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Moore, James W., Schneider, Susanne A, Schwingenschuh, Petra, Moretto, Giovanna, Bhatia, Kailash P and Haggard, Patrick

Dopaminergic medication boosts action-effect binding in Parkinson's disease

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Running head: Action-effect binding in Parkinson's Disease

James W. Moore[1,2], Susanne A. Schneider[3,4], Petra Schwingenschuh[3,5], Giovanna Moretto [1,6],

Kailash P. Bhatia[3], Patrick Haggard[1]

1. Institute of Cognitive Neuroscience, University College London, UK

2. Brain Mapping Unit, Department of Psychiatry, Downing Site, University of Cambridge,

UK

3. Sobell Department of Motor Neuroscience and Movement Disorders, Institute of

Neurology, Queen Square, University College London, UK

4. Schilling Section of Clinical and Molecular Neurogenetics at the Department of

Neurology, University of Lübeck, Lübeck, Germany

5. Department of Neurology, Medical University Graz, Austria

6. Department of Psychology, University of Bologna, Italy

Corresponding author:

Dr. James Moore

Brain Mapping Unit

Department of Psychiatry

Downing Site

University of Cambridge

Cambridge, CB2 3EB

Email: jm697@cam.ac.uk

Abstract:

Parkinson's disease (PD) is a neurodegenerative disorder affecting voluntary motor control. However, little is known about the *experience* of voluntary action in PD patients. A key component of action experience is the feeling of controlling one's own actions, and through them, external events. In healthy individuals this Sense of Agency (SoA) is associated with a subjective compression of time, such that actions and their effects are perceived as bound together across time. This action-effect binding provides an indirect measure of SoA. Nine PD patients and age-matched controls judged the time of voluntary actions and of an auditory effect (a tone) of the action. The pattern of results resembled previous studies, with the perceived time of actions showing a shift towards the subsequent tone, relative to a baseline condition involving actions without tones. Similarly, the perceived times of tones showed a shift towards the preceding action that caused the tone, relative to a baseline condition involving tones only. The patients were tested both *on* and *off* dopaminergic medication. PD patients *off* medication showed no significant change in action-effect binding relative to controls. Conversely, PD patients *on* medication showed a significant increase in action-effect binding relative to their own performance *off* medication. Increased availability of dopamine strengthened the experience of association between actions and external events, enhancing the sense of agency. These results shed light on the contribution of dopamine to the experience of instrumental action, and also on impulse control disorders and psychosis in medicated PD patients.

Introduction

Parkinson's disease (PD) is a degenerative disorder characterised by motor impairments, including bradykinesia and difficulty initiating voluntary movement. The core pathology is the loss of dopamine in the nigrostriatal pathway (Agid & Blin, 1987), resulting in reduced drive in the cortical-basal ganglia-cortical loops (Alexander, DeLong, & Strick, 1986). Accordingly, dopaminergic drugs form the standard treatment.

Whilst dopaminergic medication alleviates motor impairments in PD, its effect on cognitive function is more variable; improving certain cognitive functions, but worsening others (Gotham, Brown, & Marsden, 1986). The role of dopamine in cognitive function remains a topic of intense interest (e.g. Pillon, Czernecki, & Dubois, 2003; Dagher & Robbins, 2009), but is still poorly understood. The '*overdose theory*' of dopaminergic medication (Gotham et al., 1986; Gotham, Brown, & Marsden, 1988; Swainson et al., 2000; Cools, Barker, Sahakian, & Robbins, 2001; Cools, 2006) offers an explanation for variable of dopamine effects on cognition in PD. According to this theory, earlier stages of PD involve severe DA depletion in the dorsal striatum. Therefore, cognitive functions supported by DA activity in this region are improved by dopaminergic medication. In contrast, there is little DA depletion in the ventral striatum at this stage. Therefore cognitive functions supported by DA activity in this region are worsened by dopaminergic medication as it induces an excess, or *overdose*, of DA.

Here we focus on the effects of PD and DA on a set of key functions that involve both cognitive and motor processes, namely the sense of control in operant actions. In the animal literature the same functions have been studied under the concept of instrumental learning. Instrumental learning is one such function thought to be supported by ventral DA systems (Kelley, Smith-Roe, & Holahan, 1997; Smith-Roe & Kelley, 2000; Hernandez, Sadeghian, &

Kelley, 2002; O'Doherty et al., 2004). Dopaminergic neurons play a crucial role in prediction

of rewards (Schultz, Dayan, & Montague, 1997; Hollerman & Schultz, 1998; Tobler,

Dickinson, & Schultz, 2003), while dopaminergic areas such as the striatum play an

important role in reinforcement learning (e.g. O'Doherty et al., 2004). Consistent with the

overdose theory of dopaminergic medication in PD, performance on reversal learning tasks,

which depend on learning of instrumental contingencies, is preserved *off* medication but

impaired *on* medication (Swainson et al., 2000; Cools et al., 2001). Moreover, dopaminergic

medication appears to exaggerate PD patients' sensitivity to action outcomes and rewards

(Frank, Seeberger, & O'Reilly, 2004). Such results suggest that the formation of action-effect

associations in PD might be exaggerated when on dopaminergic medication.

In humans at least, actions that produce or predict rewards are associated with a specific

experience of voluntary motor control, termed 'Sense of Agency' (SoA; Frith, 2005). This

refers to the experience of being in control over one's own actions, and, through them, over

events in the outside world, and has been shown to reflect knowledge about the causal

relation between actions and outcomes (Moore & Haggard, 2008; Moore, Lagnado, Deal, &

Haggard, 2009). Altered SoA features in several psychiatric (e.g. schizophrenia; Frith, 1992)

and neurological (e.g. alien hand syndrome; Doody & Jankovic, 1992) disorders, suggesting

that it reflects specific brain processes. One might also expect PD patients to experience

disturbances in SoA, given their difficulty in initiating and controlling voluntary movement.

Indeed, striatal dopamine depletion disrupts the drive from the basal ganglia to frontal motor

areas such as the supplementary and pre-supplementary motor areas (Cunnington et al., 2001;

MacDonald & Halliday, 2002; Grafton, 2004; Playford et al., 1992; Nachev, Kennard, &

Husain, 2008) which play a role in generating SoA (Haggard & Whitford, 2004). Although

PD clearly involves deficits in higher order aspects of motor cognition (Falkenstein et al.,

2001; Rowe et al., 2002; Willemssen, Müller, Schwarz, Falkenstein, & Beste, 2009), no studies, to our knowledge, have specifically investigated SoA during PD, nor the relation between SoA and dopamine levels.

Classically, SoA has been tested in action-recognition tasks requiring explicit judgements of agency. The participant is given visual feedback of a voluntary action that is spatially (Daprati et al., 1997) or temporally (Farrer et al., 2008) distorted, and asked if their action is responsible for the viewed feedback or not. However, these explicit judgements of agency over feedback require that some other possible cause of the feedback exists ("the computer", or another person). They may therefore fail to capture the normal background feeling of being in control of one's everyday actions. Moreover, important functional dissociations between feelings of agency (such as binding) and judgements of agency have been described. (Synofzik, Vosgerau, & Newen, 2008).

