Brain and Cognition 68 (2008) 134–143

Contents lists available at ScienceDirect

Brain and Cognition

journal homepage: www.elsevier.com/locate/b&c

Neural substrates of cognitive skill learning in Parkinson's disease

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ARTICLE INFO

Article history:
Accepted 14 March 2008
Available online 5 May 2008

Keywords:
Parkinson's disease
Procedural learning
Memory
Tower of London
Caudate nucleus
Medial temporal lobe
Dorsolateral prefrontal cortex
Positron emission tomography

ABSTRACT

While cognitive skill learning is normally acquired implicitly through frontostrial circuitry in healthy individuals, neuroimaging studies suggest that patients with Parkinson's disease (PD) do so by activating alternate, intact brain areas associated with explicit memory processing. To further test this hypothesis, 10 patients with PD and 12 healthy controls were tested on a modified, learning version of the Tower of London task while undergoing positron emission tomography at four different time points over the course of learning. Despite having less accurate problem solving abilities than controls, PD patients were able to acquire the skill learning task. However, as compared to controls, they maintained higher levels of cerebral blood flow activity in the dorsolateral prefrontal cortex and hippocampus and showed an increase in activity in the frontopolar cortex and posterior cingulate over the course of learning. These findings reflect a shift to the explicit memory system in PD patients, enabling them to learn this cognitive skill, which is normally acquired by control subjects using implicit learning strategies and frontostriatal circuitry.

1. Introduction

Cognitive skill learning refers to the capacity to acquire a new skill gradually and implicitly through practice of a task demanding mental operations. It can be measured using a variety of paradigms, each tapping into slightly different neural systems according to the demands of the task, though there is a general consensus that frontostriatal circuits are involved. For instance, neuroimaging studies using probabilistic classification (Poldrack, Prabhakaran, Seger, & Gabrieli, 1999; Seger & Cincotta, 2005) and problem-solving (Tower of London, Tower of Hanoi) (Beauchamp, Dagher, Aston, & Doyon, 2003; Fincham, Carter, van Veen, Stenger, & Anderson, 2002) paradigms have both revealed activity in the prefrontal cortex and the caudate nucleus over the course of learning, suggesting that these regions play an important role in the acquisition of new cognitive skills. Accordingly, studies in clinical populations have focused largely on patients with Parkinson's disease (PD) who suffer from a progressive loss of dopaminergic innervation of the striatum, consequently affecting normal transmission of information through frontostriatal circuitry (Owen, Doyon, Dagher, Sadikot, & Evans, 1998). However, the nature and prevalence of cognitive skill learning deficits in this group remains unclear.

In particular, recent observations from our laboratory suggest that PD patients may be unimpaired at acquiring a modified, learning version of Shallice's (1982) "Tower of London" (TOL) task. Results from other studies have shown that PD patients may be successful at accomplishing certain cognitive tasks only through the use of alternate brain areas compared to those activated by healthy control subjects. Neuroanatomical evidence for such compensation effects has previously been reported using cognitive (Dagher, Owen, Boecker, & Brooks, 2001) and skill learning (Mentis et al., 2003; Moody, Bookheimer, Vanek, & Knowlton, 2004) tasks. Specifically, Dagher and colleagues (2001) found that, despite having comparable behavioural levels of performance on the TOL task, PD patients and control subjects differed in their patterns of regional cerebral blood flow (rCBF) activation: while controls activated the right caudate nucleus, patients did not. Furthermore, right hippocampus activity was suppressed in the controls and enhanced in the PD patients, possibly as a result of impairments within the frontostriatal system. That is, recruitment of the hippocampus, known for its involvement in declarative memory, may have served to compensate for deficits in the procedural system (Dagher et al., 2001). Moody and colleagues (2004) reported a similar interaction during a probabilistic classification task. Indeed, contrary to

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doi:10.1016/j.bandc.2008.03.008

the results of a previous behavioral experiment (Knowlton, Mangels, & Squire, 1996), the PD patients in their imaging study were not impaired at learning the task. However, compared to controls, the patients had less activation in the caudate nucleus and greater activation in medial temporal regions, as well as in the rostral prefrontal cortex (Broadmann area [BA] 10), both of which have also been linked to explicit memory retrieval (Moody et al., 2004). These findings again suggest that patients with PD may rely on intact explicit memory systems for tasks that are normally learned implicitly by healthy control subjects using frontostriatal circuitry.

In the present study, we aimed to test the generality of these findings by extending them to a different type of cognitive skill learning task. We used a modified version of the TOL task (Shallice, 1982), which has previously been learned successfully in our laboratory by both younger and older healthy adults (Beauchamp et al., 2003; Ouellet, Beauchamp, Owen, & Doyon, 2004). The TOL is well-known as a task used to measure planning performance in a variety of populations (Unterrainer & Owen, 2006). In the current study, a modified version was developed which had the added value of assessing subjects' acquisition of the task over time, thus enabling its use as a cognitive skill learning task. Similar cognitive skill learning tasks used in the past, such as the Tower of Hanoi and Tower of Toronto (Allain et al., 1995; Daum et al., 1995; Saint-Cyr, Taylor, & Lang, 1988; Vakil & Herishanu-Naaman, 1998), are not ideal because subjects are presented with the same problem on every trial of a particular level of difficulty, thus making learning very specific to one particular solution, and thereby limiting the ecological validity of the task in a skill learning context. Moreover, because extended practice on these tasks implies searching for a repeating strategy, this can eventually lead to explicit knowledge of a particular strategy. Our version of the TOL is not confounded by aspects of declarative memory because the solution is different for each TOL problem presented.

