Orienting of attention and Parkinson’s disease: tactile inhibition of return and response inhibition

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Summary

There is growing evidence for cognitive impairments in Parkinson’s disease (PD), including in the orienting of attention and inhibition of return (IOR). IOR refers to the slowing of a response to a target stimulus presented in the same location as a previous stimulus. While some researchers have reported normal levels of visual IOR in PD patients using cue-target tasks, others have reported significant reductions in IOR in this patient group. However, the inhibitory effects observed in cue-target tasks may reflect non-ocular response inhibition associated with withholding a response from the cue stimulus, rather than attentional or oculomotor processes. Many researchers working with normal participants have circumvented this confound by using a target-target task, in which a response is made to all peripheral stimuli. Here, we compared IOR measured in cue-target and target-target tasks, using tactile rather than visual stimuli. Both the PD and the control groups exhibited significant inhibitory effects in the cue-target task, but only the control group exhibited significant IOR in the target-target task. Our results demonstrate a reduction, or elimination, of IOR in PD and this change may have been underestimated in previous studies, in which methodologically flawed cue-target tasks were used. This reduction in IOR may reflect impaired inhibitory processes or hyper-reflexive orienting in parkinsonian patients.

Keywords: attention; basal ganglia; inhibition of return; Parkinson’s disease; tactile

Abbreviations: BG = basal ganglia; IOR = inhibition of return; LED = light emitting diode; MH = Mill Hill vocabulary scale; MMSE = Mini Mental State Examination; NART = National Adult Reading Rest; PD = Parkinson’s disease; RT = reaction time; SOA = stimulus onset asynchrony; UPDRS = Unified Parkinson’s Disease Rating Scale

Introduction

Parkinson’s disease (PD) has conventionally been considered to be a motor disorder, but there is growing evidence that cognition, and in particular attention, may also be impaired by the disease (Brown and Marsden, 1988; Hayes et al., 1998). For example, overactive attentional orienting may underlie motor symptoms such as ‘freezing’ (McDowell and Harris, 1997) but, conversely, attentional strategies can be used to improve movement in PD (Morris et al., 1996).

One important approach in research on attention has been to investigate covert orienting, which involves the orienting of attention to stimuli in the absence of eye movements (Posner, 1980; Spence and Driver, 1994). Inhibition of return (IOR) (Posner et al., 1985) refers, in this context, to the slowing of a response to a target stimulus presented in the same location as a previous stimulus (for a review see Klein, 2000). IOR has been attributed to an attentional bias; that is, attention is ‘grabbed’ by a peripheral cue and after moving away from the cued location, is biased against returning there again (Posner et al., 1985). Indeed, IOR may have evolved in the interests of efficient scanning of the environment and has been shown to guide behaviour, such as visual search in complex scenes and eye movements (Abrams and Dobkin, 1994; Rafal et al., 1994; Klein and McInnes, 1999). The phenomenon was observed originally using visual stimuli but has been reported subsequently between all combinations of visual, auditory and tactile stimuli (Spence and Driver, 1998a, b; Spence et al., 2000). It is thought that, rather than activating separate attentional mechanisms, cues in any
modality may tap into the same supramodal attention system (Spence, 2001; Eimer, 2003). There is converging evidence for collicular mediation of IOR (Sapir et al., 1999): the superior colliculus is thought either to generate the inhibitory tag, or to receive descending inputs encoding the inhibition of the cued location (for a review see Klein, 2000). Given the close anatomical and functional links between the superior colliculus and the basal ganglia (BG) (Parent and Hazrati, 1995), which are affected by PD, it might be expected that IOR is also affected by PD.

IOR is typically measured using the cue-target task, in which a peripheral cue and target are presented successively and subjects are required to respond as quickly as possible to the target (Posner, 1980; Spence and Driver, 1994). When the stimulus onset asynchrony (SOA) between the cue and target is short, responses are faster at the cued than at the uncued location (facilitation), but at longer SOAs, IOR is observed (Posner and Cohen, 1984; Lupiáñez et al., 1997).

