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The time course of spatial and object learning in Parkinson's disease

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Abstract—Parkinson's disease (PD) is characterized by spatial memory dysfunction, but the selectivity of the deficit remains unclear. We addressed this issue by comparing performance on spatial and object variants of a conditional associative learning task, and by analysing the data with time series analytical techniques. The 11 PD subjects and 15 normal control subjects learned stimulus–stimulus pairings through trial-and-error learning. PD subjects were selectively impaired on the spatial condition: they required more trials to achieve criterion, learned at a slower rate and displayed a working memory deficit. The groups did not differ in the object condition. These results suggest a distinction between material-specific spatial and object visual memory systems. Further, they indicate that spatial learning and memory are selectively impaired in early PD, suggesting that interactions between the basal ganglia and prefrontal cortex are important for the mediation of high-level cognition. © 1997 Elsevier Science Ltd

Key Words: working memory; memory; dopamine; basal ganglia; caudate nucleus.

Introduction

The prefrontal cortex in primates is a heterogeneous region with many functionally discrete subdivisions [18, 20, 34, 35, 45, 49, 58]. Among the models that attempt to map the functional organization of this region for memory, two have been particularly influential. Goldman-Rakic and colleagues [20, 62] have postulated an important distinction between the dorsolateral prefrontal cortex (the tissue surrounding the principal sulcus in the monkey), which they believe supports visual–spatial working memory function (the 'where' system), and the more ventrally situated lateral cortex (the inferior convexity in monkey), that supports visual–object working memory function (the 'what' system).§ Petrides and coworkers [39, 46] have also studied the functional relevance of the dorsal–ventral distinction, but rather than emphasizing a 'what vs where' organization, their model posits that the ventrolateral prefrontal cortex is the site of initial processing and short-term memory storage of sensory information, and that dorsolateral regions are recruited by demands on executive processing and monitoring of responses. Additionally, Petrides *et al.* [45, 47] have presented considerable evidence for a functional distinction among prefrontal regions lying along the rostral–caudal axis, with dorsolateral regions 46 and 9 supporting performance on self-ordered choosing tasks, and the more posterior prefrontal area 8 supporting performance on conditional associative learning tasks. Reciprocal connections between the basal ganglia and prefrontal cortex add to the complexity of its functional organization. The neostriatum receives highly processed and topographically organized projections from cortical regions throughout the brain that are funneled through the thalamus and then directed toward discrete prefrontal targets [3, 33]. These connections afford the opportunity to study aspects of frontal-lobe function by testing subjects with lesions of the basal ganglia. Prior studies on the cognitive deficits of subjects with Parkinson's disease (PD) (e.g., [22, 23, 30, 48, 57]) attest to the importance of prefrontal cortical–basal ganglia interactions, and to the power of this approach.

PD is a neurological disease characterized clinically by resting tremor, muscular rigidity and bradykinesia (slowness of movement). The principal neuronal damage in PD occurs in the substantia nigra pars compacta and

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§More recently, Goldman-Rakic and colleagues have suggested that a 'what/where' distinction in human visual working memory may manifest itself in a pattern of lateralized differences of activation in the prefrontal cortex [32].

in other pigmented nuclei of the brainstem [1]. These lesions lead to a depletion of dopamine in the striatum, including in the caudate nucleus neurons that participate in cortico-basal ganglia–thalamo-prefrontal cortical circuits. Many of the cognitive deficits in PD subjects are similar to those seen in patients with focal lesions in the prefrontal cortex. Owen *et al.* [38, 40], for example, have demonstrated that PD subjects are impaired on tests of planning and of spatial working memory that are sensitive to frontal-lobe lesions. Other groups have also demonstrated a deficit in spatial working memory in PD [8, 36, 57], but these studies have left unclear whether this visual working memory deficit is restricted to spatial material, or whether it also extends to non-spatial visual material.

The conditional associative learning paradigm, introduced by Petrides [43, 44], has been used extensively to study frontal-lobe function. In tests of this design, subjects must learn arbitrary stimulus–stimulus pairings among individual items from each of two groups of stimuli through trial-and-error learning. Monkeys are impaired at learning to associate individual responses from a repertoire of prelearned motor responses with different visual cues after lesions of the periarcuate cortex [43], premotor cortex [25] and motor thalamus [10]. Similarly, humans with damage to the premotor cortex show deficits in learning to associate different arm movements with different tactile or auditory cues [24]. Humans with frontal-lobe lesions are impaired at learning arbitrary stimulus–stimulus associations in spatial and non-spatial variations of the task, and humans with unilateral hippocampal removals show material-specific deficits that vary with the side of the lesion [44]. A positron emission tomography study contrasting conditional associative learning and a subject-ordered choosing working memory task revealed a double dissociation of prefrontal regions activated by the two tasks, with the former activating area 8, and the latter activating areas 9 and 46 [47].

