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The effect of feedback on non-motor probabilistic classification learning in Parkinson's disease

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ABSTRACT

It has been proposed that procedural learning is mediated by the striatum and, it has been reported that patients with Parkinson's disease (PD) are impaired on the weather prediction task (WPT) which involves probabilistic classification learning with corrective feedback (FB). However, PD patients were not impaired on probabilistic classification learning when it was performed without corrective feedback, in a paired associate (PA) manner; suggesting that the striatum is involved in learning with feedback rather than procedural learning per se. In Experiment 1 we studied FB- and PA-based learning in PD patients and controls and, as an improvement on previous methods, used a more powerful repeated measures design and more equivalent test phases during FB and PA conditions (including altering the FB condition to remove time limits on responding). All participants (16 PD patients, H&Y I–III and 14 matched-controls) completed the WPT under both FB and PA conditions. In contrast to previous results, in Experiment 1 we did not find a selective impairment in the PD group on the FB version of the WPT relative to controls. In Experiment 2 we used a between groups design and studied learning with corrective FB in 11 PD patients (H&Y I.5–IV) and 13 matched controls on a more standard version of the WPT similar to that used in previous studies. With such a between groups design for comparison of FB and PA learning on the WPT in PD, we observed impaired learning in PD patients relative to controls across both the FB and PA versions of the WPT. Most importantly, in Experiment 2 we also failed to find a *selective* impairment on the FB version of the WPT coupled with normal learning on the PA version in PD patients relative to controls. Our results do not support the proposal that the striatum plays a specific role in probabilistic classification learning with feedback.

1. Introduction

It has been suggested that the striatum and its cortical projections support procedural (sometimes called implicit or unconscious) learning; whereas the cortico-limbic-diencephalic structures are considered the substrate for declarative (sometimes referred to as explicit or conscious) learning (Butters, Wolfe, Martone, Granholm, & Cermak, 1985; Cohen & Squire, 1980). The question of whether procedural learning can be genuinely unconscious in humans is controversial (e.g. Wilkinson & Shanks, 2004).

One task that has been employed to study procedural learning in humans is the 'weather prediction task' (WPT) initially devised by Knowlton, Squire, and Gluck (1994) and subsequently employed by several other investigators (e.g. Aron, Gluck, & Poldrack, 2006; Gluck, Shohamy, & Myers, 2002; Hopkins, Myers, Shohamy, Grossman, & Gluck, 2004; Knowlton, Mangels, & Squire, 1996; Knowlton, Squire, et al., 1996; Lagnado, Newell, Kahan, & Shanks, 2006; Poldrack, Prabhakaran, Seger, & Gabrieli, 1999; Poldrack et al., 2001; Sage et al., 2003). The WPT is a non-motor probabilistic classification task involving incremental learning over many trials which is considered to occur without any explicit knowledge. On each trial participants are presented with a particular arrangement of 1, 2, or 3 of 4 possible tarot cards each of which have different patterns on them (e.g. squares, diamonds, circles or triangles). Participants are required to use the cards presented on each trial to predict a binary outcome, i.e. whether the weather will be rainy or fine. Each of the four cards is independently associated with the two possible outcomes with a fixed probability and overall, each outcome occurs equally often. For example, the squares, diamonds, circles and triangles respectively predict the outcome

Abbreviations: BDI, Beck Depression Inventory; BG, basal ganglia; DA, dopamine; FB, feedback; HD, Huntington's disease; H&Y, Hoehn & Yahr; MMSE, Mini Mental State Examination; MTL, medial temporal lobe; NART, National Adult Reading Test; PA, paired associate; PD, Parkinson's disease; UPDRS, Unified Parkinson's Disease Rating Scale; WPT, weather prediction task.

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'fine' with a fixed probability of 0.2, 0.4, 0.6, and 0.8. Typically participants perform around 200 trials of the WPT with corrective feedback on each trial. The feedback consists of a 'thumbs up' or 'thumbs down' message following correct and incorrect responses respectively.

By learning the independent cue-outcome associations across trials, participants can improve their predictive accuracy on the WPT. For instance in one study, healthy controls were able to achieve 74.5% predictive accuracy across all trials (well above chance) despite the fact that they performed poorly on subsequent tests of explicit knowledge (Gluck et al., 2002). In particular, in post-experiment questionnaires the participants gave inaccurate estimates of cue-outcome probabilities and there was little correspondence between how they reported that they learned the task and their actual task performance. Such findings have led to the conclusion that participants have little or no awareness of the cue-outcome contingencies that they acquire during the WPT (Gluck et al., 2002) and this apparent dissociation between learning and awareness has been taken as evidence for the existence of two separate procedural and declarative learning systems.

1.1. Evidence from clinical, brain imaging and animal studies

Several studies demonstrate that patients with Parkinson's disease (PD) and Huntington's disease (HD) are impaired at WPT learning from the start of training (Knowlton, Mangels, et al., 1996; Knowlton, Squire, et al., 1996; Moody, Bookheimer, Vanek, & Knowlton, 2004; Witt, Nuhsman, & Deuschl, 2002a) and implicate the striatum in procedural probabilistic classification learning. Consistent with these findings, patients with moderate (but not mild) PD and one patient with a focal striatal lesion were impaired on an equivalent habit learning task (Hay, Moscovitch, & Levine, 2002) and a similar perceptual categorization task (Filoteo, Maddox, & Davis, 1998; Filoteo, Maddox, Salmon, & Song, 2005) whereas patients with frontal lesions (Knowlton, Mangels, et al., 1996) and those with cerebellar disease (Witt et al., 2002a) learned the WPT task normally; suggesting that deficits seen in PD and HD patients are not due to prefrontal dysfunction, but are related to striatal pathology in particular.