In early studies of visual peripheral cueing in PD patients, facilitation was observed at short SOAs (<600 ms) (Rafal et al., 1984, 1988; Posner et al., 1985), and was not affected by medication (Rafal et al., 1984), whereas IOR was observed at an SOA of 1000 ms (Posner et al., 1985). However, small numbers of patients were involved in these studies, and there were no healthy control groups. Subsequently, there have been reports of PD patients with both normal facilitation (Bennett et al., 1995; Filoteo et al., 2002) and changed patterns of facilitation. Yamada et al. (1990), for example, reported no cueing effect with visual stimuli, whereas Bradshaw et al. (1993) found reduced costs for targets presented at the uncued location with vibrotactile stimuli. Recent comparisons across SOAs in PD have revealed normal facilitation effects at short SOAs, but changes at longer SOAs: Filoteo et al. (1997) reported reduced IOR in PD patients at an SOA of 1000 ms, and Yamaguchi and Kobayashi (1998) found that facilitation did not change with increased SOA in PD patients, but facilitation was reduced in the control group at an SOA of 800 ms (corresponding to IOR). Thus, in both studies, PD patients displayed reduced IOR. Similarly, Pollux et al. (2001) observed a non-significant IOR effect in their control group and no effect of cueing in the PD group at an SOA of 600 ms.

Of critical importance, however, are the conflicting results of two recent studies, which suggest that IOR is not affected by PD. First, Briand et al. (2001) used a task in which subjects made a saccadic eye movement to the target location and they found no difference in cueing effects between seven PD patients ‘OFF’ medication and a control group at SOAs of 67, 133 and 1000 ms (note that unless otherwise indicated, all studies described here involved patients tested while ‘ON’ medication). Furthermore, the magnitude of IOR increased with PD disease stage. Secondly, Kingstone et al. (2002) observed an IOR effect of normal magnitude in eight PD patients at an SOA of 288 ms. How can these conflicting results be reconciled? An important possibility is that the reduction of inhibitory effects observed in PD patients could have been produced by several factors other than by a genuine reduction in the magnitude of IOR.

First, cue-target tasks have been used in all previous studies of PD and IOR, and there is a motoric confound in such paradigms: when a cue is presented, subjects must inhibit any tendency to respond to it, and this response inhibition may carry over to affect subsequent responses to target stimuli presented at the same location (Harvey, 1980). Thus, non-oculcular response inhibition may produce IOR-like results in cue-target paradigms (Posner et al., 1985; De Jong et al., 1994; Spence and Driver, 1998a; Poliakoff et al., 2002a; Tassinari et al., 2002). Response inhibition can be ruled out by measuring inhibitory effects occurring between successive targets in so-called target-target tasks, as subjects respond to both stimuli (Terry et al., 1994; Spence and Driver, 1998a, b; Spence et al., 2000; Poliakoff et al., 2002a; Prime and Ward, 2002; Tassinari et al., 2002). Indeed, in normal subject groups, IOR of a smaller magnitude has been observed in target-target tasks than in cue-target tasks using visual (Maylor and Hockey, 1985), auditory (Spence and Driver, 1998a; Tassinari et al., 2002) and tactile (Poliakoff et al., 2002a) stimuli. Thus, the inhibitory effects reported in previous studies of PD patients could include response inhibition as well as, or even instead of, genuine IOR.

Secondly, IOR may have been masked by facilitation, as only Posner et al. (1985) and Briand et al. (2001) used central reorienting cues to withdraw attention from the cued location. Even in healthy young subjects, the magnitude of IOR can be reduced when no central reorienting event is included (Spence et al., 1998b; Ro and Rafal, 1999).

Thirdly, IOR may be reduced by a temporal overlap between the cue and the target stimuli in normal subjects (Maruff et al., 1999). Prolonged cues were used in both PD studies in which reduced IOR was observed (Filoteo et al., 1997; Yamaguchi and Kobayashi, 1998), whereas Briand et al. (2001) and Kingstone et al. (2002) used brief cues and observed normal IOR.

Fourthly, only Briand et al. (2001), Pollux et al. (2001) and Kingstone et al. (2002) used non-predictive peripheral cues, which carried no information about the likely target location. Thus, endogenous (voluntary) and exogenous orienting have been confounded in all other studies of IOR in PD (Briand et al., 2001; cf. Rafal and Henik, 1994; Spence and Driver, 1996). The importance of using an appropriate paradigm to measure IOR was highlighted by Faust and Balota (1997), who observed no IOR in patients with Alzheimer’s disease in a task involving predictive peripheral cues, but normal levels of IOR in a task involving non-predictive cues and a central reorienting event.

Fifthly, eye movements were not monitored by Filoteo et al. (1997), nor by Posner et al. (1985), and so overt orienting may have confounded the results.

Finally, dopamine metabolism in the retina can be affected by PD (Bodis-Wollner, 1990), which can lead to impaired visual acuity (Harris, 1998), so it is of importance to
determine whether IOR is also affected in non-visual modalities.