The conditional associative learning paradigm has also been employed to investigate cognitive function in PD, but the results have been inconclusive. One study found no significant impairment in PD subjects relative to age-matched normal control subjects (NCS) on two tasks of conditional associative learning (a visual–motor task and a visual–visual task); there was a tendency for older PD subjects in the sample to perform more poorly than the group mean [11]. Two other studies found that PD subjects were impaired on tests of conditional associative learning. Linden *et al.* [31] reported impaired PD performance on a visual–verbal task, and also reported that PD subjects were unable to benefit from arbitrary (but predictive) cues in a speeded reaction time (RT) task. Recordings of slow cortical potentials during RT task performance indicated disordered frontal-lobe function [31]. In a separate study, Sprengelmeyer *et al.* [55] compared the performance of PD subjects with that of subjects with Huntington's disease (HD; a neurological disorder characterized by degeneration of neurons in the caudate nucleus) and with NCS. They found that PD and HD subjects were unable to learn arbitrary associations between colors and words. This study also revealed a deficit in PD subjects in the decision-time as well as the motor-time components of the RT measure in a motor conditional associative learning task. In each of these experiments, testing was halted after a small number of trials, and thus left unresolved whether PD subjects were never able to learn an entire set of arbitrary associations, or whether they were merely slower in learning [55].

We designed the present study to investigate three questions. First, is the spatial memory deficit in PD a circumscribed deficit, or does it extend to other classes of visual material? By pitting a spatial learning task against a non-spatial object learning task, we could examine this question, and we could investigate the possible presence of material-specific visual memory modules. Second, what is the time course of learning in PD? By employing a design that would require subjects to continue performing until they achieved a stringent criterion level of performance [44], and by examining the data with time series analytical techniques, we could extend knowledge about the interaction between learning and nigrostriatal degenerative disease. Third, does the deficit in spatial working memory in PD contribute to the deficit in long-term associative learning in PD? Results from our study could bear on interactions among functionally distinct areas of the prefrontal cortex (e.g., areas 9/46 and area 8).

Methods

Subjects

The participants were 11 subjects with PD and 15 NCS (Table 1). The two groups did not differ significantly in mean age or in mean years of education. None of the subjects was demented or depressed. The PD subjects were selected from the Massachusetts General Hospital Movement Disorders Unit, where the diagnosis of idiopathic PD was established by clinical examination according to standard neurological criteria [9]. All PD subjects were in the early stages of disease (Hoehn and Yahr Stages 0–II), and all were tested while taking optimal doses of anti-parkinsonian medications (one was taking an anticholinergic drug).

Procedure

The conditional associative learning test was modified from Petrides [44]. The two conditions, spatial and object, were formally the same. In each condition, subjects saw two distinct groups of stimuli: six at the top of a computer screen and six at the bottom. On each trial one stimulus from the top group was highlighted, and subjects had to indicate, by pointing and clicking with a computer mouse, which stimulus in the bottom group was paired with the highlighted stimulus in the top group. Visual and auditory feedback were provided on each selection. Incorrect selections ('errors') elicited negative feedback consisting of a bright red 'X' covering the incorrectly selected

Table 1. Subject characteristics

Group	Number of subjects (M/F)	Mean age (S.D.)	Mean years of education (S.D.)	Mean Blessed Dementia Scale score: memory and orientation section* (S.D.)	Hoehn and Yahr rating† (max. = 5)
Parkinson's disease	11 (7/4)	64.9 (8.2)	15.3 (2.9)	0.18 (0.4)	0–2
Normal control	15 (6/9)	70.2 (6.9)	16.5 (1.8)	0.6 (1.0)	—

*Blessed *et al.* (1968) [7a].
†Hoehn and Yahr scores: 0 ($n=1$); I ($n=1$); II ($n=9$).

