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Levodopa medication improves incidental sequence learning in Parkinson's disease

M. Beigi[a,b], L. Wilkinson[a,c], F. Gobet[d], A. Parton[b,1], M. Jahanshahi[a,*,1]

[a] Sobell Department of Motor Neuroscience and Movement Disorders, UCL Institute of Neurology, Queen Square, London WC1N 3BG, UK
[b] Division of Psychology, Department of Life Sciences, Brunel University, Uxbridge UB8 3PH, UK
[c] Behavioral Neurology Unit, National Institute for Neurological Disorders and Stroke, 10 Center Drive, Bethesda, MD, United States
[d] Department of Psychological Sciences, University of Liverpool, Liverpool L69 7ZA, UK

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ABSTRACT

Empirical evidence suggests that levodopa medication used to treat the motor symptoms of Parkinson's disease (PD) may either improve, impair or not affect specific cognitive processes. This evidence led to the 'dopamine overdose' hypothesis that levodopa medication impairs performance on cognitive tasks if they recruit fronto-striatal circuits which are not yet dopamine-depleted in early PD and as a result the medication leads to an excess of dopamine. This hypothesis has been supported for various learning tasks including conditional associative learning, reversal learning, classification learning and intentional deterministic sequence learning, on all of which PD patients demonstrated significantly worse performance when tested on relative to off dopamine medication. Incidental sequence learning is impaired in PD, but how such learning is affected by dopaminergic therapy remains undetermined. The aim of the current study was to investigate the effect of dopaminergic medication on incidental sequence learning in PD. We used a probabilistic serial reaction time task (SRTT), a sequence learning paradigm considered to make the sequence less apparent and more likely to be learned incidentally rather than intentionally. We compared learning by the same group of PD patients (n=15) on two separate occasions following oral administration of levodopa medication (on state) and after overnight withdrawal of medication (off state). Our results demonstrate for the first time that levodopa medication enhances incidental learning of a probabilistic sequence on the serial reaction time task in PD. However, neither group significantly differed from performance of a control group without a neurological disease, which indicates the importance of within group comparisons for identifying deficits. Levodopa medication enhanced incidental learning by patients with PD on a probabilistic sequence learning paradigm even though the patients were not aware of the existence of the sequence or their acquired knowledge. The results suggest a role in acquiring incidental motor sequence learning for dorsal striatal areas strongly affected by dopamine depletion in early PD.

1. Introduction

Levodopa medication has been described as the most significant advance in the treatment of Parkinson's disease (PD) (Olanow et al., 2004; Poewe, et al., 2010; Stocchi, 2005). By ameliorating the effects of dopamine depletion in the basal ganglia, levodopa can improve the major motor symptoms with considerable benefits for patients' quality of life. Nonetheless, the consequent widespread increase in dopamine levels can impair functions in brain networks that are relatively spared in the early stages of the disease, such as the limbic and orbitofrontal striatal circuits. This 'dopamine overdose' can result in cognitive deficits that have a negative impact on the quality of life of patients with the disease (Schrag et al., 2000). Fundamental processes such as learning and memory have been linked to dopamine release, especially within the pre-frontal cortex and striatum (see for example Gabrieli, 1998; Packard and Knowlton, 2002; Shohamy et al., 2008; Williams and Goldman-Rakic, 1995). Therefore, studying such effects has potentially important implications for the management of PD as well as increasing our theoretical understanding of the role of dopamine in modulating neural pathways instantiating cognition and learning.

Incidental procedural learning is the gradual acquisition of a cognitive or motor skill in long-term memory through repetitive task performance (Nissen and Bullemer, 1987; Reed and Johnson, 1994; Shanks et al., 2003). In contrast, intentional declarative learning involves the active acquisition of factual knowledge. Incidental motor learning has been widely investigated using the serial reaction time

* Correspondence to: UCL Institute of Neurology, 33 Queen Square, London WC1N 3BG, UK.
E-mail address: m.jahanshahi@ucl.ac.uk (M. Jahanshahi).
[1] Both Dr Parton and Professor Jahanshahi have contributed equally and should be jointly be considered senior author.

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task (SRTT). Typically, in this task, participants respond to the appearance of a target at one of several locations by pressing the corresponding response button without knowing that the targets follow a pre-determined sequence (Nissen and Bullemer, 1987). Learning of the sequence is demonstrated by the speeding up of reaction times (RTs) on sequence relative to random (or pseudorandom) trials. Many researchers argue that such learning can occur in the absence of awareness due to the existence of good incidental learning in normal participants who cannot demonstrate explicit awareness of the sequence structure (Berns et al., 1997; Cleeremans et al., 1998; but see also Shanks et al. (2003), Shanks (2004)) and the presence of relatively preserved incidental learning in patients with intentional learning deficits, such as Korsakoff's syndrome (Nissen and Bullemer, 1987) and Alzheimer's (Knopman and Nissen, 1987). Nonetheless, researchers concede that parallel mechanisms of intentional (explicit) learning may be engaged in SRTTs if the sequence structure is insufficiently concealed (Rowland and Shanks, 2006; Shanks et al., 2005).