The experiment described here was conducted to determine whether the magnitude of tactile IOR is reduced in PD patients compared with healthy controls. As in a recent study of young healthy subjects (Poliakoff et al., 2002a), both a cue-target and a target-target paradigm were used to quantify the effect of response inhibition on performance. Brief, non-predictive cues and a central reorienting cue were used to ensure that attention was redirected to fixation prior to the onset of the second stimulus (Posner and Cohen, 1984; Spence and Driver, 1998b). In addition, eye movements were monitored in a subset of subjects in order to rule out a possible role for overt orienting in any observed effects.

Preliminary details of some of the results described here have been reported previously in abstract form (Poliakoff et al., 2002b).

Patients and methods

Subjects

Twenty-four patients diagnosed as having idiopathic PD (19 male, 5 female) and 24 healthy controls (13 male, 11 female) participated in the experiment. Mean (SD) age was 62.6 (8.4) years for the PD group and 65.0 (7.0) years for the control group, and did not differ significantly between the groups \[ t(46) = 1.1, P = 0.30 \]. Mean (SD) years in education was 11.7 (3.2) for the PD group and 13.3 (3.4) for the control group, and did not differ significantly between the groups \[ t(46) = 1.7, P = 0.10 \]. All subjects were right-handed with laterality quotients >50 (Oldfield, 1971). The PD patients were recruited from PD clinics at the Walton Centre (Liverpool), Hope Hospital (Manchester) and Manchester Royal Infirmary. Testing sessions were conducted at both Fazakerly Hospital (Liverpool) and Manchester Royal Infirmary. Approval was received from the local health authority research ethics committees of Central Manchester and South Sefton and testing was performed in accordance with the ethical standards laid down in the 1991 Declaration of Helsinki. Control subjects were either friends or partners of the PD patients or were recruited from panels of volunteers at Liverpool and Manchester Universities. Written informed consent was obtained from all subjects prior to testing and they were reimbursed with their travel expenses.

PD patients were selected at Hoehn and Yahr stage III or less (Hoehn and Yahr, 1967), who were on dopaminergic medication with minimal ON/OFF fluctuations and dyskinesias. They had a mean (SD) score of 18.2 (5.1) on the motor subsection of the Unified Parkinson’s Disease Rating Scale (UPDRS) (Fahn and Elton, 1987). The PD patients were all tested under their normal medication regime, during a stable ‘ON’ period. Fifteen patients were taking combination drugs (levodopa and a peripheral dopa-decarboxylase inhibitor) and 17 were taking dopamine agonists. In addition, some patients were taking anticholinergics (four), catechol-o-methyltransferase inhibitors (two) or monoamine oxidase inhibitors (two). All subjects were screened for history of major psychiatric illness, neurological impairment, previous alcohol or drug abuse and current use of centrally acting medication. All subjects were screened for dementia using the Mini Mental State Examination (MMSE) (Folstein et al., 1975) and were included only if they scored in the normal range (>25 out of 30).

Owing to the demanding nature of the IOR task, several subjects who had passed the initial screening procedure were unable to complete the task. Eleven patients were replaced due to dyskinesias (six), tremor (two), anxiety (two) and problems feeling the experimental vibrotactile stimuli (one). Three control subjects were replaced due to problems feeling the experimental vibrotactile stimuli (one) and equipment problems (two). In addition, subjects were replaced after testing if they had made more than a total of 60 errors in the 192 experimental trials: three control subjects were replaced for this reason.

Structure of the testing session

At the start of the session, subjects took the MMSE to assess dementia. The patients’ parkinsonian symptoms were then assessed using the motor subsection of the UPDRS. In addition, both patients and controls were asked screening questions about their current health and medical history. After completion of the experimental IOR task, handedness was assessed using the Edinburgh Laterality Questionnaire (Oldfield, 1971). Intelligence quotient (IQ) was estimated using the National Adult Reading Test (NART) (Nelson, 1958). Subjects were given the opportunity to take 2–3 min breaks throughout the testing session, which lasted ~90 min.