stimulus, accompanied by a 500-msec buzz. Following negative feedback, the trial continued until the subject selected the correct stimulus. Correct selections were followed by positive feedback in which the correctly selected stimulus flashed rapidly twice, accompanied by two rapid beeps. Subjects were told that their initial selections would be governed by trial-and-error guessing, but that they should strive to learn the arbitrary stimulus–stimulus pairings as quickly as possible. Stimuli from the top group were highlighted in a different pseudorandom order in each block of six trials. Testing continued until subjects achieved a criterion level of performance of 18 consecutive correct selections with no errors, or when 180 trials had been completed. We told subjects that the test would continue until they achieved a certain number of consecutive correct selections, but they were not told the criterion number. Subjects who did not reach criterion in both conditions of the experiment were excluded from the analyses,† from Table 1 and from the figures. The dependent measures were errors per trial, response time (measured by the computer from trial onset until the selection of the correct paired associate), number of trials to criterion and working memory errors. We obtained a measure of working memory performance by counting the number of responses within a single trial in which a subject returned to a previously selected incorrect stimulus (for which the subject had received negative feedback). The total number of working memory errors for a subject, divided by the total number of trials in the test for that subject, yielded a normalized measure of working memory errors. This measure provided an index of a subject's ability to store and monitor previous responses within the same trial, to use this trial-specific information to govern selections and to discard this information at the beginning of each new trial. These operations are similar to those proposed by Baddeley [5] in his model of working memory. The working memory errors measure can also be understood in the context of Olton *et al.*'s model of working memory [37], because information about the reinforcement value of each stimulus was only useful for one trial. Our experimental design did not permit us to distinguish between these two models of working memory.

The conditional associative learning tasks were administered on Macintosh computers programmed in our laboratory. Testing sessions for each condition were preceded by a brief training session consisting of verbal instructions and a demonstration by the experimenter, and a training block in which the subject performed the task for a small number of trials (<20). Training sessions used different testing forms from those used in the test sessions. In the spatial condition, each stimulus in the top pool looked identical to the other five (cartoon light bulbs), and each stimulus in the bottom pool looked identical to the other five (cartoon playing cards) (Fig. 1a). Thus, featural cues could not be used to distinguish among the stimuli of the same group. The stimuli in the spatial condition were, however, stationary throughout the test and therefore could be distinguished from one another by spatial cues; each stimulus was defined by its

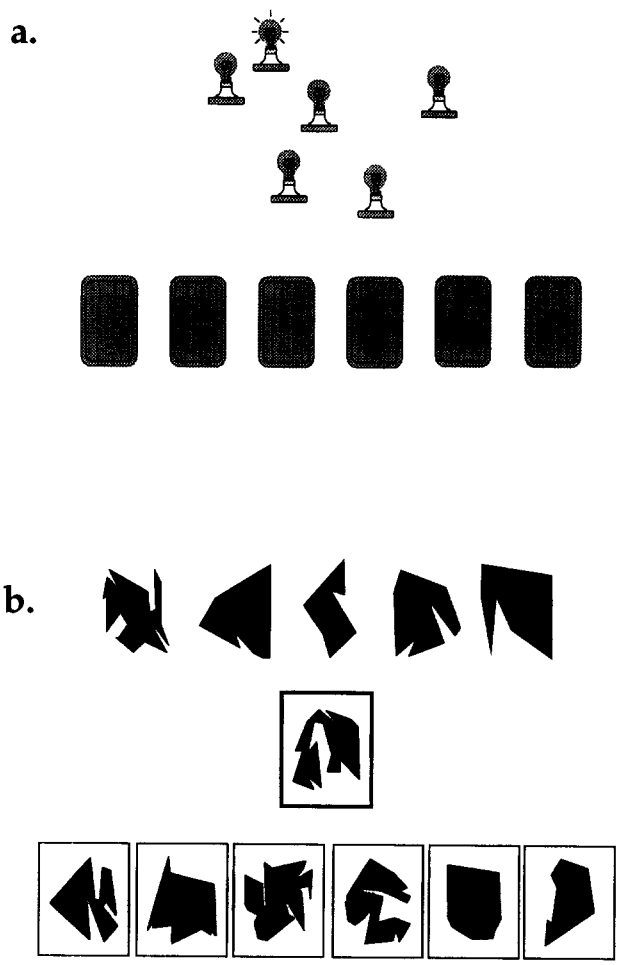

Fig. 1. Stimulus arrays for the spatial condition (a) and the object condition (b).