We predicted that the PD patients in this experiment would be unimpaired at learning the TOL task, but would show a different pattern of brain activity over the course of learning compared to healthy age-matched controls. We expected that differences in brain activation during implicit learning of the TOL task would reflect compensatory mechanisms in PD patients, in particular, the recruitment of brain areas normally associated with explicit memory retrieval, such as medial temporal lobe regions and related cortical structures.

2. Materials and methods

2.1. Participants

Ten right-handed patients (6 men/4 women, mean age ± SD = 60.0 ± 7.1 years, mean education = 16.5 ± 2.4 years) who were diagnosed as having typical idiopathic PD according to the criteria established by Gelb and colleagues (1999) participated in this study. Five other patients were enrolled, but were unable to complete the study: three were incapable of performing the task, one had an anxiety attack in the scanner, and one had an adverse reaction to the withdrawal of medication. All patients were non-demented according to their performance on the Mini-Mental State examination (MMSE $\geqslant$ 27, mean score = 28.8 ± 1.0) (Folstein, Folstein, & McHugh, 1975). They were also non-depressed as indicated by their answers on the Beck Depression Inventory (BDI) (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961); patients either received a score corresponding to "normal mood fluctuations" ($n = 7$) or "mild to moderate mood disturbance" ($n = 3$) (mean score = 8.1 ± 4.0). The latter were included in the study because their higher scores on the inventory were due to items describing somatic symptoms directly related to PD. Patients with a significant history of psychiatric or neurological illness were not included in the study. The severity of clinical symptoms was assessed according to the Unified Parkinson's Disease Rating Scale (mean = 17.9 ± 6.0) (Fahn & Elton, 1987), the Hoehn and Yahr 5-point rating scale (Stage I–III, mean = 2.0 ± 0.5) (Hoehn & Yahr, 1967) and the duration of the disease (mean = 8.5 ± 3.6 years). The patients' mean age at disease onset was 53.0 ± 6.3. All patients in the study were receiving a combination of anti-parkinsonian medications including dopamine agonists (Pergolide), Levodopa/Carbidopa or Amantadine. Only one patient was taking a monoamine oxidase inhibitor (Selegiline). Some patients were taking additional medication to treat other, unrelated conditions, including anti-hypertensives ($n = 5$), Sildenafil ($n = 3$), Alendronate ($n = 1$), Levothyroxine ($n = 2$), Zopiclone ($n = 1$) and Simvastatin ($n = 1$). Also, two patients were taking benzodiazepines (Clonazepam 0.5 mg per day, prescribed at bedtime in one case and p.r.n. in the other) and one was taking amitriptyline (Elavil 20 mg q.h.s.); however, at the low doses prescribed, it is unlikely that any of these medications would have had any significant impact or interaction with the results observed in the present study. In addition, these medications were taken by the patients on a regular basis and they were therefore not in a state of withdrawal at the time of testing. In order to minimise any acute effects of medication on cognitive functions, patients were asked to discontinue their antiparkinsonian medications the night before the PET scan was scheduled to take place. Thus, at the time of scanning, all subjects were in a "practical off" state, considered to be relatively hypodopaminergic (at least 12 h off medication) (Manuchair & Pfeiffer, 2005).

The patient group was compared to twelve previously tested, right-handed, control participants (6 men/6 women, mean age = 56.8 years ± 5.5 years, mean education = 14.4 ± 5.7) who had no history of depression, neurological or psychiatric diseases. The PET data from these subjects was reported in an earlier study (Beauchamp et al., 2003). Independent *t*-tests revealed that the patients did not differ from the control group with respect to their age ($p = 0.3$) and level of education ($p = 0.1$). All subjects gave informed, written consent for participation in the study, which was approved by the Ethics Committee of the Montreal Neurological Institute.

2.2. Cognitive skill learning paradigm

The modified, computerised TOL task consisted of a series of visuo-spatial problems in which subjects had to displace coloured balls in order to reproduce a goal-configuration (Beauchamp et al., 2003; Ouellet et al., 2004). TOL problems were presented on a touch-sensitive screen which was lowered in front of the participants at an ideal distance to promote comfortable reaching towards the screen. All subjects used their right hand to execute the task. In this version of the TOL task, subjects were presented with two sets of coloured balls. They were told that the set at the top of the screen was the model display, while the set at the bottom corresponded to the working display. Each set was composed of three coloured balls (red, blue, green) distributed in any of three sockets, which could contain one, two or three balls. On each trial, the coloured balls appeared in predetermined locations in each of the displays. The goal of the task was to reproduce, in a minimum number of moves, the configuration of the model display by rearranging the configuration of the balls in the working display. Subjects were asked to adhere to a set of three instructions when displacing balls. They were not allowed to: (1) move a ball if another one was placed directly above it; (2) move a ball to an available position in the same column; and finally, (3) move a ball to a location that was already occupied. The program was set such that it would not