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Stimulus timing by people with Parkinson's disease

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Abstract

Previous literature suggests that Parkinson's disease is marked by deficits in timed behaviour. However, the majority of studies of central timing mechanisms in patients with Parkinson's disease have used timing tasks with a motor component. Since the motor abnormalities are a defining feature of the condition, the status of timing in Parkinson's disease remains uncertain. Data are reported from patients with mild to moderate Parkinson's disease (both on and off medication) and age- and IQ-matched controls on a range of stimulus timing tasks without counting. Tasks used were temporal generalization, bisection, threshold determination, verbal estimation, and a memory for duration task. Performance of patients was generally "normal" on all tasks, but significant differences from performance of controls were found on the memory for duration task. Among the "normal" effects noted were arithmetic mean bisection, asymmetric temporal generalization gradients, and subjective shortening on the memory for duration task. The results suggest (a) that some previous reports of timing "deficits" in Parkinson's patients were possibly due to the use of tasks requiring a timed manual response and (b) small differences between patients and controls may be found on tasks where two stimuli are presented on each trial, whether patients are on medication or off it.

Keywords: Time perception; Temporal generalization; Bisection; Verbal estimation; Thresholds; Parkinson's disease

1. Introduction

The present article reports data on the timing of stimuli by people with mild to moderate Parkinson's disease (PD), compared with an age- and IQ-matched control population, and when the performance of patients is compared on and off their usual dopaminergic medication. Why should timing in PD patients be of any interest, and why stimulus timing in particular?

The first part of the question relates to work which appears to critically implicate dopaminergic processes, and areas of the basal ganglia, in the control of timed behaviour. A popular idea in time perception research is that the "raw material" for time judgements in animals and humans comes from a pacemaker-accumulator internal clock (Gibbon, Church, & Meck, 1984). Here, a pacemaker which produces "pulses" or "ticks" at some fast rate is gated via a switch to an accumulator which stores the pulses. So, for example, when a stimulus is to be timed (as in all the experiments reported in the present article), stimulus onset causes the switch to close, establishing a connection between the pacemaker and accumulator. After switch closure, pulses accumulate until the switch opens again, at stimulus offset, when the connection is cut. The number of pulses accumulated constitutes the basic representation of the duration of the stimulus that has been timed.

An early interest in dopaminergic processes in timing came from the claim that pacemaker speed (more commonly just referred to as "clock speed") was manipulable

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by changing dopamine levels. Maricq, Roberts, and Church (1981), and Meck (1983) tested rats on a bisection timing task, and both increased (Maricq et al., 1981; Meck, 1983) dopamine levels by administration of amphetamine, or both increased and decreased them (the latter effect being produced by haloperidol, by Meck, 1983). Animals behaved as if their rate of temporal accumulation ("clock speed") varied systematically with drug administration, with amphetamine "speeding up" the clock, and haloperidol "slowing it down" (see Meck, 1996, for detailed discussion). More recent research with animals using amphetamine and haloperidol has complicated these conclusions, suggesting that both drugs may affect attentional processing in animals as well as possibly having effects on clock speed (Buhusi, 2003; see also Cevik, 2003, for other recent work on effects of amphetamine on animal timing).

The manipulation of dopamine levels in humans has produced less clear effects on timing, but this may be because of procedural differences between the studies with animals and humans. An important feature of the animal experiments was the use of a "state-change" design, where the animals were trained in one drug condition (e.g. amphetamine or saline control), then tested in another one, which makes the potential effects of the drug easy to observe. A series of psychopharmacological studies of humans by Rammsayer (1989,1997) and Rammsayer and Vogel (1992) manipulated dopamine and noradrenaline levels, using between-group comparisons, and generally employed an adaptive timing procedure where people received two stimuli on each trial, and had to decide which was the longer one. Correct responses reduced the duration difference between the stimuli on the next trial and incorrect responses increased it, with the eventual result that the procedure converges on the smallest difference in duration (the threshold) that people can reliably detect. In general, compared with placebo administration, drugs which decrease dopamine levels (e.g. haloperidol, Rammsayer, 1993) increased thresholds (i.e. made the discrimination between the two stimulus durations poorer), whereas drugs which increase dopamine levels made the thresholds smaller, implying improved temporal discrimination.

However, some recent studies, which also implicate dopaminergic processes in timing, report results which may not be readily interpretable in terms of the idea that raising dopamine levels increases pacemaker speed. For example, Lustig and Meck (2005) found that patients who had received long-term administration of haloperidol were deficient in using the feedback given to them on a time interval reproduction task. In addition, a recent article by Rakitin, Scarmeas, Li, Malapani, and Stern (2006) reported that administering l-dopa to neurologically normal participants resulted in the time intervals produced lengthening compared with control conditions, the opposite effect to that predicted if increasing dopamine levels caused pacemaker speed to increase.

As is well known, PD is an illness resulting from the loss of dopamine- containing neurons in the substantia nigra pars compacta (SNPC), which project to the two parts of the striatum, the putamen and the caudate nucleus. Both striatal components also receive cortical input but neither project back to the cortex. The putamen receives afferent projections from the motor cortex, whilst the caudate nucleus appears to receive most of its afferent input from the dorsolateral prefrontal cortex (Feinberg & Farah, 1997). The dopamine depletion in PD patients is very severe: Parkinsonian symptoms only manifest themselves after around 80% dopamine loss, and post-mortem studies suggest that up to 98% of dopamine-containing neurons in some areas of the SNPC may be lost (Braak et al., 2003; Damier, Hirsch, Agid, & Graybiel, 1999), which presumably also results in a severe loss of dopaminergic projections from the SNPC to the striatum. One reason why this loss would suggest potential timing deficits in PD patients is that recent imaging studies have often found apparently specific time-related activation in the striatum. For example, Nenadic et al. (2003) used fMRI to study brain activation during the adaptive timing procedure described above, and contrasted this activation with that resulting from a very similar task, but this time involving pitch discrimination. Activation of the right putamen was restricted to the timing task only, suggesting that it played a central role in temporal processing (see also Ferrandez et al., 2003; Harrington et al., 2004, for two other scanning studies suggesting basal ganglia involvement in timing).

Another reason for suspecting that timing deficits would be present in PD patients comes from theoretical models attempting to link timing processes to brain mechanisms. For example, Meck (1996, Fig. 3, p. 231) discussed mapping of the different parts of a psychological timing system onto brain structures, and identified the SNPC as having a time-keeping role, responsible for providing pacemaker input to striatal structures, which integrate this input, with prefrontal areas being essentially responsible for decision processes. This position has been supplanted by a new model, that of Matell and Meck (2004, see also Buhusi & Meck, 2005) but, obviously, any suggestion that the SNPC is the pacemaker of the internal clock implies severe timing deficits in PD patients, in any situation in which this clock is used. In addition, other commentators have suggested that dopaminergic processes in the striatum may play a role in the attentional control of timing (Buhusi, 2003; Meck & Benson, 2002), in decision processes (e.g. Ivry & Spencer, 2004, p. 229) presumably by virtue of connections with the prefrontal cortex, or in the ways that intervals to be timed are learned or remembered (Lustig & Meck, 2005; Malapani et al., 1998). However, whatever the exact role posited for striatal dopaminergic systems, almost all attempts to relate timing behaviour to brain processes posit some critical function for striatal dopamine pathways, so in general timing deficits in PD patients, in whom such pathways are severely compromised, are predicted, whether or not motor tasks are used.

What evidence is there that PD patients actually have timing deficits? The answer is complicated by that fact that