†Two NCS and three PD subjects were excluded because they were unable to achieve the criterion level of performance in both conditions. The mean number of years of education for the excluded subjects was NCS = 12 years and PD = 12.7 years, both well below the means of the subjects whose data are presented in this report (Table 1). Our experience from administering this test was that education was a strong predictor of ability to perform to criterion.

position relative to the other stimuli.† We took several steps to ensure that subjects used a spatial memory strategy in the spatial condition, rather than an alternative strategy such as assigning a number to each stimulus. First, we gave each subject explicit instructions to use a spatial strategy during the training session. Second, if we determined during the training session that a subject was not using a spatial strategy, we repeated the training session until the subject learned to use a spatial strategy. Third, we debriefed each subject after the spatial conditional associative learning test to confirm that the subject had used a spatial strategy, asking, among other questions, "Did you use a strategy of assigning numbers to each stimulus?" A trial in the spatial condition was initiated when one of the six light bulb stimuli became 'illuminated' by turning yellow. In the object condition, each of the 12 stimuli were black abstract silhouette shapes judged difficult to verbalize by normative testing [4, 61]. The stimuli in each group appeared in a horizontal line, one near the top of the screen, one near the bottom; the selected stimulus from the top group appeared in a box in the center of the screen (Fig. 1b). In the object condition, every stimulus changed position after each trial (but the two groups remained separated); thus, subjects could not rely on spatial cues to learn the associations between stimuli. The stimuli remained stationary, however, for the duration of a trial, and therefore the working memory errors measure in the object condition contained a spatial component. During the training session preceding the object test we encouraged subjects to encode distinctive features of objects, rather than to assign names to each stimulus. Most subjects, however, assigned names to at least a portion of the stimuli during the course of the object conditional associative learning test. The order of testing was counterbalanced within each group, and testing in the two conditions was separated by several hours.

In addition to memory testing, we measured basic motor functions, complex motor functions and spatial functions for each subject. These measures were used to calculate three composite scores, each used as a covariate in assessing learning on the conditional associative learning tasks. These analyses enabled us to separate learning performance from fundamental perceptual and motor dysfunction that may have interacted with learning. Basic motor function was assessed using simple tasks that did not require visual guidance: Fine Finger Movement [13], Finger Tapping (subjects depress a button as many times as possible for 30 sec with the index finger of the left hand, the right hand and both hands simultaneously) and Grip Strength [56]. These measures contributed to a composite Basic Motor Score, and were selected on the basis of an oblique factor analysis of data from another study of PD in our laboratory [14]. The Basic Motor Score for each subject was computed as the sum of these variables (each measured with the subject's preferred hand), each weighted by the reciprocal of its S.D. (in order to standardize the influence of the measures). The formula for computing the Basic Motor Score was

$$((1/8.17) \times \text{Fine Finger Movement Unimanual}) + ((1/8.48) \times \text{Fine Finger Movement Bimanual}) + ((1/10.75) \times \text{Finger Tapping Unimanual}) + ((1/11.02) \times \text{Finger Tapping Bimanual}) + ((1/22.55) \times \text{Grip Strength})$$

† It is not possible for us to determine the reference frame in which subjects encoded the stimuli in the spatial condition; head-centered, body-centered or allocentric coordinate frames are all possibilities. This ambiguity of spatial reference frame is a characteristic of most spatial tests that are administered on a computer screen.

Complex motor function was assessed using tasks that (i) required high-order planning and precise coordination between sensory input and motor output, and (ii) were sensitive to bradykinesia: Thurstone Tapping [59] and Grooved Pegboard (LaFayette Instrument Company, Lafayette, IN, U.S.A.). These measures contributed to a composite Complex Motor Score, and were similarly selected on the basis of an oblique factor analysis of data from a previous study [14]. The formula for the Complex Motor composite score, computed as the sum of these variables (each measured with the subject's preferred hand), each weighted by the reciprocal of its S.D., was

$$((1/21.24) \times \text{Thurstone Tapping Unimanual}) + ((1/11.19) \times \text{Thurstone Tapping Bimanual}) + ((-1/27.77) \times \text{Grooved Pegboard Unimanual})$$

Spatial function was assessed using two tasks: the Matchsticks Test [7] and the Body Scheme Test [53]. These measures, also selected on the basis of previous work with PD [14], contributed to a composite Spatial Function Score. The formula for the Spatial Function composite score, computed as the sum of these variables, each weighted by the reciprocal of its S.D., was

$$((-1/0.97) \times \text{Matchstick}) + ((1/4.88) \times \text{Body Scheme})$$

Data analysis

In order to compare the extent and rate of learning for PD subjects and NCS, we developed an application of time series analysis that assessed change and differential change across trials. In these analyses, autocorrelated error within subjects was estimated and removed to permit unbiased assessment of the effects of interest, and to permit valid significance tests. This method assumed that residual error terms were correlated from trial to trial for an individual subject and took this correlation into account. Four separate analyses were performed, pairing each of two dependent variables (errors, response time) with both conditions (spatial, object). In each analysis we employed maximum likelihood methods to estimate a first-order (one trial apart) autoregressive term within subjects, linear and curvilinear (quadratic) terms for trials, and group effects and interactions. We then repeated these procedures, using the basic motor, complex motor and spatial composites as covariates. The SAS (Statistical Analysis System) Mixed procedure (mixed and random effects) was employed for these analyses [51]. This time series analysis method was preferable to a traditional analysis of variance (ANOVA) because a traditional ANOVA does not take autocorrelated error into account, and because analysis of data with a different number of trials for each subject with a traditional ANOVA is computationally awkward.

