-D-B, and the subsequence B-C-B-A-C-D**,** the incorrect subsequence, B-C-D-A-C-B, contains the pairs B-C, C-D, D-A, A-C, and C-B, which are all

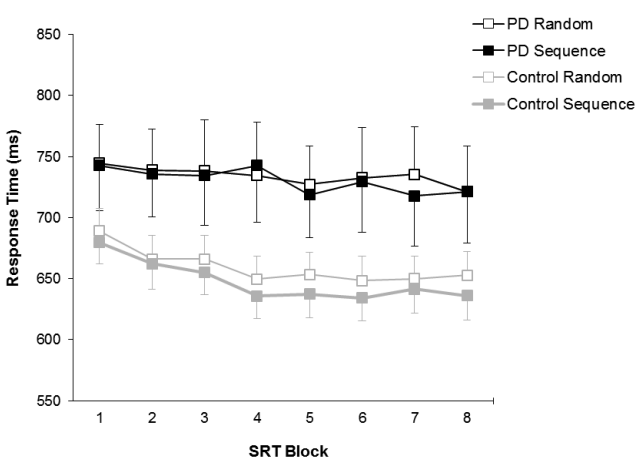

Fig. 1. SRT response time performance on sequence and random trials for PD (n=15) and control (n=18) groups. Error bars represent the standard error of the mean.

legal, but that specific series of six stimuli does not occur in the complete sequence). Within each set of 12 nonsequence items, 8 were of the first type (containing pairwise violations) and 4 were of the second type (consisting of higher-order violations).

Participants were instructed to watch the screen without making any overt response as they were shown sequences of stimulus-locations of varying length. For each of the trials (i.e., patterns), the first stimulus was presented for 700 ms while the remaining stimuli were presented for 350 ms each. The inter-stimulus interval was the same as the RSI in visuomotor response phase of the SRT task (500 ms). At the conclusion of each stimulus presentation, participants were requested to indicate whether or not the pattern was correct, that is, whether or not it followed the pattern presented in the SRT verbal response (acquisition phase) blocks. Subjects were instructed to respond using one of two specially designed large keys with brightly coloured markings (one on the left side of the keyboard and the other on the right side), each denoting a response indicating a 'right' or 'wrong' sequence. The specific task instructions were identical to that of Seger (1997), with a strong emphasis on participants relying on their intuition and feelings of knowing as opposed to conscious recollection:

"This may sound like a difficult task, especially if you were not aware of any pattern during the first part. However, we ask that you rely on your instincts and intuitions in making your judgments, not on conscious knowledge of the pattern. If the sequence 'looks right' or 'feels right', then indicate that it is correct. If the sequence 'looks wrong' or 'feels wrong', then indicate that it is incorrect." (p. 115)

Participants were presented with one example of a pattern to provide an indication of the speed at which the sequences were going to be presented and to gain a general feel for the task.

RESULTS

SRT visuomotor sequence learning

Accuracy was very high in the SRT task presumably because the stimulus–response (S–R) mapping demands in the verbal version are fairly straightforward. All participants achieved a response error rate of less than 3.1% while the mean error rate of both PD and control groups was below 1%. Therefore, analysis focussed on

response time (RT), which is considered the primary measure of learning in SRT experiments. RTs were summarised for each block by taking the median RT for all sequence trials and the median RT for all random stimuli. The first stimulus of each block was excluded from RT analyses. Additionally, because of its unpredictability, the first stimulus of each sequence cycle was considered in the analysis as belonging to the random stimuli. Only RTs of responses that were correct were included in sequence learning analyses.

Figure 1 shows the median sequence and random scores on each SRT block for the PD and control groups. A Group (PD vs. control) × Learning (random vs. sequence) × Block (1–8) ANOVA computed from participants' summary RTs in each condition, revealed a strong learning effect, in that overall participants responded faster on sequence trials than on random trials: $F_{1,31}$=8.90, P=0.006, MSE=882.09, PES=0.22. Participants also became faster across SRT blocks: $F_{7,217}$=3.68, P<0.001, MSE=2 065.80, PES=0.11. But there was no Learning × Block interaction ($F_{7,217}$=1.06, p=0.39), indicating that RT differences between sequence and random conditions did not increase with training. There was a significant effect of group ($F_{1,31}$=4.14, P=0.049, MSE=195 202.05, PES=0.12), signifying that, overall, patients tended to respond to SRT stimuli more slowly than did controls. However, there was no significant interaction between learning and group, indicating that differences in RT between sequence and random trials were not significantly greater in controls compared to PD patients: $F_{1,31}$=2.31, P=0.139. All remaining interactions with group failed to approach significance (F<1.07, P>0.38).

Differences in baseline RT between PD and control participants complicate interpretation of learning effects. The analysis of SRT performance revealed a large variance in general RT level within the group of PD participants, and interestingly, a moderate association between mean RT and mean learning score (i.e., difference between median response times for random and sequence trials on each block averaged across the 8 blocks): r_{13}=−0.60, P=0.019. This suggests that PD patients who generally responded more quickly throughout SRT blocks tended to evidence the most sequence-specific learning across all blocks. To better examine this hypothesis, the PD group was split in half into the fastest (PD-fast: n=8, range of mean RT = 553–720 ms) and slowest (PD-slow: n=7, range = 745–1 057 ms) overall responders. This division appeared appropriate given the mean (overall) RT of the PD-fast group (638 ms, SD = 54) was highly comparable with that of controls (652 ms, SD = 75, P=0.633), while not surprisingly, both were significantly faster than the overall RT of the PD-slow group (839 ms, SD = 136, for both pairwise comparisons, P<0.007).