 A reliable, implicit and quantitative correlate of SoA is the attraction between the perceived time of actions and of their effects in the "intentional binding" paradigm (Haggard et al., 2002; see Figure 1). In this paradigm, participants are asked to judge the time of actions (e.g. key presses) and effects (e.g. tones), using a clock hand rotating around a clock face. Typically, participants perceive their voluntary actions as occurring later when they are followed by an external effect (e.g., a tone), compared to actions not followed by an effect. Conversely, participants perceive external effects as occurring earlier when preceded by a voluntary action, compared to external effects not preceded by a voluntary action. Prolonged action-effect intervals, random intervals (Haggard et al., 2002), or effects occurring in the absence of actions, all weaken binding, suggesting that it follows the traditional pattern of associative, causal learning. Furthermore, involuntary movements produced a reversal of the

binding effect (Haggard et al., 2002) with the movements perceived as earlier and the effects perceived as later than those same events in isolation. In this way, voluntary actions and effects are *bound* in conscious experience, whilst involuntary movements and effects are *separated* in conscious experience. Furthermore, no binding occurs between pairs of sensory stimuli (Haggard, Aschersleben, Prinz, & Gehrke, 2002) or between involuntary movements and subsequent effects (Haggard, Clark, & Kalogeras, 2002) or for actions that others are observed to make (Engbert, Wohlschläger, & Haggard, 2008). Therefore, the subjective shortening of the action-effect interval is a useful quantitative measure for the sense of agency.

Figure 1 about here

We have investigated the role of dopamine in SoA by measuring intentional binding in PD. If dopamine boosts action-effect associations, then we might expect the intentional binding effect to be *greater* in PD patients *on* than *off* medication. We also compared measures from PD patients with age-matched healthy controls.

Methods

The study was approved by UCLH Ethical Committee. Patients and volunteers participated on the basis of written informed consent, and in accordance with the Declaration of Helsinki.

Participants

Nine patients with idiopathic PD were recruited from the PD clinics at the National Hospital for Neurology and Neurosurgery, London (see Table 1 for patient details). Inclusion criteria were: idiopathic PD according to UK Parkinson's Disease Society Brain Bank clinical

diagnostic criteria; age 55-80 years; on dopaminergic medication; no current depressive illness; no known dementia based on prior cognitive assessment; Hoehn and Yahr stages 2 or 3 at last clinic visit. Exclusion criteria included presence of features suggestive of a diagnosis other than idiopathic PD (like atypical Parkinsonism), presence of an impulse control disorder (such as medication overuse, punding etc.), and adverse reactions to withdrawal or delay of dopaminergic medication.

Patients completed two testing sessions (*off* and *on*) on the same day. Patients were kept off Levodopa (L-dopa) overnight and also withheld from morning doses of all antiparkinsonian medication on the day of the experiment, in order to induce an *off* state. After completion of the task patients immediately took their medication and returned after 1 hour to repeat the task in the *on* state. Just as *on* patients may not be maximally *on*, so the *off* state is not as great as could have been achieved by prolonged withdrawal. However, the withdrawal period was sufficient to induce a clinically significant change in symptoms (see Table 1). Participants were asked to stop short-acting dopaminergic medications (standard preparations of L-dopa and short-acting dopamine agonists) at least 12 h before the experiment, and long acting preparations (like controlled release preparations of L-dopa) at least 24 h before the experiment. Several patients were taking dopamine agonists alone or in combination with L-dopa (see Table 1).

9 age-matched healthy controls were recruited from a database of participants from the same institution (see Table 1). None had a current neurological or psychiatric history. Control patients were tested on the same task in a single session. Control subjects were not treated with L-dopa.

Table 1 about here

Experimental design

PD patients and controls made judgements about the perceived time of voluntary actions and of tones that followed voluntary actions. Their mean judgements were used to calculate a measure of "intentional binding", an implicit measure of agency. The procedure was based on that developed by Haggard, Clark, and Kalogeras (2002). The trial structure for the experimental *agency* conditions is shown in Figure 2. In these conditions, participants were instructed to press a key with their right index finger at a time of their choosing. A response key with an area of 5cm^2 was used to ensure patients had no trouble pressing the key. This key press then caused a brief tone (duration 75 ms) to occur 250ms later. At the same time, a clock hand was rotating about a clock face at a rate of one revolution every 2560ms (Libet, Gleason, Wright, & Pearl, 1983). The clock hand then continued rotating for a random time, and then stopped. The participant was prompted to report verbally the position of the clock hand at which they pressed the key, or the time at which they heard the tone onset. Action and tone judgements were blocked, so that in each experimental condition the participant always judged just actions, or just tones. Each condition consisted of 20 trials.

Figure 2 about here

There were two additional baseline conditions, each 20 trials long. In the *baseline action* condition participants made a key press at a time of their choosing. This key press did not cause a tone, and participants simply judged the time of their key press. In the *baseline tone* condition, participants were instructed not to press the key and instead wait for a tone to be delivered at a random latency generated by the computer. Participants judged the time of tone

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onset. Agency and baseline blocks were intermixed, and the order was randomised anew for each session.

PD patients were tested both *on* and *off* medication. At the end of each patient testing session (i.e. after *off* and *on* medication sessions) a qualified neurologist assessed motor disability using the Unified Parkinson's Disease Rating Scale motor examination (UPDRS-III; Fahn & Elton, 1987).

Data analysis

Because individuals differ widely in their biases on cross-modal time-estimation tasks, time estimates in a single condition are not particularly informative. However, these biases may be removed by analysing differences between estimates of the same physical event in different conditions. Our interest lay in how action-effect associations might modulate the experience of action and tone. Therefore, we subtracted the perceived time of actions in the baseline action only condition of each session from the perceived time of actions in the agency (action +tone) condition of the same session. Similarly, we subtracted the perceived time of baseline tones in each session from the perceived time of tones caused by actions in the same session.

This procedure gives a measure of the shift in awareness, or binding, for actions and for tones in the agency condition. By convention a positive shift indicates delayed awareness, while a negative shift indicates anticipatory awareness. In this way, positive shifts for actions and negative shifts for tones indicate a perceptual attraction or binding between action and effect. Therefore, we computed an overall binding measure for each participant (mean action shifts minus mean tone shifts), and analysed the overall binding measure statistically. This

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combined measure corresponds to the perceived linkage between action and effect, and provides an implicit, quantitative measure of SoA (Haggard et al., 2002; Haggard & Clark, 2003; Engbert et al., 2008). We compared overall binding scores in controls and PD patients *off* medication to test whether PD itself is associated with changes in SoA. We also compared overall binding scores in PD patients *off* medication and those same patients *on* medication.

Results

UPDRS scores were significantly higher *off* medication (mean = 27.00) than *on* (mean = 16.11), t(8) = 8.34, p = .00003.

Figure 3 about here

The shifts in perceived time of events in agency conditions relative to the appropriate baseline are shown in Table 2 and Figure 3 for each group (control, PD *off*, and PD *on*). Since the direction of shifts in action and tone awareness relative to baseline follows directly from the concept of binding, and from previous studies (Haggard et al., 2002), we used 1-tailed t-tests to confirm the binding effects in each group/session. These are also shown in Table 2. As can be seen from the table, the intentional binding effect is present in all three groups (control, PD *off*, and PD *on*). Specifically, actions were perceived later when they were followed by a tone, than in a baseline condition without a tone (although this effect only reaches the borderline of significance for control participants, p = 0.054). Tones produced by voluntary actions were perceived earlier than baseline tones. Tone binding was both numerically larger and statistically more reliable than action binding, as in previous studies (Haggard et al., 2002). Finally, the composite binding measure, reflecting both action and

tone binding, was also statistically significant, again on 1-tailed testing (see final column Table 2). The composite binding data implies that participants perceived the action-effect interval as significantly shorter than it really was, although the interval duration was not judged directly.