Results

The four dependent variables in our experiment were: trials-to-criterion, errors, response time and working memory errors. We examined response time in two ways: by analysing the change in response time across trials to obtain one of the measures of learning rate, and by summing across trials to obtain a measure of the duration of the entire test. Debriefing following the spatial conditional associative learning test confirmed that all subjects used a spatial strategy to perform this task.

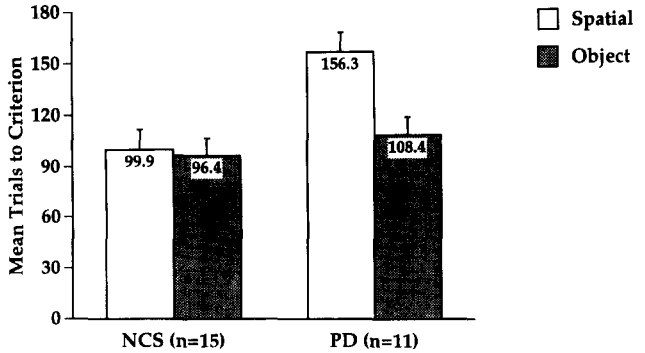

Fig. 2. PD subjects were significantly impaired in the spatial condition, as measured by mean trials-to-criterion. Error bars indicate standard error of the mean.

Trials-to-criterion

An analysis of trials-to-criterion indicated that NCS required fewer trials to achieve criterion levels of performance than did PD subjects in the spatial condition only: a mixed between-subject (group: PD/NCS) and within-subject (condition: spatial/object) ANOVA revealed a significant interaction between group and condition ($P=0.015$; Fig. 2). *Post-hoc* t-tests indicated that the interaction was due to a significant difference between PD subjects and NCS for the spatial condition ($P=0.003$), but not for the object condition. Adjusting separately for the three composite scores did not change this result (see below). In the spatial condition, one NCS and five PD subjects were unable to reach criterion, whereas in the object condition only one NCS was unable to do so. We also performed within-group regression analyses to determine whether trials-to-criterion for the two conditions were correlated. In the NCS group the correlation was statistically significant ($r=0.56$; $P<0.05$), in the PD group it was not ($r=0.23$; $P=0.5$).

Rate of learning

To assess rate of learning (i.e. rate of change across trials), we performed time series analyses consisting of four separate analyses that paired the dependent measures of errors and response time separately with each condition. The principle result of these analyses was that, in the spatial condition only, NCS displayed a faster decrease in the number of errors across trials than did PD subjects. In each of the analyses we detected a significant ($P<0.0001$) first-order autoregressive term, and removed these autocorrelated components from the data. Errors and response times for both groups declined in a decelerating manner to an asymptote for both conditions, as indicated by a significant quadratic trend across trials ($P<0.05$ in each case). The NCS group mean score was lower than the PD group mean score as measured by both variables in both conditions ($P=0.0004$–0.04, depending on condition and dependent variable).

In the spatial condition, NCS showed a sharper decline in errors across trials (i.e. NCS displayed a faster rate of learning as measured by the number of errors across trials), as revealed by a Group × Trials interaction ($P=0.01$; still significant with Bonferroni correction, $P=0.04$). The absence of a Group × Trials interaction in the object condition, however, indicated that learning (as measured by the decrease in errors over trials) was comparable between the two groups in the object condition (Fig. 3). Analysis of response times yielded no Group × Trials interaction in either condition.

Next, we adjusted the analyses for effects of the motor and spatial composites, and the results for the Group × Trials interactions were not affected by inclusion of the covariates. Importantly, the significant difference in rate of change of spatial errors between groups continued to achieve significance when the composites were entered into the model as covariates [basic motor: $P=0.02$; complex motor: $P=0.07$ (marginally significant); spatial: $P=0.006$; Fig. 4]. The main effect for group in the object/errors analysis was eliminated upon inclusion of each composite, as were the main effects for group in the spatial/response time and object/response time analyses when the complex motor composite was the covariate.

Response time

To assess total time to achieve criterion (or to complete 180 trials) we analysed mean response time summed across trials with a mixed between-subject (group: PD/NCS) and within-subject (condition: spatial/object) ANOVA. Main effects of condition ($P<0.001$) and group ($P<0.05$) indicated that subjects in both groups took longer to achieve criterion in the object condition, and that NCS required less time than PD subjects to achieve criterion in both tests (Table 2).