The RT analysis (mixed-model ANOVA) was performed again with Subgroup (PD-fast, PD-slow, controls) as a between-subjects factor and Learning (random vs. sequence) and Block (1–8) as within-subjects factors. This analysis confirmed the main effect of Subgroup: $F_{2,30}$=12.91, P<0.001, MSE=122 914.51, PES=0.46. As before, sequence learning was significant ($F_{1,30}$=6.16, P=0.019, MSE=629.55, PES=0.17), but differed between the three subgroups ($F_{2,30}$=8.34, P=0.001, MSE=629.55, PES=0.36), reflecting the poor visuomotor performance of the PD-slow patients. No other interactions with Subgroup were significant (F<1.04, P>0.42).

The mean learning scores of PD-slow, PD-fast, and control groups is depicted in Figure 2. One-sample t-tests confirmed that sequence learning across the SRT task was highly significant in the PD-fast subgroup (mean learning score = 14.91 ms, SD = 9.51, t_7=4.43, P=0.003), and in the control group (mean learning score = 11.69 ms, SD = 14.55, t_{17}=3.41, P=0.003). In contrast, slow-responding patients did not show any evidence of acquiring the pattern of visuomotor responses as evidenced by a negative mean learning score (−8.89 ms, SD = 9.02). Separate pairwise

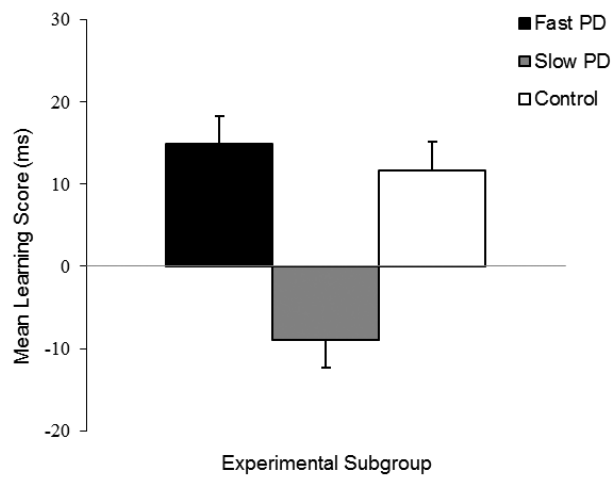

Fig. 2. Mean learning score across SRT blocks for PD-fast (n=8) and PD-slow (n=7) subgroups and control participants (n=18). Error bars represent the standard error of the mean. The learning score for each participant was calculated by averaging the differences between median response times for random and sequence trials across the 8 blocks.

Table II

Results of explicit knowledge measures on the SRT task

	PD All (*n*=15)	PD-fast (*n*=8)	PD-slow (*n*=7)	Controls (*n*=18)
Sequence Awareness Measure				
Mean Recall (0 to 12)	1.80 (2.08)	2.12 (2.59)	1.43 (1.40)	1.89 (2.08)
Mean Recognition (−100 to 100)				
Whole-sequence	2.16 (25.75)	−4.82 (28.40)	10.14 (21.62)	12.05 (25.18)
Fragment	0.44 (10.22)	4.58 (10.49)	−4.29 (8.16)	1.01 (11.73)
Total	1.30 (12.59)	−0.12 (15.48)	2.93 (9.20)	6.53 (14.32)

Notes: For recognition measures chance performance = 0. Standard deviations are presented in parentheses.

comparisons revealed that both PD-fast and control groups demonstrated better learning for SRT sequences than the PD-slow group (for both comparisons, t>3.46, P<0.003), but learning was comparable in magnitude between PD-fast and controls: t_{24}=0.57, P=0.57. As a whole, these results strongly suggest that PD participants who responded to SRT stimuli at a comparable speed to controls were as able to demonstrate sequence-specific learning. However, those patients with PD who responded at a significantly slower pace than the rest of their group evidenced no sequence learning, indicating a visuomotor sequence performance deficit in this subgroup. The relevance of PD response speed to learning was subsequently considered in group analyses of explicit knowledge and pattern judgment.

Explicit sequence learning

Explicit knowledge of the sequences was assessed by a free recall task and whole sequence and fragment recognition measures. Not surprisingly, many subjects could not recall any patterns at all (and were not willing to guess) and scored zero on this measure: PD-fast = 4/8; PD-slow = 3/7; Control = 10/18. The bottom of Table II lists the mean recall and recognition scores for all PD patients, each subgroup, and control participants. A one-way ANOVA showed no difference between PD subgroups' and controls' abilities to explicitly recall the SRT sequence: $F_{2,30}$=0.21, P=0.81.