We then proceeded to compare the degree of binding between the various groups in our study. PD patients *on* medication showed greatest binding for both actions and tones, followed by PD patients *off*¸ followed by controls. Two-tailed t-tests were used to investigate differences in binding between groups/sessions. These showed that action binding did not differ between PD *off* and controls, t(16), p = .500 (2-tailed), nor between PD *off* and *on*, t(8) = 1.08, p = .314 (2-tailed). Similarly, tone binding did not differ between PD *off* and controls, t(16) = .512, p = .615 (2-tailed), nor between *PD off* and *on* medication, t(8) = 1.34, p = .216 (2-tailed). However, our principal interest focussed on the *overall* level of binding, as a reflection of the total linkage between action and effect, rather than on either actions or effects individually.

Table 2 about here

Overall binding in PD patients *off* medication (mean = 122ms) was not significantly different from overall binding in healthy controls (mean = 92ms), t(16) = .800, p = .435 (2-tailed). This suggests that PD itself is not associated with abnormal action awareness or SoA. However, as predicted, overall binding in PD patients *on* medication (mean = 186ms) was significantly greater than in the same PD patients *off* medication (mean = 122ms), t(8) = 2.71, p = .027 (2-tailed). This suggests that dopaminergic medication enhanced the experience of agency in PD patients.

Table 2 suggests differences in baseline judgements between the groups. Baseline action judgements showed no significant differences between controls and PD *off*, t(16) = 1.350, p = .196 (2-tailed)*,* or controls and PD *on*, t(16) = .425, p = .504 (2-tailed). However, there was a near significant difference between baseline action judgements in PD o*ff* and PD *on*, t(8) = 2.126, p = .066 (2-tailed). For baseline tone judgements, none of the comparisons were significant (PD *on* vs. PD *off:* t(8) = 1.519, p = .167; PD *on* vs. Control: t(16) = 1.433, p = .171; PD *off* vs. Control: t(16) = .456, p = .504 – all 2-tailed)

Consistency of time estimation

In a further analysis we compared the standard deviations *across repeated trials* of time estimates in each condition. These provide a general measure of perceptual timing ability: a high standard deviation across repeated trials indicates inconsistent timing performance. This could reflect poor temporal information about the judged event, difficulty in using the clock for timing judgements, erratic allocation of attention either to the action or to the clock, or general confusion. The data are presented in Table 3. Standard deviations across trials were comparable with data reported previously (Haggard et al., 2002). For baseline judgements, there were no significant differences in standard deviations between controls and PD *off* (baseline action: t(16) = 1.40, p = .182; baseline tone: t(16) = .362, p = .722) and between PD *off* and PD *on* (baseline action: t(8) = .687, p = .512; baseline tone: t(8) = 1.05, p = .327). For agency conditions, there were no significant changes in standard deviations between controls and PD *off* (judgements of action for action+tone condition: t(16) = .263, p = .796; judgements of tone in action+tone condition: t(16) = 1.05, p = .308) and between PD *off* and PD *on* (judgements of action for action+tone condition: t(8) = .610, p = .559; judgements of tone in action+tone condition: t(8) = .702, p = .503). The absence of any significant

differences in this measure of timing precision suggests that time perception ability overall was not affected either by the disease state, or by taking of dopaminergic medication. Therefore, the effects on intentional binding levels shown in Table 2 are unlikely to be a result of general differences in timing ability, such as poor attention to time.

Time-dependent effects

The design included a confound between time of testing and medication state. Therefore, the increase in binding may be due to general learning effects, such as learning, familiarity or fatigue, rather than drug treatment. We could not independently estimate time-dependent effects over the experiment as a whole. However, we were able to investigate them at a finer temporal scale by comparing the first and second half of each *block*, using the same methods as before. Data from the first half of each action block and the first half of each effect block were used to estimate composite binding on *early* trials, and data from the second half of each action block and the second half of each effect block were used to estimate composite binding on *late* trials The data are presented in Figure 4.

Figure 4 about here

We found that composite binding for the patients was somewhat stronger for the *late* trials than for *early* trials, but this effect was not quite statistically significant, $F(1,8) = 4.19$, $p = .075$. More importantly, there was no evidence of any interaction between the *early-late* and *off-on* factors, $F(1,8) = .001$, $p = .977$.

Discussion

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In this study we investigated the influence of Parkinson's disease and dopaminergic medication on the temporal experience of voluntary instrumental actions, as an implicit measure of Sense of Agency (SoA). Both PD patients and healthy volunteers showed the "intentional binding" effect reported previously: actions were perceived as shifted towards their subsequent effects, while effects were perceived as shifted towards the preceding action which caused them. Although significant binding was found in each group, statistical analyses showed that the extent of this shift was strongest in PD patients *on* medication, and weakest in controls. These shifts serve as an index of SoA. Dopaminergic medication boosted action-effect binding in PD patients relative to action-effect binding in the same patients *off* medication. Furthermore, action-effect binding in PD patients *off* medication was not significantly different from controls. These results suggest that the disease state itself is not associated with changes in SoA, at least in the earlier stages. Rather, changes in SoA are caused by dopaminergic medication used to treat the disease. Interestingly, we found a significant effect of dopminergic medication on overall binding, but not on the binding of the action or tone tested individually. This suggests that dopamine indeed influences the experienced *linkage* between action and effect, rather than the experience of the action or effect alone. The pattern of results we obtained is consistent with the group as a whole showing modified experience of action-effect linkage, but with some individuals expressing this in their experience of the action, and others in their experience of the tone. To our knowledge, this is the first study to directly investigate SoA in PD and the associated impact of dopaminergic medication.

Alternative interpretations:

Confounds due to time of testing

Our study design includes a confound between time of testing and medication state. As in some previous studies (e.g. Corcos, Chen, Quinn, McAuley, & Rothwell, 1996; Brown, Corcos, & Rothwell, 1997), patients were always tested *off* medication first. Therefore, any difference between the first *off* phase and the second *on* phase of the experiment could reflect either the effect of medication, or some other time-dependent effect, such as practice effects over the course of the experiment. The analysis of binding in the first and second half of each block, however, suggests that our results are not simply due to practice, learning or other time-dependent effects. The modest changes in binding over the course of a block were equally present in the *on* and *off* conditions. This suggests that any learning/time-order effects are unlikely to explain the difference *between* the medication conditions

General timing deficits

Could it be that the exaggerated binding in PD patients *on* medication simply reflects general changes in time perception, rather than specific changes in agency experience? Our analyses of the standard deviation of time estimates across trials suggests not: timing judgements were equally consistent for PD patients *on* and *off* medication, and for patients and controls.

Previous studies have suggested slowing of an internal pacemaker in PD (e.g Artieda, Pastor, Lacruz, & Obeso, 1992; Pastor, Artieda, Jahanshahi, & Obeso, 1992), although the data are somewhat inconsistent (see Ivry & Spencer, 2004, for a review). More recent work by Wearden and colleagues (Wearden et al., 2008; Wearden et al., 2009) shows that central timing mechanisms in PD are generally spared, and that dopaminergic medication used to treat PD does not significantly alter time perception on a range of tasks. This point is important, since a recent study showed that intentional binding was associated with a transient drop in temporal discrimination performance, consistent with temporary slowing of

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an internal clock in the interval between actions and effects (Wenke & Haggard, 2009). However, changes in speed of an internal clock seem unlikely to explain our effect: they would require dopaminergic medication to slow down an internal clock, so that *fewer* clock pulses occur between action and effect. As a result, the interval between action and effect would seem shorter, producing the effect seen in our composite binding data. However, current opinion suggests that dopamine is likely to *speed up* clock function, rather than slow it down (Meck, 1996; Meck & Benson, 2002; Buhusi & Meck, 2005; Cheng, Ali, & Meck, 2007).