Working memory

Finally, we examined whether the selective spatial learning deficit in PD was related to a working memory deficit. Mann–Whitney Signed Rank tests indicated that PD subjects made significantly more working memory errors than did NCS in the spatial condition (NCS mean = 0.023; PD mean = 0.042; $P=0.01$), but that the two groups did not differ significantly in the object condition (NCS mean = 0.045; PD mean = 0.061; $P>0.1$). Regression analyses, however, revealed no significant

Table 2. Mean response time summed across trials (min)

Group	Spatial condition (S.D.)	Object condition (S.D.)
Parkinson's disease	31.6 (22.4)	37.3 (24.2)
Normal control	16.2 (11.3)	25.2 (9.5)

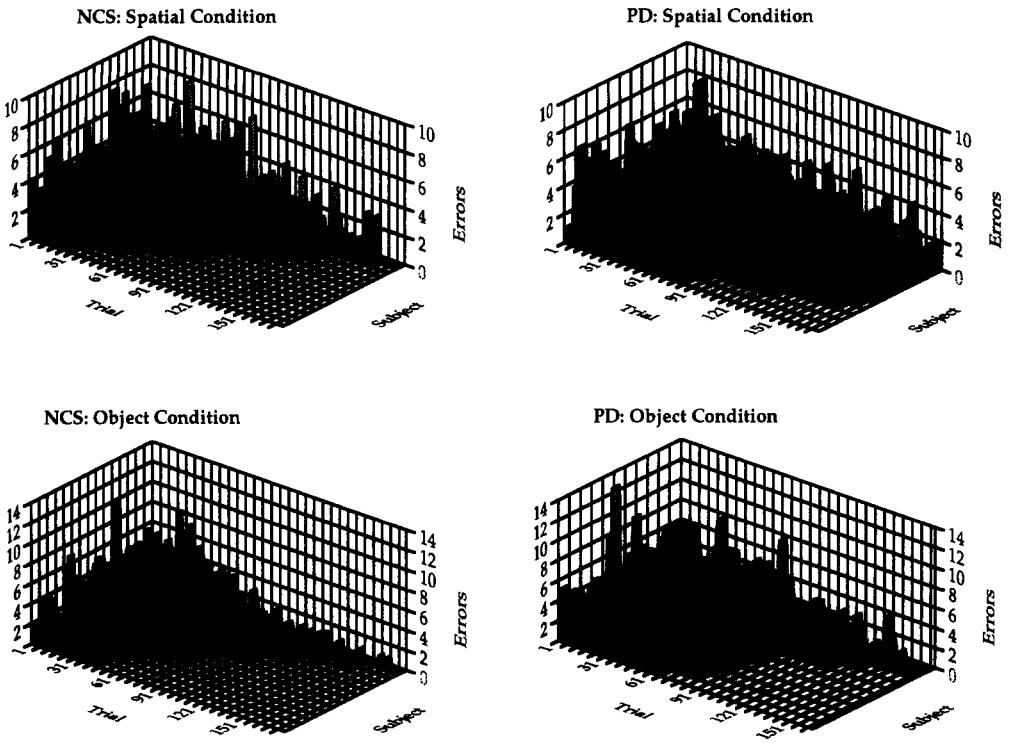

Fig. 3. The raw error data for each subject, presented by group and by condition. This figure illustrates that individual subjects in the PD group tended to make more errors across a larger number of trials than NCS in the spatial condition. Blackened areas on the 'floor' of the graph (the x–z plane) indicate trials for each subject in which no errors were made.