Recognition accuracy for each test (whole sequence and fragment) was determined by finding a mean rating to distractor sequences and then finding the difference of this mean and the rating of the target sequence (or mean of target fragment sequences). Accordingly, chance performance on recognition measures would produce scores of zero while perfect recognition of the SRT sequence would yield scores of 100. As anticipated, recognition performance was, generally speaking, poor. One-sample t-tests showed that only controls' whole-sequence recognition performance (t_{17}=2.03, P=0.058) and total recognition score (obtained by averaging the scores from the whole sequence and fragment recognition measures; t_{17}=1.94, P=0.070), approached significance, with all other scores nonsignificant. One-way ANOVAs revealed that there were no differences between PD-fast, PD-slow, and control groups' explicit SRT knowledge on whole-sequence, fragment, or total recognition measures (for each of these measures, F<1.28, P>0.29).

Table III

Correlations (Pearson *r*) of SRT implicit visuomotor sequence-specific learning (Visuomotor) and pattern judgment accuracy (Judgment) with scores on each explicit knowledge test for PD and control participants

	PD Patients All (*n*=15)		PD-fast (*n*=8)		PD-slow (*n*=7)		Controls (*n*=18)	
Explicit Measure	Visuomotor	Judgment	Visuomotor	Judgment	Visuomotor	Judgment	Visuomotor	Judgment
Recall	−0.23	0.59*	0.17	0.81*	0.26	−0.17	0.12	0.64**
Recognition								
Whole-sequence	−0.17	−0.18	0.49	0.01	−0.43	−0.21	0.17	0.27
Fragment	0.43	0.70**	0.27	0.55	−0.11	0.83*	0.12	0.32
Total	0.01	0.10	0.54	0.19	−0.55	0.12	0.20	0.37

Notes: * $P<0.05$, ** $P<0.005$. Only 15 PD patients were administered the pattern judgment test (6 in the PD-slow group).

Pattern judgment task performance

One PD participant was unable to complete the pattern judgment task. Participants' scores were calculated by the percentage of sequence and nonsequence items judged correctly. PD-fast subjects classified 59.73% (SD = 6.72) of the patterns correctly, PD-slow subjects classified 54.86% (SD = 4.87) of the patterns correctly, and controls classified 59.03% (SD = 10.06) of the patterns correctly. Both PD-fast and control groups' scores were significantly above chance (i.e., 50%: PD-fast, t_7=4.09, P=0.005; controls, t_{17}=3.81, P=0.001), while PD-slow narrowly missed significance: t_5=2.44, P=0.058. A one-way ANOVA confirmed there were no significant differences in judgment accuracy between the (sub)groups: $F_{2,29}$=0.65, P=0.53.

Association of explicit knowledge with SRT visuomotor sequence learning and pattern judgment performance

The relationship between performance measures of sequence learning and explicit knowledge was considered with correlations. Table III presents Pearson's correlations between each explicit knowledge measure and SRT performance (visuomotor sequence learning score and pattern judgment) for (sub)groups of participants considered in sequence learning analyses. It is clear from Table III that for control participants and the patient group as a whole, associations concerning visuomotor sequence learning are weak and all are nonsignificant. Interestingly, however, PD-fast and -slow subgroups demonstrated distinct (albeit nonsignificant) associative patterns, with the former evidencing a moderate positive relationship between (total) recognition and visuomotor sequence learning and the latter showing a moderate negative relationship (the lack of significance likely reflects the small number in each group but confirms the preliminary nature of the data). In contrast to visuomotor sequence learning, pattern judgment accuracy was significantly related to measures of explicit learning. This was most apparent for sequence recall and fragment recognition measures, one or both of which shared moderate-to-high associations with pattern judgment in all experimental (sub)groups. Notably, performance on visuomotor- and judgment-linked measures of sequence learning shared no relationship with each other in the modified SRT paradigm in the control group (r_{16}=0.02, P=0.94) or in the PD-slow group: r_4=−0.28, P=0.60. However, PD-fast participants did show a moderate association between accuracy in the pattern judgment task and overall visuomotor sequence learning scores: r_6=0.61, P=0.11 (again, small numbers likely precluded significance).

Table IV

Demographic and clinical data and neuropsychological tests results for PD-fast and PD-slow subgroups

	PD-fast (*n*=8)	PD-slow (*n*=7)		
Variable/Test	Mean (SD)	Mean (SD)	*F*	*P*
Age	61.88 (7.55) 57.95	63.71 (13.26)	0.11	0.742
Education	11.88 (2.34)	13.71 (3.15)	1.68	0.218
Hoehn and Yahr stage	2.12 (0.99)	2.29 (0.95)	0.10	0.755
Disease duration (yrs)	5.71 (3.45)	5.86 (3.50)	0.23	0.642
MMSE	28.62 (0.74)	29.00 (0.82)	0.87	0.369
BDI-II	12.14 (5.11)	7.71 (3.40)	3.64	0.081
NART	117.85 (6.55)	117.85 (6.55)	0.00	0.999
COWAT	35.00 (12.33)	39.14 (11.67)	0.44	0.517
ANT	21.88 (5.38)	17.71 (7.48)	1.56	0.234
Spatial span	14.50 (3.30)	14.29 (3.15)	0.02	0.900
LNS	8.88 (3.31)	9.43 (3.65)	0.10	0.763
WCST-64				
No. of categories	2.25 (1.39)	2.00 (1.53)	0.11	0.745
Total errors	24.88 (9.78)	22.57 (10.81)	0.19	0.672
Perseverative errors	11.38 (5.83)	9.86 (6.96)	0.21	0.653
TCC	12.75 (2.92)	20.29 (19.61)	1.16	0.300