IOR task

Apparatus and stimuli

Subjects sat on a comfortable chair with their hands resting on a horizontal surface in front of them, ~30 cm to either side of the midline. A red light emitting diode (LED) located directly in front of the subject’s eyes, at a distance of 55 cm, was used as a fixation point. Two green LEDs located immediately on either side of the fixation light were used to present a central visual cue. The LEDs were 1 cm in diameter and subtended a visual angle of ~1°. Vibrotactile stimuli were delivered via miniature linear actuators (tactors), with pointed striking surfaces, driven by a white noise generator with a 50–500 Hz frequency range. One tactor was attached, with double-sided tape, to the dorsal surface of each of the middle segments of a subject’s index fingers. Subjects’ hands were obscured from their view.

In order to attenuate any ambient noise and ensure that the activation of the tactors was not audible, subjects wore sound-attenuating headphones. Small audio phones were...
embedded within the headphones to allow the relay of instructions by the experimenter during the experimental session. The eye movements of 14 subjects in each group were monitored using electro-oculography. A spike processor (trigger device) was used which alerted the experimenter to the occurrence of a lateral eye movement of >5°.

**Procedure**

The locations of the tactors and the intensities of the tactile stimuli delivered to the two hands were subjectively matched by the subject. The relative timing of the successive stimuli presented within a trial was identical in the two tasks (Fig. 1). At the start of the trial, a central visual cue (illumination of the two green LEDs) was presented for 100 ms. The first vibrotactile stimulus (duration 50 ms) was presented after a delay of either 400 or 800 ms. After a further delay of 1000 ms, a second central visual cue was presented. The second vibrotactile stimulus (duration 100 ms) was presented 400 or 800 ms after the onset of the central visual cue. Vibrotactile stimuli were presented to the left or right hand with equal probability, so that the side of the first stimulus did not predict the side of presentation of the second stimulus. The SOA between the two successive vibrotactile stimuli was either 1400 or 1800 ms. The inter-trial interval was 4000 ms, and reaction times (RTs) of >1000 ms were not recorded. The long inter-trial interval was chosen to minimize subject fatigue.

The order of presentation of the cue-target and target-target tasks was counterbalanced across subjects. In the cue-target task, subjects were instructed to respond only to the second vibrotactile stimulus in each pair. In the target-target task, subjects were required to respond to both vibrotactile stimuli, so both stimuli were targets. Each task consisted of four experimental blocks of 48 trials, preceded by a practice block, during which 20 pairs of stimuli were presented with an extra 750 ms delay after each target, to facilitate task acquisition. The central red LED was illuminated throughout each block of trials, and subjects were instructed to fixate this LED continuously. Subjects responded by lifting the toe of their right foot, which was positioned on a comfortably located foot pedal.

**Results**

Trials in which RTs were <150 ms were removed and designated anticipation errors. Trials in which a significant eye movement (<4% of trials) or an error were made were not included in subsequent analyses. Errors included responding prior to stimulus presentation, not responding, or not having the foot depressing the pedal at the start of the trial. The number of errors was significantly higher in the PD group than in the control group for the cue-target task ($Z = 2.6, P = 0.008, 8.6\%$ compared with 5.1%) but not for the target-target task ($Z = 1.5, P = 0.13, 11.4\%$ compared with 8.0%). The RTs for each subject in each subcondition were then subjected to an outlier removal process (VanSelst and Jolicoeur, 1994) and median RTs were calculated. The RTs were analysed separately for each task and each group of subjects using a three-way ANOVA (analysis of variance).
IOR was calculated for each individual in each sub-condition by subtracting the median RT for stimuli presented on the opposite side to the previous stimulus from the RT to stimuli presented on the same side. Thus, IOR is indexed by a positive value.

The mean scores of the PD group on both the MH [19.5 compared with 23.3; t(46) = 3.5, P = 0.001] and the NART [110.1 compared with 117.0; t(46) = 3.2, P = 0.002] were significantly lower than those of the control group, indicating that the mean IQs of the two groups differed significantly. As there was a strong correlation between MH and NART scores across all subjects (r = 0.80, P < 0.0005), MH was taken as single index of IQ, and was used as a covariate in initial between-group analyses of performance data using analysis of covariance. As the covariate MH proved not to be statistically significant in any of these analyses, between-group differences in performance data were subsequently re-examined using ANOVA, the results of which are reported here.

**Cue-target task**

For the PD group, there were significant main effects of ‘SOA’ [F(1.23) = 24.6, P < 0.0005] and Side [F(1.23) = 5.8, P = 0.024]; PD patients responded more rapidly at the longer SOA and when the target was on the opposite side, as compared with the same side, as the cue (Fig. 2A); that is, they showed a significant IOR effect. None of the other effects or interactions was significant.