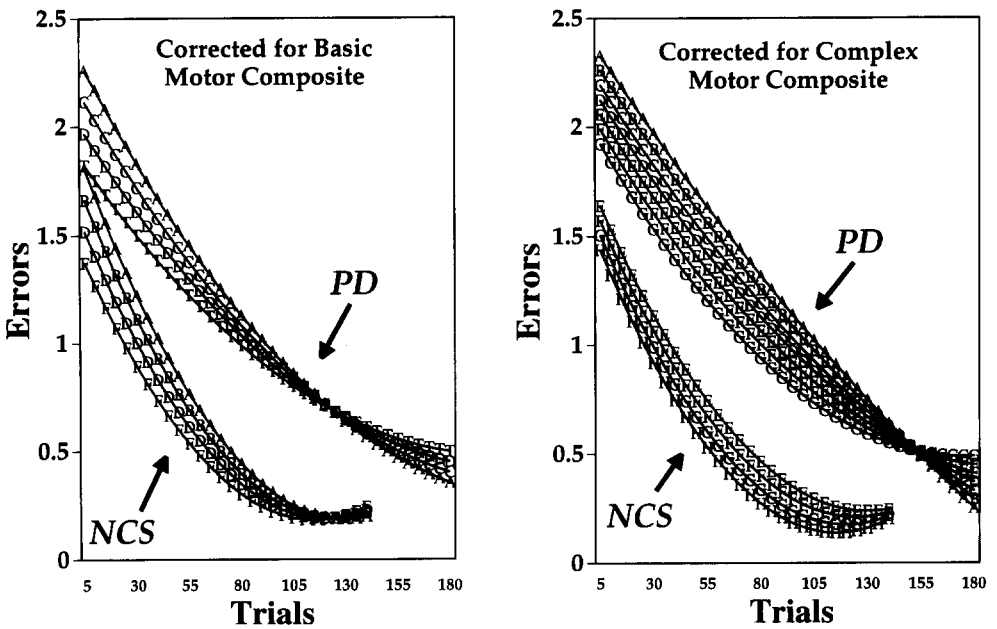

Fig. 4. The group difference in spatial learning (as indexed by a Group × Trial interaction), illustrated by the differences in the slopes of the NCS and the PD curves. The curves are maximum likelihood estimated surfaces (autoregressive component removed) for spatial errors vs trials, corrected for basic motor and complex motor composite scores. An individual line represents the predicted path for subjects with a particular composite score ('A' = 1, 'B' = 3, 'C' = 5, 'D' = 7, 'E' = 9, 'F' = 11, 'G' = 13, 'H' = 15; all scores transformed to be > 0). For example, in the Basic Motor Composite, the fact that the curve labeled 'A' in the NCS group is lower than the corresponding curve in the PD group indicates that NCS with a score of 1 on the Basic Motor Composite made fewer errors than PD subjects with the same Basic Motor Composite score. The composite curves for NCS are truncated to remove a slight upturn that is an artifact of the quadratic term.

correlations between working memory errors and trials-to-criterion for either group in either condition.

Discussion

We tested PD subjects and NCS on a test of conditional associative learning to assess the specificity of the spatial learning deficit in PD, and to analyse the time course of learning in PD. Our results indicated that PD subjects in the early stages of disease were selectively impaired on the spatial condition of the conditional associative learning test. PD subjects required more trials to achieve criterion level performance than NCS in the spatial, but not the object, condition. Consistent with this finding were the results of regression analyses of trials-to-criterion for the object and spatial conditions. The correlation was positive and significant for NCS, indicating that associative learning performance in one condition was predictive of associative learning performance in the other. There was no predictive relation between trails-to-criterion scores in the two conditions for the PD group, however, reflecting the impaired performance of the PD subjects in the spatial condition. Time series analyses indicated that PD subjects learned at a slower rate than NCS in the spatial condition, as measured by the rate of decline in errors over trials. This effect remained significant when adjustments were made for individual differences in levels of motor and spatial function. In contrast, the two groups learned at the same rate in the object condition. Analysis of working memory errors within individual trials indicated that PD subjects displayed a working memory deficit in the spatial condition, but not in the object condition. Interpretation of the differences between spatial working memory errors and object working memory errors must be tempered by the fact that the object working memory errors measure contained a spatial component, and by the fact that regression analyses revealed no significant correlations between working memory errors and trials-to-criterion. The relation between working memory and conditional associative learning in our study remains unclear.

Subjects in both groups took significantly more time to achieve criterion in the object condition than in the spatial condition, consistent with our subjective impression from post-test debriefing of subjects that the object condition of our task was more difficult than the spatial condition. This interpretation is also consistent with the fact that subjects in both groups made more working memory errors in the object condition than in the spatial condition. Although the mean errors and response times indicated significantly poorer performance for the PD group than for the NCS group in both conditions, the differences in response times (in both conditions) and in errors (in the object condition) were no longer significant when the motor and spatial composites were entered into the analyses. This result suggests that the lower level of performance in the PD group, as measured by these variables, was secondary to motor and spatial impairments. Motor and spatial impairments, however, do not explain the slower rate of learning in the spatial condition in the PD group, because the finding persisted when the influence of these variables was eliminated with ANCOVA.