Notes: MMSE - Mini Mental Status Examination, BDI-II - Beck Depression Inventory II, NART - National Adult Reading Test (expressed as a Wechsler Adult Intelligence Scale - Revised Full Scale equivalent), COWAT - Controlled Oral Word Association Test, ANT - Animal Naming Test, LNS - Letter-Number Sequencing, WCST-64 - short form of the Wisconsin Card Sorting Test; TCC - Trials to complete first category. Only 7 PD-fast participants were administered the BDI-II. Only 7 PD-fast participants performed the NART.

Neuropsychological and clinical correlates of PD sequence learning performance

Visuomotor sequence learning performance shared little relationship with PD patient neuropsychological test performance, including those tests which PD patients exhibited reduced scores, such as the COWAT (r_{13}=−0.19, P=0.51) and the LNS (r_{13}=−0.09, P=0.74). Similarly, pattern judgment was not significantly associated with any test score. There was a marginally significant relationship between LNS performance and accuracy on the pattern judgment task (r_{12}=0.49, P=0.078), possibly suggesting a relationship between PD working memory and pattern judgment. PD severity (illness stage) did not predict performance on any of the SRT learning measures (P>0.05). Similarly, despite the elevated BDI-II scores of the PD patients, there was again no evidence to suggest patients' visuomotor learning was (negatively) related to depression scores in this group (P>0.05). Only a limited number of patients were receiving anticholinergic or dopamine agonist treatment (exclusion of these patients from analyses did not alter results), and so sequence learning deficits were unlikely to be attributable to any specific (undesirable) effects these drugs may have had.

Exploratory comparisons of demographic and clinical characteristics and neuropsychological test performance between PD-fast and PD-slow subgroups (see Table IV), intended to gain more insight in the visuomotor sequence learning impairments of the PD-slow group, revealed no discernible demographic or clinical feature in this group. Furthermore, as Table IV shows, the neuropsychological profiles of PD-fast and -slow patients were strikingly similar, suggesting visuomotor sequence learning deficits in the latter group were unlikely to stem from mnemonic and/or executive dysfunction.

DISCUSSION

The objective of this study was to compare PD patients' visuomotor learning with pattern judgment and explicit knowledge in a single sequence learning paradigm that minimised motor demands on participants. The critical finding is that whereas SRT performance on visuomotor- and judgment-linked measures was essentially normal in fast-responding patients, those patients who responded slowly to SRT stimuli demonstrated a marked deficit in visuomotor sequence learning. Correlational analyses revealed that pattern judgment performance was not associated with visuomotor sequence learning in control participants (or PD-slow patients) supporting the idea that in healthy individuals at least, motor- and judgment-linked learning for SRT sequences rely on independent mechanisms. There was a moderate association in the PD-fast group, but this failed to achieve statistical significance. Explicit knowledge, assessed in the form of recall tests and confidence-rating recognition measures, was low in all experimental groups. But while visuomotor sequence learning tended to be poorly predicted by participants' (minimal) declarative knowledge, there was a much closer relationship between pattern judgment accuracy and explicit learning scores in all experimental groups, suggesting the two measures may tap the same underlying cognitive (and neural) processes.

The preserved ability of a subgroup of PD patients to learn visuomotor sequences on the SRT task is noteworthy in itself and adds weight to the hypothesis that basal ganglia dysfunction due to the pathological effects of PD does not uniformly impair sequence learning on the SRT (Deroost et al. 2006, Seidler et al. 2007, Stephan et al. 2011). As noted earlier, although Parkinson's patients have frequently been examined in a variety of behavioural SRT studies, results have been inconsistent. Some studies have reported intact performance of sequential regularities (Smith et al. 2001, Werheid et al. 2003, Kelly et al. 2004), while others have found deficits relating to sequence-specific learning (Jackson et al. 1995, Deroost et al. 2006, Gawrys et al. 2008, Smith and McDowall 2004). The discrepancy across PD studies likely reflects, at least in part, the different clinical characteristics of the experimental samples employed. Several studies have indicated that the implicit acquisition of sequences on the SRT is more likely to be impaired in PD patients in more advanced stages of the illness (Smith and McDowall 2006, Muslimović et al. 2007, Gawrys et al. 2008, Price and Shin 2009, Wilkinson et al. 2009, Stephan et al. 2011). Furthermore, a number of studies have suggested that a decline in executive function contributes to sequence learning deficits in PD (Jackson et al. 1995, Deroost et al. 2006, Price and Shin 2009, Vandenbossche et al. 2009). The results of the present study, however, indicate that the slowing of visuomotor responses of a select group of PD patients in the SRT task hindered the acquisition and/or expression of visuomotor sequence knowledge.