Finally, changes in clock speed should alter the precision of time estimation, as well as any bias (Wenke and Haggard, 2009). However, our analysis of standard deviations across trials showed no significant changes in precision of time estimation. Therefore, we think it unlikely that the observed changes in mean action-effect binding in our data merely reflect changes in a general purpose internal timing apparatus, such as that posited by scalar timing theory. Our effects seem to reflect changes in the experience of action-effect linkage, rather than deficits in basic time perception.

Cross-modal synchronisation

Cross-modal synhcronisation judgements differ widely across individuals. Therefore, our study, like several others, is based on statistical analysis of the *difference* between experimental and baseline estimates (e.g. Haggard et al 2002). Baseline judgements vary widely both across people and across groups (Haggard, Martin, Taylor-Clarke, Jeannerod, & Franck, 2003), and may reflect individual strategies in the attention paid to the clock. In order to control for such individual differences, each participant's judgement in the baseline condition is subtracted from their judgement in the agency conditions. In general, a single

time-estimate is difficult to interpret, whereas a difference between estimates of the same physical event in different experimental conditions is much more interpretable (Libet et al., 1983; Haggard, 2008).

Inspection of Table 2 suggests that there were differences between groups and sessions in terms of baseline judgements. Any changes in baseline are important because they contribute to our measure of binding effects: a change in our binding measure between conditions could arise from changes in action-effect linkage, or from changes in the basic perception of actions or tones. In fact, differences in baseline between groups and differences between *on* and *off* states were never statistically significant, and their complex overall pattern did not suggest any general change in perception or time estimation (Meck & Benson, 2002). The largest change in baseline judgements was an earlier action baseline for PD *on* than *off*. However, since this change was not found either for baseline tones, or for actions followed by tones, explanations based on drug effects on time estimation seem ad hoc. Moreover, we do not think that baseline estimates should be interpreted in isolation. The difference between baseline and agency conditions in our design remains the most appropriate way to measure modulation of experience of agency. Interestingly, the *on-off* difference in composite binding in our data arose from both action shifts and tone shifts that were numerically almost equal in size, though opposite in direction. While the effects of medication on action binding involved a change in baseline action judgements, the effects on tone binding involved almost no change in baselines at all. Therefore, we consider that dopaminergic modulation of binding cannot be fully or parsimoniously explained by changes in baseline time estimates.

Finally, although our sample size is consistent with previous published work on movement disorders (e.g. Bloxham, Mindel, & Frith, 1984; Desmurget et al., 2004), the relatively small

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size of the study means that a degree of caution is required, particularly when interpreting null results. In particular, while we found no *significant* difference between PD patients *off* medication and healthy controls, a larger sample would be required to confidently assert that PD does not alter the temporal experience of agency.

Models of dopamine effects on cognition

Although no previous research of which we are aware has directly investigated SoA in PD, our results are consistent with the reported effects of medication on cognitive function in PD. According to the overdose theory, the differential effects of dopaminergic medication on cognitive function are due to the pattern of dopamine depletion in the course of PD progression (Gotham et al., 1986; Gotham et al., 1988; Swainson et al., 2000; Cools et al., 2001; Cools, 2006). In the earlier stages of the disease, dopamine in the dorsal striatum is more severely depleted than in the ventral striatum. Therefore, cognitive functions supported by the dorsal striatum are improved by dopaminergic medication, whilst cognitive functions supported by the ventral striatum are worsened by dopaminergic medication (there is an *overdose*).

Our data lend indirect support to the overdose theory, and particularly to the suggestion that cognitive functions of the ventral striatum are adversely affected by DA excess. The ventral striatum plays a key role in instrumental learning and performance (Kelley et al., 1997; Smith-Roe & Kelley, 2000; Hernandez et al., 2002; O'Doherty et al., 2004). We previously showed that very recent reinforcement of action-effect association contributes to the binding effect (Moore & Haggard, 2008). Specifically, we found that the perceived time of an action was more strongly shifted towards an effect when the participants had just experienced an action-tone pair on the immediately preceding trial, compared to when they had just

experienced the action without the tone. Interpreted in this way, boosting of action-effect

binding in PD patients *on* medication may be due to an overdosing of the ventral striatal

dopamine system. This may induce exaggerated action-effect binding by strengthening

action-effect associations.

Several dopaminergic mechanisms may contribute to the experience of action-effect

associations. On one view, phasic striatal dopamine activity encodes "prediction error", i.e.,

degree of mismatch between expected and actual outcomes of actions (typically *rewarding*

action outcomes; Schultz et al., 1997). Prediction error is also a key parameter in theories of

causal learning (Dickinson, 1981). A recent study has shown that dopaminergic medication in

PD patients indeed modulates striatal reward prediction error signals, and boosts formation of

associations between actions and positive outcomes (Pessiglione, Seymour, Flandin, Dolan,

& Frith, 2006). Although the consequences of actions in our paradigm were not rewarding in

themselves, we suggest exaggerated action-effect binding *on* medication may be similarly

caused by modulation of phasic dopamine prediction error signals.

Role of dopamine in regulation of agency

Our study also clarifies the neural basis of SoA, by showing a clear link to dopamine.

Several previous studies have investigated changes in SoA in schizophrenia. The positive

symptoms of schizophrenia have been attributed to excessive dopamine (Laruelle et al., 1995;

Abi-Dargham et al., 1998). Interestingly, schizophrenic patients also show stronger action-

effect binding than controls (Haggard et al., 2003). The similarity between effects of putative

dysregulation of dopamine systems in schizophrenia and of dopaminergic medication in PD

is intriguing given the fact that dopaminergic medication is known to induce psychotic-like

symptoms in up to 30% of PD patients (Cummings, 1991). The altered experiences of action

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that we have described could be a relevant marker for formation of drug-induced psychosis in some patients.

Impulse control disorders are thought to occur in about 14% of PD patients on dopamine agonist treatment (Voon et al., 2006). At the neural level, these disorders are thought to be linked to excessive stimulation of dopamine receptors in the limbic striatum (Dagher & Robbins, 2009). This excessive stimulation may contribute to the development of such disorders through the promotion of instrumental action-effect associations, via increased learning (Schultz et al., 1997; Schultz, 2006) and incentive (Berridge & Robinson, 1998) signalling. We suggest that an excessive sense of agency may contribute to impulse control disorders. If one perceives one's actions as highly effective, or as highly likely to produce rewards, one might make actions that would otherwise be inhibited. For example, pathological gambling behaviour (Voon et al., 2006) may arise because the patient has an abnormally heightened perception of the association between betting and winning. The excessive action-effect binding in patients *on* medication in our study supports this line of reasoning. None of the patients in our sample had been diagnosed with impulse control disorders. However, we speculate that difficulties in impulse control should correlate with an excessive SoA.