Our study supports the existence of an anatomical and physiological distinction between spatial and non-spatial material-specific systems of visual memory in humans, as has been suggested by psychological [54, 60] and neuroimaging [15, 54] investigations. Our data cannot confirm directly whether this spatial–object dissociation falls into a dorsal–ventral organizational scheme [15, 62], into a hemispheric lateralization scheme [32, 54], or into a third, as yet unarticulated, functional map. It is important to note that subjects in both groups adopted a strategy of assigning names to at least some of the stimuli in the object condition. Thus, the measure of object conditional associative learning performance in this study probably contains object recognition and verbal components.

A second implication of our study, consistent with the results of other work by our group [48], is that spatial learning and memory are selectively impaired in early PD, while visual learning and memory with non-spatial material are relatively spared. These results extend previous investigations of visual working memory in PD [8, 36, 38, 40, 57] by suggesting that working memory functions are not uniformly vulnerable to initial disease processes. These results also extend previous studies of conditional associative learning in PD [11, 31, 55], indicating that PD subjects learn at a slower rate than NCS when stimuli are defined by spatial cues. Almost one-half of the PD subjects in our sample were unable to learn the full complement of six spatially defined paired associates within 180 trials, as compared with only one NCS who failed in the spatial condition.

The spatial learning deficit in PD suggests an important role for interactions between the basal ganglia and prefrontal cortex in the mediation of high-level cognition. Earlier work has associated lesions in discrete regions of the caudate nucleus with behavioral impairments that mirror those that follow lesions to their prefrontal cortical afferents [6, 17, 50]. Heterogeneous patterns of parkinsonian nigrostriatal degeneration lead to uneven distributions of dopamine depletion in the neostriatum [28, 29], and could explain the selective vulnerability of spatial learning in early PD. PD pathophysiology results in a disproportionately high degree of dopamine depletion in the dorsolateral head of the caudate nucleus [28, 29], the region of the neostriatum that receives projections from the posterior parietal cortex [52] and from the dorsolateral prefrontal cortex [42], and whose efferents are focused on the dorsolateral prefrontal cortex [3, 26, 33]. Such an anatomically discrete lesion could disrupt a neuronal circuit important for spatial learning and memory. This model is consistent with the conclusions of previous studies, which have also been interpreted as evidence for an important role for the basal ganglia in

mediating high-level cognitive processes [16, 19, 21, 41, 57]. We hypothesize that the selective deficit in spatial learning and memory in PD is not due to dopamine decreases directly in the prefrontal cortex, because degeneration of neurons in the ventral tegmental area (the major dopamine projection to the frontal cortex) lags behind degeneration of the substantia nigra pars compacta in early stages of the disease [2].

Alternatively, the selective spatial learning deficit in PD that we describe in this report may be understood as a result of neurotrasmitter abnormalities in structures that support the spatial computations required for motor control. For example, it has been suggested that the striatum is a site where coordinate transformations are computed for obstacle avoidance; transformations from cartesian sensory maps of the environmental location of objects to limb-centered coordinate frames that are necessary for motor control [12]. Another model posits that the basal ganglia make an important contribution to the voluntary control of visuospatial attention [27]. From the perspective of these and similar models, our results may not reflect preferential interference with a discrete 'spatial' channel in a basal ganglia–thalamocortical circuit, as we have hypothesized, but may instead be the result of dysfunction in a structure that is specialized for spatiomotor computations. This alternative interpretation does not require the topography of the dopamine depletion in early PD to be as circumscribed as we have proposed.

It is likely that dopamine depletion does not, alone, explain the spatial learning deficit in PD, because dopamine replacement therapy, an effective palliative for the motor deficits of all PD subjects in our sample, did not resolve their cognitive dysfunction. Multiple neurotransmitter systems are compromised in PD, due to degeneration of dopaminergic and noradrenergic neurons of the midbrain, and of cholinergic neurons of the basal forebrain [23], and each may have an impact on higher cognitive functions during the course of the disease.

The excessive spatial working memory errors in PD suggest an interaction between working memory and long-term memory: PD subjects demonstrated more difficulty remembering the locations of negatively rewarded stimuli within a single trial (disordered spatial working memory), and also took longer on average to establish long-term mnemonic representations of stimulus–stimulus pairings. Our results do not permit us, however, to hypothesize a direct link between these two memory systems, because we did not find evidence of strong relations between working memory and long-term memory measures within individual subjects in our study. The role of working memory in conditional associative learning remains an important topic for future studies. Petrides *et al.* [47] have established that dorsolateral areas 9 and 46 are recruited during performance of a working memory task, and that area 8 is recruited during performance of a conditional associative learning task. Our results suggest that the function of one or both of these cortical areas is disrupted by PD pathology, and that faulty interactions between these functionally distinct regions of the prefrontal cortex may contribute to the spatial memory deficits that characterize PD.

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