This is not the first sequence learning study to find worse visuomotor performance in PD patients who respond slowly to SRT stimuli. Shin and Ivry (2003) evaluated the relationship between response speed and the amount of sequence learning in PD patients and reported significant negative correlations with mean reaction time for both spatial and multidimensional sequence learning. Deroost and colleagues (2006) examined visuomotor sequence learning using FOC and SOC sequences in a PD sample in which all patients had been classified as being in Stage 3 on the Hoehn and Yahr (1967) scale. The authors found that whereas SRT performance of a slow PD subgroup was severely impaired for both sequence types, a fast PD subgroup demonstrated sequence-specific learning that was comparable in magnitude to that of control participants. However, the patients in the slow PD subgroup in the Deroost and others (2006) study also evidenced higher scores on the UPDRS and lower scores on measures of cognitive functioning than did fast-responding patients, so learning deficits may have reflected specific deficits of cognitive functioning associated with more severe disease. By contrast, in the present study, PD-fast and -slow patients were not distinguishable by any demographic or clinical variable, or level of cognitive functioning as measured by the battery of neuropsychological tests used here. Thus, failure to demonstrate visuomotor sequence learning was related to slow response speed independently of illness severity or any (mild) cognitive dysfunction.

One possibility is that the absence of learning in the PD-slow group reflects that for all SRT participants, irrespective of whether or not they suffer from basal ganglia dysfunction, observed levels of learning diminishes as baseline response time increases. It is well established that timing on the SRT task is an integral part of forming associations between stimulus events. For example, a number of studies with healthy participants have found that longer RSIs (1 000 ms or greater) yield less sequence learning than shorter intervals (500 ms or less; Frensch and Miner 1994, Soetens et al. 2004). Additionally, sequence learning in young adults is poorer when variable RSIs or task changes that influence event timing are introduced (Stadler 1995, Howard et al. 2007). Frensch and Miner (1994) have argued that a short RSI is beneficial for learning, because, in comparison to slower presentation rates, it allows more stimuli to be simultaneously active in short-term memory, where an associative mechanism may detect sequential regularities between subsequent stimuli. Extending this argument, Soetens and colleagues (2004) have emphasised how with short RSIs, automatically facilitated response monitoring processes, whereby participants make comparisons of a prepared response on the basis of the predicted stimulus with the actually required response coded by the presented stimulus, are likely to play a critical role in detecting sequential regularities. In long RSI conditions, however, monitoring processes have decayed by the time of the arrival of the next stimulus and consequently, contribute less to sequence learning. So it is possible that some of the PD-slow deficits in learning observed in the present study are due to differences in the timing of the events, rather than to changes in fundamental learning or sequencing mechanisms brought about by the illness. From this view, the inability to form associations regarding a series of spatial locations or responses in the slow-responding PD participants may result from increased noise levels associated with the representation of the relationships between successive events, a consequence of greater working memory load and/or decreasing response-monitoring processes created by longer inter-stimulus intervals (Frensch and Miner 1994, Soetens et al. 2004).

Impaired performance of the PD-slow group may equally reflect slow motor response selection, a hallmark of the illness, or other possible (PD-specific) impairments including bradyphrenia (Rogers et al. 1987, Hayes et al. 1998). A number of authors studying sequence learning in PD have emphasised how the expression of sequential knowledge in the SRT is likely to be a highly time-critical process, in which knowledge about what the next element in the sequence element can be detected only if it is transmitted to the response system faster than information about the relevant next response transmitted through the perceptual system (*via* seeing the next stimulus on the screen) (Helmuth et al. 2000, Werheid et al. 2003, Seidler et al. 2007). Given one common consequence of basal ganglia dysfunction is taking longer to make use of internal signals to prepare motor commands (Jennings 1995, Hayes et al 1998), accompanied by a failure to benefit from predictable conditions (Henderson and Goodrich 1993), the established sequence knowledge about what stimulus and response to expect next may be transmitted too slowly in some PD patients, impeding improvement in RT on the SRT task. In line with this view, two SRT studies have shown evidence of

sequence-specific learning when measured on the basis of errors rather than RT changes (Sommer et al. 1999, Seidler et al. 2007). Further, increased reaction time in PD patients has been associated with the degree of impairment evidenced in a declarative visual sequence learning task (Marinelli et al. 2010). It is possible then that for patients who show abnormal baseline response speed in sequencing tasks, such as those in the present study, response priming is impaired due to slow access of learned representations (rather than by a lack of learning per se; Seidler et al. 2007).