To conclude, this is the first direct investigation of the subjective experience of voluntary action in PD of which we are aware. We used the perceived temporal association between actions and effects as an implicit measure of the sense of agency. Our results showed no difference between healthy volunteer participants and PD patients *off* medication. However, dopaminergic medication significantly strengthened the temporal binding between actions and effects, which we interpret as a heightened sense of agency. Prediction-error learning is

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one possible mechanism underlying this boosting of action-effect binding. Our study sheds new light on the neurobiological basis of SoA, which may be relevant to other movement disorders and to psychiatric conditions. Moreover, it offers new avenues for research into the cognitive, motor and experiential effects of dopamine.

References

Abi-Dargham, A., Gil, R., Krystal, J., Baldwin, R. M., Seibyl, J. P., Bowers, M., et al. (1998). Increased striatal dopamine transmission in schizophrenia: confirmation in a second cohort. *The American Journal of Psychiatry*, *155*(6), 761-767.

Agid, Y., & Blin, J. (1987). Nerve cell death in degenerative diseases of the central nervous system: clinical aspects. *Ciba Foundation Symposium*, *126*, 3-29.

Alexander, G. E., DeLong, M. R., & Strick, P. L. (1986). Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annual Review of Neuroscience*, *9*, 357-381. doi: 10.1146/annurev.ne.09.030186.002041.

Berridge, K. C., & Robinson, T. E. (1998). What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? *Brain Research. Brain Research Reviews*, *28*(3), 309-369.

Bloxham, C. A., Mindel, T. A., & Frith, C. D. (1984). Initiation and execution of predictable and unpredictable movements in Parkinson's disease. *Brain: A Journal of Neurology*, *107 (Pt 2)*, 371-384.

Brown, P., Corcos, D. M., & Rothwell, J. C. (1997). Does parkinsonian action tremor contribute to muscle weakness in Parkinson's disease? *Brain: A Journal of Neurology*, *120 (Pt 3)*, 401-408.

Buhusi, C. V., & Meck, W. H. (2005). What makes us tick? Functional and neural mechanisms of interval timing. *Nat Rev Neurosci*, *6*(10), 755-765. doi: 10.1038/nrn1764.

Cheng, R., Ali, Y. M., & Meck, W. H. (2007). Ketamine "unlocks" the reduced clock-speed effects of cocaine following extended training: Evidence for dopamine-glutamate interactions in timing and time perception. *Neurobiology of Learning and Memory*, *88*(2), 149-159. doi: 10.1016/j.nlm.2007.04.005.

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Cools, R. (2006). Dopaminergic modulation of cognitive function-implications for L-DOPA treatment in Parkinson's disease. *Neuroscience and Biobehavioral Reviews*, *30*(1), 1-23. doi: 10.1016/j.neubiorev.2005.03.024.

Cools, R., Barker, R. A., Sahakian, B. J., & Robbins, T. W. (2001). Enhanced or Impaired Cognitive Function in Parkinson's Disease as a Function of Dopaminergic Medication and Task Demands. *Cereb. Cortex*, *11*(12), 1136-1143. doi: 10.1093/cercor/11.12.1136.

Corcos, D. M., Chen, C. M., Quinn, N. P., McAuley, J., & Rothwell, J. C. (1996). Strength in Parkinson's disease: relationship to rate of force generation and clinical status. *Annals of Neurology*, *39*(1), 79-88. doi: 10.1002/ana.410390112.

Cummings, J. L. (1991). Behavioral complications of drug treatment of Parkinson's disease. *Journal of the American Geriatrics Society*, *39*(7), 708-716.

Cunnington, R., Egan, G. F., O'Sullivan, J. D., Hughes, A. J., Bradshaw, J. L., & Colebatch, J. G. (2001). Motor imagery in Parkinson's disease: a PET study. *Movement Disorders: Official Journal of the Movement Disorder Society*, *16*(5), 849-857.

Dagher, A., & Robbins, T. W. (2009). Personality, addiction, dopamine: insights from Parkinson's disease. *Neuron*, *61*(4), 502-510. doi: 10.1016/j.neuron.2009.01.031.

Dagher, A., & Robbins, T. W. (2009). Personality, Addiction, Dopamine: Insights from Parkinson's Disease. *Neuron*, *61*(4), 502-510. doi: 10.1016/j.neuron.2009.01.031.

Daprati, E., Franck, N., Georgieff, N., Proust, J., Pacherie, E., Dalery, J., et al. (1997). Looking for the agent: an investigation into consciousness of action and self-consciousness in schizophrenic patients. *Cognition*, *65*(1), 71-86.

Desmurget, M., Gaveau, V., Vindras, P., Turner, R. S., Broussolle, E., & Thobois, S. (2004). On-line motor control in patients with Parkinson's disease. *Brain: A Journal of Neurology*, *127*(Pt 8), 1755-1773. doi: 10.1093/brain/awh206.

Dickinson, A. (1981). *Contemporary Animal Learning Theory* (1st ed.). Cambridge
University Press.

Doody, R. S., & Jankovic, J. (1992). The alien hand and related signs. *Journal of Neurology,
Neurosurgery, and Psychiatry*, *55*(9), 806-810.

Engbert, K., Wohlschläger, A., & Haggard, P. (2008). Who is causing what? The sense of
agency is relational and efferent-triggered. *Cognition*, *107*(2), 693-704. doi:
10.1016/j.cognition.2007.07.021.

Fahn, S., & Elton, R. L. (1987). *Members of the UPDRS Development Committee. Unified
Parkinson's disease rating scale*. Macmillan Health Care Information.

Falkenstein, M., Hielscher, H., Dziobek, I., Schwarzenau, P., Hoormann, J., Sunderman, B.,
et al. (2001). Action monitoring, error detection, and the basal ganglia: an ERP study.
Neuroreport, *12*(1), 157-161.

Farrer, C., Frey, S. H., Van Horn, J. D., Tunik, E., Turk, D., Inati, S., et al. (2008). The
angular gyrus computes action awareness representations. *Cerebral Cortex (New
York, N.Y.: 1991)*, *18*(2), 254-61. doi: 10.1093/cercor/bhm050.

Frank, M. J., Seeberger, L. C., & O'Reilly, R. C. (2004). By carrot or by stick: cognitive
reinforcement learning in parkinsonism. *Science (New York, N.Y.)*, *306*(5703), 1940-
3. doi: 10.1126/science.1102941.

Frith, C. D. (1992). *The Cognitive Neuropsychology of Schizophrenia* (1st ed.). Psychology
Press.

Frith, C. (2005). The self in action: lessons from delusions of control. *Consciousness and
Cognition,* 14(4), 752-770.

Gotham, A. M., Brown, R. G., & Marsden, C. D. (1986). Levodopa treatment may benefit or
impair "frontal" function in Parkinson's disease. *Lancet*, *2*(8513), 970-1.

Gotham, A. M., Brown, R. G., & Marsden, C. D. (1988). 'Frontal' cognitive function in patients with Parkinson's disease 'on' and 'off' levodopa. *Brain: A Journal of Neurology*, *111 (Pt 2)*, 299-321.

Grafton, S. T. (2004). Contributions of functional imaging to understanding parkinsonian symptoms. *Current Opinion in Neurobiology*, *14*(6), 715-719. doi: 10.1016/j.conb.2004.10.010.

Haggard, P. (2005). Conscious intention and motor cognition. *Trends in Cognitive Sciences,* 9(6), 290-295.

Haggard, P. (2008). Human volition: towards a neuroscience of will. *Nat Rev Neurosci*, *9*(12), 934-946. doi: 10.1038/nrn2497.