In addition, other evidence indicates that the pattern of performance on the WPT in PD patients is due to a deficit in early but not in later learning. For example, PD patients showed an improvement in performance in the later phase of the WPT (Witt et al., 2002a). Moreover, procedural learning on this task is considered to be independent of the medial temporal lobe structures because amnesic patients learn the WPT normally during the first 50 trials, although they are impaired relative to controls with further training on the task (Knowlton et al., 1994; Knowlton, Mangels, et al., 1996). Taken together, these findings suggest that early learning on the WPT can proceed independently of the MTL but not the BG and can be considered procedural; whereas the MTL but not the BG become important for later declarative learning of the task. However, in contrast to this view, Hopkins et al. (2004) observed that patients with focal damage to the hippocampus performed significantly worse than controls both early on in training and across the entire experiment, suggesting that the MTL is necessary for WPT learning across all trials. Imaging studies demonstrate that in healthy controls there is activation in fronto striatal circuits during WPT performance including the midbrain, striatal and frontal regions (Aron, Shohamy, Myers, Gluck, & Poldrack, 2004; Aron et al., 2006; Poldrack et al., 1999, 2001; Seger & Cinotta, 2005); confirming striatal involvement in the task.

There is considerable evidence for the role of the striatum in habit learning from animal lesion studies (Atallah, Lopez-Paniagua, Rudy, & O'Reilly, 2007; Bailey & Mair, 2006; Broadbent, Squire, & Clark, 2007; Faure, Haberland, Conde, & El Massioui, 2005; Featherstone & McDonald, 2005; Fernandez-Ruiz, Wang, Aigner, & Mishkin, 2001; Legault, Smith, & Beninger, 2006; McDonald & Hong, 2004; McDonald & White, 1993; Packard, Hirsh, & White, 1989; Packard & McGaugh, 1992; Yin, Knowlton, & Balleine, 2004) and from studies of single cell recordings in the striatum in rats (Jog, Kubota, Connolly, Hillegaart, & Graybiel, 1999). Furthermore, several studies of primates have identified dopamine producing cells in the striatum which fire in response to both reward associated stimuli and aversive stimuli (tonically active neurons, TANs) and alter their activity through learning (Aosaki, Graybiel, & Kimura, 1994; Aosaki, Tsubokawa, et al., 1994; Apicella, Legallet, & Trouche, 1997; Kimura, Yamada, & Matsumoto, 2003; Matsumoto, Minamimoto, Graybiel, & Kimura, 2001; Pasquereau et al., 2007; Ravel, Legallet, & Apicella, 2003; Raz, Feingold, Zelanskaya, Vaadia, & Bergman, 1996; Rolls, Thorpe, & Maddison, 1983; Schultz, 1997; Shimo & Hikosaka, 2001). Graybiel (1995) proposed that long-term habit learning is built up and expressed under conditions of modulatory control by striatal dopamine. In contrast, a recent study of probabilistic reasoning in monkeys, in which a variant of the WPT task was employed, identified neurons in the parietal cortex which fired in response to the process of addition and subtraction of probabilistic quantities during the task. This finding suggests that important computations that underlie decision-making during the task, may take place outside of the basal ganglia (Yang & Shadlen, 2007).

1.2. Probabilistic classification learning with and without corrective feedback

A further problem for the procedural/declarative memory distinction is that PD patients are impaired on the WPT but they show normal learning on another supposedly procedural task, artificial grammar learning (Reber & Squire, 1999; Smith, Siegert, McDowall, & Abernethy, 2001; Witt, Nuhsman, & Deuschl, 2002b). What characteristics of a skill learning task other than the presence or absence of awareness determine whether the striatum is necessary for performance? It has been suggested that it is the probabilistic nature of the WPT which is the critical feature (Knowlton, Mangels, et al., 1996). However, another aspect of the task which could be the critical feature in determining whether the striatum is involved in learning is the provision of corrective feedback during task performance.

Consistent with the view that the striatum modulates feedback-based learning Poldrack et al. (2001) studied brain activation in healthy participants during performance on the standard WPT (with feedback, FB) and a paired associate (PA) version of the task in which participants were initially required to perform training trials during which they observed cues and outcomes but they were not required to respond. They were then tested for their knowledge of WPT cue-outcome contingencies. It was found that the caudate nucleus was more active during the FB compared to the PA version of the WPT; whereas the MTL was less active in the FB condition and more active in the PA condition. From these findings Poldrack et al. (2001) suggested that the FB-based WPT relies more on procedural memory systems (with less MTL involvement) than the PA version of the task which is more declarative in nature. In a more recent imaging study of healthy participants Seger and Cinotta (2005) demonstrated that activation within the caudate and other striatal structures during the WPT with FB can be further subdivided into regions associated with actual learning (body and tail of the caudate and putamen) and with processing of feedback (head of caudate and ventral striatum).

In a further study of PD patients to investigate the importance of the striatum during WPT learning with FB, Shohamy, Myers, Grossman, et al. (2004) employed a different but equivalent ver-