Interest in incidental motor sequence learning in patients with PD has been fuelled by studies in normal participants that both identify task-related activity in brain networks known to be affected by PD and suggest a significant role for dopamine in task performance. Functional imaging studies of incidental SRTT in healthy participants relate performance to change in activation within the basal ganglia, especially the caudate and putamen (Grafton et al., 1995; Rauch et al., 1997; Schendan et al., 2003; Willingham et al., 2002), and to cortical regions associated with the fronto-striatal network, including the pre and supplementary motor areas (SMA) (Grafton et al., 1995; Hazeltine et al., 1997; Honda et al., 1998) and, during early stages of learning, the dorsolateral prefrontal cortex (DLPFC) (Meehan, et al., 2011). Furthermore, a systematic release of dopamine in the left putamen and bilaterally in the anterior caudate during SRTT performance has been documented using PET to measure changes in the concentration of the dopamine receptor ligand ^{11}C-raclopride (Badgaiyan et al., 2007). Learning was attributed to activity in the left caudate as it was not found in a matched motor planning task, whilst the activity common to both tasks (left putamen and right caudate) was proposed to underlie movement selection. Finally, the administration of raclopride (a D2 antagonist) produces impairment in learning proportional to the dose administered (Tremblay et al., 2009). Taken together, these studies indicate that learning on the SRTT relies on the striatal motor and associative circuits known to be adversely affected by dopamine depletion in PD, and that successful learning appears to be related to a systematic release of dopamine. Nonetheless, as the relation of dopamine to performance is described by an inverted U curve, where too little or much dopamine may be detrimental to performance, it is unclear the degree to which patients with PD will be impaired on SRTT learning on or off medication (Cools et al., 2001; Goldman-Rakic, 1999; Williams and Goldman-Rakic, 1995).

Several studies have investigated performance of the SRTT in patients with PD on levodopa therapy. The majority reported impaired learning compared to age matched controls (e.g. Brown et al., 2003; Jackson et al., 1995; Kelly et al., 2004; Muslimovic et al., 2007; Shin and Ivry, 2003; Wilkinson et al., 2009), but a few studies found little difference between PD and control groups (Doyon et al., 1997; Feigin et al., 2003). Nonetheless, a meta-analysis of SRTT studies in PD patients taking L-Dopa concluded that learning was impaired (Siegert et al., 2006). However, it is not possible to differentiate, on the basis of these studies, the degree to which impairments were a consequence of the disease or its medical treatment with dopamine replacement therapy.

Only two studies have specifically reported data on SRTT learning in PD patients who were either not taking levodopa (Muslimovic et al., 2007) or tested off-medication after a washout period (Wilkinson and Jahanshahi, 2007). In the first study, Muslimovic and colleagues (2007) assessed learning in a large sample of PD patients (n=95) performing a 10 item SRTT. The patients displayed some sequence learning but this was attenuated in comparison to healthy age matched controls. Yet, the learning for a subgroup of 'de novo' patients (n=24) who were not receiving dopamine therapy was indistinguishable from aged matched participants. However, in examining a sub-group of 'de novo' patients who did not require levodopa as yet, the effects of medication are inextricably confounded with disease stage and severity in this study. This is demonstrated by the non-medicated patients being significantly more recently diagnosed and less impaired (on both the Hoehn and Yahr and UPDRS scales) compared to the remaining patients. Furthermore, on the SRTT the non-medicated patients had similar overall RTs to control participants whereas medicated patients were significantly slower. In the second study, Wilkinson and Jahanshahi (2007) demonstrated that SRTT learning in PD patients (treated with dopaminergic medication) tested *off* dopaminergic medication was impaired compared with healthy age matched controls. Hence, this suggests that impaired learning on the SRTT can occur as a function of the disease and not simply as a side-effect of the medication. However, patients were only tested off-medication and comparisons of the magnitude of the effect with published studies are not really possible due to large inter-individual variability in the presentation of the disease and the considerable differences in task procedures across studies. As a consequence, the relationship between impairments in PD patients on and off dopamine medication remains undetermined.

The current study aims to address the effects of PD and levodopa medication on incidental motor sequence learning by assessing the same group of patients both on and off dopamine medication. As learning on the task is likely to be mediated by both the motor and associative fronto-striatal circuits, it was predicted that similar to the motor symptoms of PD, sequence learning would be greater on medication compared to the off state. Importantly, the study uses an SRTT in which the sequence is presented probabilistically, which is considered ideal for minimising explicit knowledge of the sequence and ensure the sequence learning remains implicit (Cleeremans and McClelland, 1991; Stadler, 1992).

2. Methods

2.1. Participants

Fifteen individuals (13 male; 14 right handed and one ambidextrous) meeting the Parkinson's Disease Society Brain Bank diagnostic criteria for idiopathic PD (Hughes et al., 1992) gave written informed consent to participate, which included the willingness to be assessed prior to taking medication following an overnight washout period (see below). They received reimbursement for travel expenses. Ethics approval for the study was obtained from the Joint Ethics Committee of the UCL Institute of Neurology & the National Hospital for Neurology and Neurosurgery. Informed consent was obtained from all participants. Participants were aged between 54 and 75 (M=67.1, SD=6.1), had been diagnosed for between 3 and 21 years (M=8.9, SD=5.3) and were classified by a neurologist as being in the mild to moderate stages of the disease, i.e. with Hoehn & Yahr (1967) scores between 1 and 3 (M=1.8, SD=.7). Severity of motor symptoms was assessed using the motor section of the Unified Parkinson's Disease Rating Scale (UPDRS, part III Fahn & Elton, 2005) with scores ranging between 12 and 62 (M=30.8, SD=13.8) off medication and between 5 and 39 (M=15.0, SD=8.8) on medication. Participants were non-demented with mean scores on the Mini-Mental State Examination (Folstein, Folstein, & McHugh, 1975) of 29.4 (SD=.7) and non-depressed with average scores of 7.43 (SD=3.7) on the Beck Depression Inventory (Beck, et al. 1961). Pre-morbid IQ was estimated using the National Adult Reading test (Nelson and O'Donnell, 1978). All participants were taking levodopa (Sinemet, Madopar or Staleva) and the mean levodopa equivalent daily dose (LEDD) was 694.89 (SD=462.44) milligrams (Tomlinson et al., 2010). Information about