Keele and others (2003) has proposed a computational model of sequence learning in which the basal ganglia "provide a 'proceduralization' function in the real-time conversion from one segmental representation of a sequence to another" (p. 332). In this model, the function of the basal ganglia in the SRT centres around the provision of internal motor cues which act to trigger submovements in a learned sequences, and PD deficits on SRT tasks are likely to occur when patients cannot make fluent and rapid transitions between one portion of a sequence, as the representation of one sequence chunk must be suppressed as the next is activated (Curran 1995). It is also worth considering the growing body of evidence indicating that dopamine plays an essential role in automated movement chunking during sequence learning and execution (Peigneux et al. 2000, Destrebecqz et al. 2005), with activity in the striatum likely to be critical in building up representations of motor and cognitive action sequences to be implemented as performance units (Graybiel 1998, Tremblay et al. 2010). Tremblay and colleagues (2010) have recently shown how PD patients seen after a 12-hour withdrawal of dopaminergic medication were successfully able to learn a 14-item sequence but evidenced marked impairments in grouping isolated response movements into integrated motor sequences, indicating that the nigrostriatal dopamine system plays a primary role in response chunking during motor sequencing. Thus, PD patients who respond slowly to (sequenced) SRT stimuli may have more difficulty with chunking discrete responses into motor sequences, hindering their ability to demonstrate RT advantages for sequenced stimuli.

Because no control group with slow baseline RT (or condition designed to artificially slow control participants' responses to match that of the PD-slow group) was employed in this experiment, it is not possible to distinguish between these hypotheses. Furthermore, no measure of reaction time or motor response speed independent of the SRT task was taken, nor any task specifically dedicated to (explicit) motor sequencing ability, motor response selection, or movement chunking, administered. As such, particularly in the absence of any discernible cognitive or disease-related differences between PD-fast and slow patients, it is difficult to characterise the nature of the observed deficit in latter group, and determine whether these patients' failure to express sequence knowledge in the SRT reflects slow access of learned representations due to faulty motor program control or a more general (learning) deficit related to slowness of thought or motor response. Further research with a greater focus on individual differences in visuomotor sequence learning abilities among patients with PD is required to better establish which functional aspects of the illness disrupt visuomotor performance on SRT tasks.

Whereas a subgroup of PD patients evidenced marked shortcomings in the visuomotor response phase of the SRT experiments, PD patients as a whole were better able to correctly classify short series of stimulus patterns as belonging or not belonging to the sequence in the SRT, performing comparably with control participants. Although the category learning knowledge evidenced by both patient and control groups was relatively limited (less than 60% correct), learning was nevertheless reliable. Furthermore, performance levels on the judgment task were comparable with (superficially) similar judgment-linked learning tasks, such as those involving the learning of AG or prototype pattern systems (e.g., Reber and Squire 1999, Smith et al. 2001). The findings from the PD-slow group suggest that efficiency and conceptual fluency measures, at least within the context of sequence learning on the SRT task, rely on neurally dissociable learning mechanisms. Correlational data from control participants also pointed towards the stochastic independence of visuomotor- and judgment-linked sequence learning processes, in line with the results of Seger (1997).

The hypothesis that pattern judgment performance on the SRT is based on nondeclarative memory was not supported, however. Data from both PD patients and controls suggested that pattern judgment performance was associated with explicit knowledge of the sequences. This may not be surprising, given the obvious similarities between the two tasks. It is notable that pattern judgment tasks in which sequence fragments

are presented to subjects have previously been used in SRT studies in an explicit context (Shanks et al. 2003, Gawrys et al. 2008). In these studies, emphasis is placed on explicit remembering of previous sequences and subjects are asked to provide ratings indicating how confident they are in their judgment (as they did in explicit recognition measures employed in this experiment). In the pattern judgment task administered in this study, there was no quantifiably test of whether participants can represent the epistemic status of their sequence knowledge explicitly. Rather, emphasis was placed not on conscious recollection but a "gut feeling" approach which simply required a yes/no judgment based on intuition. Interestingly, Seger (1997) reported in a similar experiment with healthy subjects that pattern judgment on the SRT was functionally and stochastically independent of both implicit visuomotor sequence learning and declarative knowledge for repeated sequences. However, Seger's explicit measures were a free generation task and an awareness questionnaire, which, at least ostensibly, have less features in common with the pattern judgment task than confidence-rating measures. One possibility then is that the pattern judgment test measured explicit sequence knowledge, and the fact that both patient and control groups demonstrated accuracy levels greater than chance merely reflects that pattern judgment skill represents a more sensitive index of explicit sequence knowledge than do (confidence-rating) recognition measures, for which performance was not significant.

Few studies have specifically examined PD patients' ability to explicitly learn sequences within the context of the SRT task. In one such study, Pascual-Leone et al. (1993, Experiment 2) reported that PD patients were slower than control participants to develop declarative knowledge of SRT sequences, indicative of an (attentional) explicit sequence learning deficit in patients with disturbed neostriatal circuitry. More recently, Wilkinson and Jahanshahi (2007) found impaired categorical judgment for six-item sequences, some of which were part of the SRT training sequence and some of which were not. More generally, it is probably significant that in so much as the striatum has been generally associated with implicit sequence learning (Rauch et al. 1997, Peigneux et al. 2000, Destrebecqz et al. 2005), activation in this region has also been found concurrently in both implicit and explicit sequence conditions (Willingham et al. 2002, Aizenstein et al. 2004, Karabanov et al. 2010), highlighting the potential role played by neostriatal circuitry in the acquisition of declarative knowledge. These findings raise the question that if performance on the pattern judgment task was mediated predominantly by explicit knowledge, why was performance on this task essentially preserved in patients with PD? One simple explanation involves the relative sensitivity of the pattern judgment task and its potential impact on PD performance. In the experiment of Pascual-Leone and colleagues (1993), explicit sequence knowledge was gauged using measures that called for participants to reproduce components of the sequence in the correct order. PD patients often experience great difficulty in those tasks that involve effortful and controlled processes, which require active organisation of the material to be remembered (Owen et al. 1993, Cools et al. 2001, Gawrys et al. 2008). The simple requirement to judge partial sequences presented to participants via a yes/no response in the pattern judgment task may have relieved PD participants of the burden normally imposed by recall or free generation measures.