Haggard, P., & Clark, S. (2003). Intentional action: conscious experience and neural prediction. *Consciousness and Cognition*, *12*(4), 695-707.

Haggard, P., & Whitford, B. (2004). Supplementary motor area provides an efferent signal for sensory suppression. *Brain Research. Cognitive Brain Research*, *19*(1), 52-8. doi: 10.1016/j.cogbrainres.2003.10.018.

Haggard, P., Aschersleben, G., Prinz, W., & Gehrke, J. (2002). Action, binding and awareness.In: Hommel, B. and Prinz, W., (eds.) *Attention and performance: Vol. XIX. Common mechanisms in perception and action*. Oxford University Press, Oxford, UK, pp.266-285

Haggard, P., Clark, S., & Kalogeras, J. (2002). Voluntary action and conscious awareness. *Nature Neuroscience*, *5*(4), 382-5. doi: 10.1038/nn827.

Haggard, P., Cartledge, P., Dafydd, M., & Oakley, D. A. (2004). Anomalous control: when 'free-will' is not conscious. *Consciousness and Cognition*, *13*(3), 646-654. doi: 10.1016/j.concog.2004.06.001

Haggard, P., Martin, F., Taylor-Clarke, M., Jeannerod, M., & Franck, N. (2003). Awareness of action in schizophrenia. *Neuroreport*, *14*(7), 1081-5. doi: 10.1097/01.wnr.0000073684.00308.c0.

Hernandez, P. J., Sadeghian, K., & Kelley, A. E. (2002). Early consolidation of instrumental learning requires protein synthesis in the nucleus accumbens. *Nature Neuroscience*, *5*(12), 1327-31. doi: 10.1038/nn973.

Hollerman, J. R., & Schultz, W. (1998). Dopamine neurons report an error in the temporal prediction of reward during learning. *Nature Neuroscience*, *1*(4), 304-309. doi: 10.1038/1124.

Ivry, R. B., & Spencer, R. M. (2004). The neural representation of time. *Current Opinion in Neurobiology*, *14*(2), 225-232. doi: 10.1016/j.conb.2004.03.013.

Kelley, A. E., Smith-Roe, S. L., & Holahan, M. R. (1997). Response-reinforcement learning is dependent on N-methyl-D-aspartate receptor activation in the nucleus accumbens core. *Proceedings of the National Academy of Sciences of the United States of America*, *94*(22), 12174-12179.

Laruelle, M., Abi-Dargham, A., van Dyck, C. H., Rosenblatt, W., Zea-Ponce, Y., Zoghbi, S. S., et al. (1995). SPECT imaging of striatal dopamine release after amphetamine challenge. *Journal of Nuclear Medicine: Official Publication, Society of Nuclear Medicine*, *36*(7), 1182-1190.

Libet, B., Gleason, C. A., Wright, E. W., & Pearl, D. K. (1983). Time of conscious intention to act in relation to onset of cerebral activity (readiness-potential). The unconscious initiation of a freely voluntary act. *Brain: A Journal of Neurology*, *106 (Pt 3)*, 623-642.

MacDonald, V., & Halliday, G. M. (2002). Selective loss of pyramidal neurons in the pre-supplementary motor cortex in Parkinson's disease. *Movement Disorders: Official Journal of the Movement Disorder Society*, *17*(6), 1166-1173. doi: 10.1002/mds.10258.

Meck, W. H. (1996). Neuropharmacology of timing and time perception. *Cognitive Brain Research*, *3*(3-4), 227-242. doi: 10.1016/0926-6410(96)00009-2.

Meck, W. H., & Benson, A. M. (2002). Dissecting the Brain's Internal Clock: How Frontal-Striatal Circuitry Keeps Time and Shifts Attention. *Brain and Cognition*, *48*(1), 195-211. doi: 10.1006/brcg.2001.1313.

Moore, J., & Haggard, P. (2008). Awareness of action: Inference and prediction. *Consciousness and Cognition*, *17*(1), 136-44. doi: 10.1016/j.concog.2006.12.004.

Moore, J. W., Lagnado, D., Deal, D. C., & Haggard, P. (2009). Feelings of control: contingency determines experience of action. *Cognition*, *110*(2), 279-83. doi: 10.1016/j.cognition.2008.11.006.

Nachev, P., Kennard, C., & Husain, M. (2008). Functional role of the supplementary and pre-supplementary motor areas. *Nature Reviews. Neuroscience*, *9*(11), 856-869. doi: 10.1038/nrn2478.

O'Doherty, J., Dayan, P., Schultz, J., Deichmann, R., Friston, K., & Dolan, R. J. (2004). Dissociable roles of ventral and dorsal striatum in instrumental conditioning. *Science (New York, N.Y.)*, *304*(5669), 452-4. doi: 10.1126/science.1094285.

Pessiglione, M., Seymour, B., Flandin, G., Dolan, R. J., & Frith, C. D. (2006). Dopamine-dependent prediction errors underpin reward-seeking behaviour in humans. *Nature*, *442*(7106), 1042-1045. doi: 10.1038/nature05051.

Pastor, M. A., Artieda, J., Jahanshahi, M., & Obeso, J. A. (1992). Time estimation and reproduction is abnormal in Parkinson's disease. *Brain: A Journal of Neurology*, *115*

Pt 1, 211-225.

Pillon, B., Czernecki, V., & Dubois, B. (2003). Dopamine and cognitive function. *Current Opinion in Neurology*, *16 Suppl 2*, S17-22.

Playford, E. D., Jenkins, I. H., Passingham, R. E., Nutt, J., Frackowiak, R. S., & Brooks, D. J. (1992). Impaired mesial frontal and putamen activation in Parkinson's disease: a positron emission tomography study. *Annals of Neurology*, *32*(2), 151-161. doi: 10.1002/ana.410320206.

Rowe, J., Stephan, K. E., Friston, K., Frackowiak, R., Lees, A., & Passingham, R. (2002). Attention to action in Parkinson's disease: impaired effective connectivity among frontal cortical regions. *Brain: A Journal of Neurology*, *125*(Pt 2), 276-289.

Schultz, W., Dayan, P., & Montague, P. R. (1997). A neural substrate of prediction and reward. *Science (New York, N.Y.)*, *275*(5306), 1593-1599.

Schultz, W. (2006). Behavioral theories and the neurophysiology of reward. *Annual Review of Psychology*, *57*, 87-115. doi: 10.1146/annurev.psych.56.091103.070229.

Smith-Roe, S. L., & Kelley, A. E. (2000). Coincident activation of NMDA and dopamine D1 receptors within the nucleus accumbens core is required for appetitive instrumental learning. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *20*(20), 7737-42.

Swainson, R., Rogers, R. D., Sahakian, B. J., Summers, B. A., Polkey, C. E., & Robbins, T. W. (2000). Probabilistic learning and reversal deficits in patients with Parkinson's disease or frontal or temporal lobe lesions: possible adverse effects of dopaminergic medication. *Neuropsychologia*, *38*(5), 596-612. doi: 10.1016/S0028-3932(99)00103-7.

Synofzik, M., Vosgerau, G., & Newen, A. (2008). Beyond the comparator model: a
multifactorial two-step account of agency. *Consciousness and Cognition*, *17*(1), 219-
39. doi: 10.1016/j.concog.2007.03.010.