A second, important point concerns the fact that in both the studies of Pascual-Leone and coauthors (1993) and Wilkinson and Jahanshahi (2007) subjects were required to respond to patterned stimuli as they did in the motor component of the SRT task during declarative knowledge assessment. In contrast, for the pattern judgment task, participants were required to simply watch the movement of the target stimulus and once the sequence had ended make a response. It is likely that PD patients' judgment performance benefited from the strictly visual (rather than visuomotor) input condition of the pattern judgment task employed here. In support of this hypothesis, Pascual-Leone and colleagues (1993) reported normal acquisition of declarative SRT sequence knowledge in patients with PD once they were simply required to observe sequences of asterisks appearing on the screen rather than motorically respond to SRT stimuli. As a whole, these results indicate that judgment-linked knowledge acquired through visuomotor performance in the SRT task may better be evidenced in patients with PD by focussing attention on the perceptual demands of the task rather than in conditions in which attention has to be divided between perceptual input and motor output (Pascual-Leone et al. 1993).

Irrespective of whether the pattern judgment task taps implicit or explicit processes (or both), that Parkinson's patients performed normally is of signifi-

cance. It is well established that the cognitive changes brought about by PD include deficits in the memory domain, qualitatively similar to those associated with frontal dysfunction (Owen et al. 1993). In the present study, PD patients showed impaired verbal fluency and a trend for reduced performance on the ANT task (semantic fluency) suggesting mild executive dysfunction in the experimental PD group. Yet despite this, patients were able to successfully acquire categorical sequence knowledge in a paradigm that was designed so as to prevent the emergence of explicit sequence representations, a surprising finding if pattern judgment relied more heavily on frontal-based attentional processes. In fact, there was little evidence here to suggest that pattern judgment accuracy was modulated by neural mechanisms underlying executive function. Only patients' (intact) performance on the LNS task shared a (marginally significant) relationship with accuracy in the pattern judgment task, and there was little or no association with other indices of executive function, including measures of WCST performance, which was intact in the patient group.

Dopaminergic loss and the consequent basal ganglia dysfunction in PD is known to affect the acquisition of categorical knowledge on a variety of judgment-linked learning tasks purported to rely on nondeclarative memory, such as probabilistic classification learning (Knowlton et al. 1996) and concurrent discrimination tasks (Shohamy et al. 2006). Unlike SRT pattern judgment, however, these tasks typically involve incremental, feedback-based learning of cue-outcome associations. Both electrophysiological and neuroimaging studies have strongly implicated midbrain dopamine in error-correcting feedback processes (Schultz et al. 1997, Aron et al. 2004), and recent PD studies have demonstrated that while patients exhibit impaired performance on a feedback-based incremental learning task, they do not show such deficits on versions of the same task that rely on non-feedback, observational learning (Shohamy et al. 2004, 2006). One critical reason patients were not impaired in the present study of judgment-linked learning, therefore, may relate to the specific processing demands of the pattern judgment task, which did not involve trial-by-trial error processing.

It is plausible that category learning of visual stimuli in the SRT could take place in cortical areas dedicated to visual information processing. As previously noted, successful performance in judgment-linked tasks such as AG and prototype learning appears not to rely on the integrity of striatal structures (Reber and Squire 1999, Witt et al. 2002). Rather, accumulating evidence suggests that perceptual and cognitive pattern learning, as well as category learning, are cases in which the sensory processing stations may themselves change, so as to benefit from the specific perceptual experiences that have occurred in the recent past (Reber et al. 2003). For example, brain-imaging studies have indicated that successful AG performance relies on high-level visual processing areas outside of the basal ganglia, such as the occipital and parietal lobes, and possibly prefrontal lobe areas associated with working memory (Seger et al. 2000, Skosnik et al. 2002). The exact localisation of pattern judgment memory and the stimulus-correlated activity associated with expressing the memory would, in all probability, differ from that of learning grammatical rules in an AG task or prototype information in dot pattern classification. Unlike these well-established tasks, pattern judgment (while distinct from the SRT blocks in that no overt response was required for each stimulus presentation) did consist of a more prominent oculomotor component, in so much as participants were required to move their eyes swiftly throughout each trial according to the shifts in stimulus-location. Nevertheless, it has previously been suggested that learning a series of spatial locations in this way may be tied to those brain systems that are assumed to underlie the control of spatial attention, such as the parietal lobe (Mayr 1996). Notably, occipito-parietal and frontal structures have also previously been activated in visuomotor sequencing phases of SRT experiments (Willingham et al. 2002, Rieckmann et al. 2010), although in other studies these structures have tended to be better associated with lower-order levels of processing associated with general RT improvements across trials or have shown greater activation in the explicit component of performance (Peigneux et al. 2000, Destrebecqz et al. 2005).

This study has some limitations. First, it included a relatively small sample of PD participants, limiting the statistical power of the statistical analyses as well as the generalisability of the findings to the wider patient community. Second, the patient group involved in the current study represented a heterogeneous sample, both with respect to age and education as well as a range of potentially important aspects of PD including duration and severity. However, the patient group was

well matched demographically to the control group and the SRT data of all groups showed relatively stable RT levels throughout the task. Also, perhaps most importantly, patient deficits on the SRT task were most obviously linked to task-specific response speed and not to variance within demographic or disease-related variables.

Third, while the data indicate that a subgroup of PD patients were as able as controls to learn the visuomotor sequence, it does not provide specific information about which brain structures were being used (or not used) during sequence acquisition and, more specifically, whether PD-fast patients recruited the same areas to learn visuomotor sequences as healthy participants. It has been suggested that motor sequence learning in PD may be accomplished by deploying a brain network involving more cortical-cortical interactions and less cortical-subcortical ones (Tremblay et al. 2010). This is broadly supported by studies showing that whereas recruitment of the striatal system is typically accompanied by relative disengagement of the MTL system on nondeclarative tasks (Poldrack and Packard 2003, Seger and Cincotta 2006), a more cooperative relationship between these brain systems has been observed in the presence of striatal pathology. Specifically, in patient groups such as PD, spared performance on sequence learning tasks normally relying on the striatum have been associated with increased MTL activation (Werheid et al. 2003, Beauchamp et al. 2008). Thus, there is emerging evidence that the neural bases of visuomotor sequence learning are likely to change as a consequence of basal ganglia dysfunction, with patients relying more on the MTL-based than the striatal-based learning system than healthy adults. It is possible that the visuomotor sequencing data of the PD-fast participants reflect the changes in network activation observed in neuroimaging experiments, and that spared SRT performance may result from (partial) neural compensation for striatal losses.

Finally, like most experimental studies with medicated patients suffering from PD, a degree of caution is warranted when interpreting behavioural deficits as indicative of basal ganglia dysfunction. Some studies of learning processes in PD patients have indicated that under certain circumstances levodopa can worsen performance. For instance, Shohamy and colleagues (2006) reported that dopaminergic medication impaired Parkinson's patients' learning on an incrementally acquired concurrent discrimination task, a deficit not found in a group of matched patients tested after medication withdrawal for approximately 16 hours. Another study has indicated that the effects of levodopa can differ even within a single task. Frank and others (2004) examined the effect of levodopa medication on PD performance on a feedback-based category learning task, and reported that while levodopa facilitated learning based on positive outcomes, it impaired learning based on negative outcomes. Recent work with patients using tasks gauging explicit motor sequence learning has suggested that levodopa tended to decrease learning performance and concomitant network activation (Kwak et al. 2010). Furthermore, a recent study found greater sequence learning deficits in patients when medicated compared to non-medicated, although knowledge acquisition in this paradigm relied on reinforcement learning (Seo et al. 2010).

The effects of dopaminergic medication on SRT (implicit) sequence learning are poorly understood, and only a few SRT studies investigating sequence learning processes in PD patients have employed patient samples that have not been medicated. One large PD study of SRT learning found that untreated patients in early stages of the disease were as able as controls to acquire sequence-specific knowledge. This was in contrast to medicated patients, who showed attenuated levels of sequence learning (Muslimović et al. 2007). However, since no significant association between sequence learning and levodopa dosage in medicated patients was found, the authors attributed medicated/non-medicated group differences to the effects of disease severity rather than those of drug treatment. Consistent with this view, Pascual-Leone and colleagues (1993) reported that PD patients evidenced mild sequence learning difficulties regardless of their medicated state, while Wilkinson and Jahanshahi (2007) observed reduced PD sequence learning in an SRT experiment administered after patients' overnight withdrawal from dopaminergic medication. Thus, while any conclusions drawn from this study of PD patients must be tempered by the recognition of the effects of dopaminergic modulation from levodopa or dopamine agonist medication, the weight of evidence at present indicates that dopaminergic modulation is most likely to disrupt mnemonic processing within a reinforcement learning framework, where knowledge acquisition is guided by (explicit) feedback provided on a trial-by-trial basis, and not sequence learning as measured by the SRT

task. As such, it appears unlikely that implicit sequence learning impairments observed in the present study are attributable to drug treatment effects.

CONCLUSIONS

PD patients show normal acquisition of a SRT sequence order with a categorical measure, suggesting that the integrity of the neostriatum is not essential for learning judgment-linked information about sequences of temporal stimulus movement. However, patients are less able to demonstrate knowledge of visuomotor sequence elements when responding motorically, a deficit that occurs almost exclusively in patients who respond slowly, irrespective of functional status. Further work is needed to elucidate the functional role of the basal ganglia in sequence learning, and more specifically, the extent to which PD difficulties on the SRT task arise because the basal ganglia is intimately involved in sequence learning per se or because its function is critical for the correct and rapid execution of the motor programmes required for sequential knowledge to enhance motor performance.

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