Tobler, P. N., Dickinson, A., & Schultz, W. (2003). Coding of predicted reward omission by
dopamine neurons in a conditioned inhibition paradigm. *The Journal of
Neuroscience: The Official Journal of the Society for Neuroscience*, *23*(32), 10402-
10410.

Voon, V., Hassan, K., Zurowski, M., de Souza, M., Thomsen, T., Fox, S., et al. (2006).
Prevalence of repetitive and reward-seeking behaviors in Parkinson disease.
Neurology, *67*(7), 1254-1257. doi: 10.1212/01.wnl.0000238503.20816.13.

Voon, V., Thomsen, T., Miyasaki, J. M., de Souza, M., Shafro, A., Fox, S. H., et al. (2007).
Factors associated with dopaminergic drug-related pathological gambling in
Parkinson disease. *Archives of Neurology*, *64*(2), 212-216. doi:
10.1001/archneur.64.2.212.

Wearden, J. H., Smith-Spark, J. H., Cousins, R., Edelstyn, N. M. J., Cody, F. W. J., &
O'Boyle, D. J. (2008). Stimulus timing by people with Parkinson's disease. *Brain and
Cognition*, *67*(3), 264-279. doi: 10.1016/j.bandc.2008.01.010.

Wearden, J. H., Smith-Spark, J. H., Cousins, R., Edelstyn, N. M. J., Cody, F. W. J., &
O'Boyle, D. J. (2009). Effect of click trains on duration estimates by people with
Parkinson's disease. *Quarterly Journal of Experimental Psychology (2006)*, *62*(1), 33-
40. doi: 10.1080/17470210802229047.

Wenke, D., & Haggard, P. (2009). How voluntary actions modulate time perception.
*Experimental Brain Research. Experimentelle Hirnforschung. Expérimentation
Cérébrale*, *196*(3), 311-318. doi: 10.1007/s00221-009-1848-8.

Willemssen, R., Müller, T., Schwarz, M., Falkenstein, M., & Beste, C. (2009). Response

monitoring in de novo patients with Parkinson's disease. *PLoS ONE*, *4*(3), e4898. doi:

10.1371/journal.pone.0004898.

Tables

Table 1. Demographic, pathology, and drug details in PD patients and controls

Number	Gender	Age	UPDRS (motor) OFF	UPDRS (motor) ON	Years (diagnosis)	Medication (mg/day)
1	M	66	10	7	6	Levodopa (400), Pramipexole base (2.1)
2	M	67	23	12	3	Pramipexole base (2.1)
3	M	60	25	14	7	Pramipexole base (3.15)
4	F	61	39	25	13	Levodopa (300)
5	M	56	28	12	10	Levodopa (900), Entacapone (1800), Cabergoline (3)
6	M	70	20	7	5	Levodopa (300), Ropinirole (6), Selegiline (10)
7	M	79	27	20	9	Levodopa (600)
8	M	71	35	22	2	Levodopa (200), Selegiline (10)
9	F	56	36	26	4	Pramipexole base (1.05)
Patients Mean (SD)	(7 Males)	65.11 (8)	27.00 (9)	16.11 (7)		
Controls Mean (SD)	(3 Males)	62.00 (6)				

Table 2. Mean shifts in the experience of actions and tones for: controls, PD patients OFF medication, and the same PD patients ON medication. Values in parenthesis show the SD of the mean **across participants.**

Group	Condition	Judged event	Mean (SD) judgement error (ms)	Intentional binding: Mean shift of judgement error from baseline (ms) (SD)	Significance level for mean of shift in judgement error from baseline (1-tailed)	Mean (SD) overall action and tone binding (ms)	Significance level for overall binding (1-tailed)
Control	Baseline	Action only Tone only	-83 (77) -62 (62)				
	Agency	Action Tone	-64 (63) -136 (62)	19 (30) -74 (80)	p = .054 p = .012	92 (83)	p = .005
PD *OFF* medication	Baseline	Action only Tone only	-33 (77) -45 (43)				
	Agency	Action Tone	-3 (60) -137 (73)	30 (47) -92 (75)	p = .043 p = .003	122 (84)	p = .001
PD *ON* medication	Baseline	Action only Tone only	-69 (52) -15 (75)				
	Agency	Action Tone	-7 (75) -139 (75)	62 (68) -124 (83)	p = .013 p = .003	186 (80)	p = .0001

Table 3. Mean standard deviations **across trials** for: controls, PD patients OFF medication, and the same PD patients ON medication.

Group	Condition	Judged event	Mean standard deviation *across trials*
Control	Baseline	Action only	79
		'Tone only'	84
	Agency	Action	87
		Tone	115
PD *OFF* medication	Baseline	Action only	121
		Tone only'	79
	Agency	Action	
		Tone	92
			92
PD *ON* medication	Baseline	'Action only'	102
		'Tone only'	109
	Agency	Action	101
		Tone	86

Figure captions

Figure 1. The intentional binding effect (adapted from Haggard, 2005). A) Participants' voluntary key-press actions are followed after 250 ms by an effect (a tone) B) Baseline estimates are obtained for actions occurring without a following tone, and tones occurring in the absence of actions. This controls for individual differences in the perception of these events, and provides a baseline against which to compare the time experience of the same events in an agency or passive context. C) In an agency context, intentional actions are perceived later and the effects are perceived earlier, than their respective baselines (hollow arrows).

Figure 2. Trial structure in the *agency* conditions (see text for details)

Figure 3. Intentional binding effect for (B) Healthy controls, (C) PD patients *off* dopaminergic treatment, and (D) PD patients *on* dopaminergic treatment. The dashed lines indicate the baseline in each condition (differences in baseline estimates between conditions are not shown in the figure for clarity, but are given in Table 2). Composite binding is the sum of the action binding and sign-reversed tone binding, and corresponds to the combined length of the two white arrows in each condition (arrows drawn approximately to scale).

Figure 4. Magnitude of composite binding in the first half and second half of trials within agency blocks (see text for details).
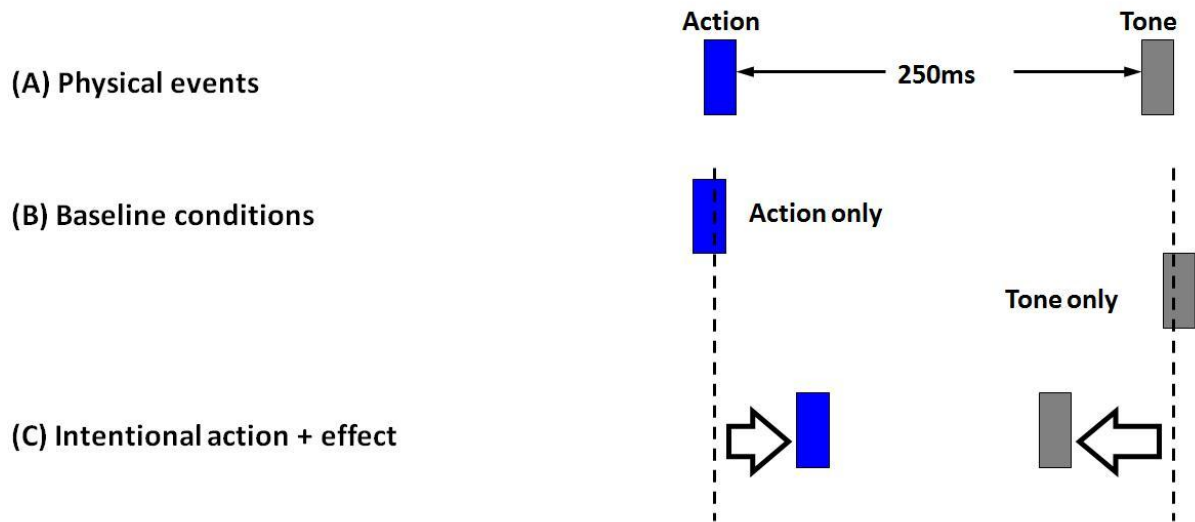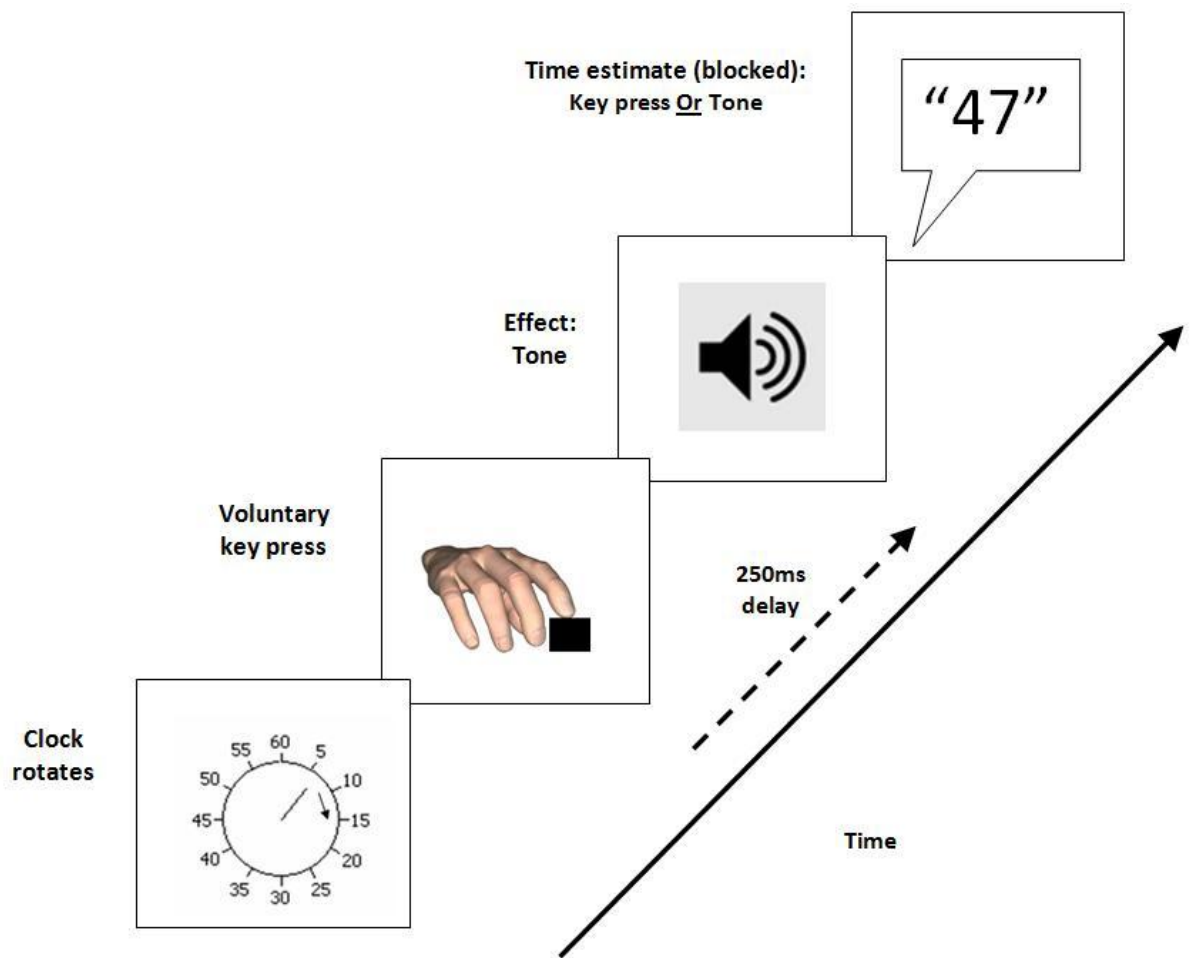
Figure 1

(A) Physical events
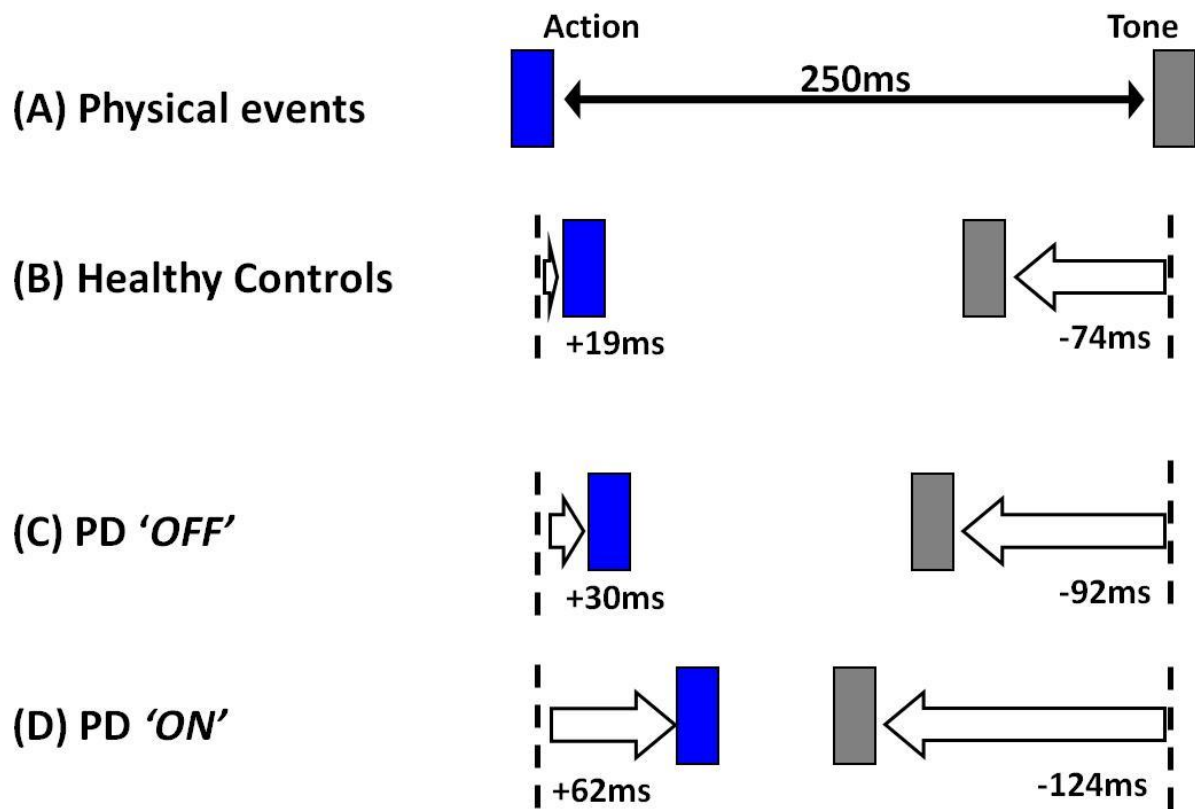
(B) Baseline conditions

(C) Intentional action + effect

Figure 2

Figure 3

Figure 4