In the control group, as in the patient group, the main effects of ‘SOA’ [F(1.23) = 16.2, P = 0.001] and ‘side’ [F(1.23) = 32.3, P < 0.0005] were significant: control subjects responded faster at the longer SOA and also exhibited a
significant IOR effect (Fig. 2C). In addition, there was a significant ‘hand’ × ‘SOA’ × ‘side’ interaction \( F(1,23) = 6.3, P = 0.02 \). This reflects the fact that the IOR effect was significantly larger at the shorter SOA for the right hand [37 ms compared with 17 ms; \( t(23) = 2.7, P = 0.014 \) but not for the left hand [23 ms compared with 23 ms; \( t(23) = 0.909, P = 0.93 \)].

**Target-target task**

For the PD group, there was a significant main effect of ‘SOA’ \( F(1,23) = 12.9, P = 0.002 \), but no other effects were significant. Thus, patients were still faster to respond at the longer SOA but, in contrast to their performance in the cue-target task, showed no IOR effect (Fig. 2B). The ‘hand’ × ‘side’ interaction approached statistical significance \( F(1,23) = 3.9, P = 0.06 \). In contrast, for the control group the main effects of ‘SOA’ \( F(1,23) = 20.2, P < 0.0005 \), ‘side’ \( F(1,23) = 7.6, P = 0.012 \) and ‘hand’ \( F(1,23) = 6.7, P = 0.016 \) were all significant. Thus, control subjects were faster to respond at the longer SOA and to stimuli presented to the right hand, and exhibited a significant IOR effect (Fig. 2D).

**Comparison of PD and control groups**

Overall mean RTs for the PD and control group were not significantly different for either the cue-target \( r(46) = 0.16, P = 0.87 \) or the target-target \( r(46) = 0.39, P = 0.70 \) tasks. Differences in the magnitude of IOR between the PD and control groups were examined using a five-way ANOVA: ‘group’ (PD, control) × ‘eye movements’ (monitored, not monitored) × ‘hand’ (left, right) × ‘task’ (cue-target, target-target) × ‘SOA’ (1400, 1800 ms). The main effect of ‘task’ \( F(1,44) = 12.0, P = 0.001 \) and the ‘task’ × ‘SOA’ interaction \( F(1,44) = 8.2, P = 0.006 \) were significant. As previously observed in healthy young subjects (Poliakoff et al., 2002a), the magnitude of tactile IOR was smaller in the target-target task than in the cue-target task, and the size of this difference was significantly smaller at the SOA of 1800 ms than of 1400 ms \( r(46) = 2.6, P = 0.014 \); Fig. 3). More important, there was a main effect of ‘group’ \( F(1,44) = 4.7, P = 0.036 \), indicating that the magnitude of IOR across the two tasks was significantly larger for the control group than for the PD group (Fig. 4). The main effect of ‘eye movement’ was not significant \( F(1,44) = 0.29, P = 0.60 \), nor did it interact significantly with any of the other factors, thus allowing us to rule out an overt orienting account of the IOR effects reported here.

**Correlation of IOR with clinical signs**

The degree to which the magnitude of IOR correlated with that of other variables was examined using Pearson’s correlation: neither the magnitude of cue-target nor target-target IOR varied significantly with age or UPDRS motor score \( r < 0.2 \).

**Discussion**

Our main findings were: (i) the control group exhibited IOR in both tasks and the PD group exhibited IOR in the cue-target task, but not in the target-target task; and (ii) the magnitude of IOR was significantly smaller in the PD group than in the control group across both tasks. We consider two potential
explanations for this pattern of results: first, that the PD patients did not exhibit IOR, but their IOR was overestimated in the cue-target task, and, secondly, that the PD patients exhibited IOR, but their IOR was underestimated in the target-target task.

The first possibility is that the apparent ‘IOR’ detected in the PD group in the cue-target task was entirely attributable to response inhibition, because it was not apparent in the target-target task. The difference in magnitude between cue-target IOR and target-target IOR, which may be attributed to response inhibition, was ~12 ms for the control and ~15 ms for the PD groups (Fig. 6). Thus, the size of the putative response inhibition component among controls (12 ms) was of a very similar magnitude to that of the entire IOR effect for the PD group in the cue-target task (15 ms). The putative response inhibition component of 12 ms among our control subjects (mean age 65 years) appears to be larger than that observed previously in younger subjects (6 ms; mean age 22 years) performing the same tasks (Fig. 6) (Poliakoff et al., 2002a). In addition, there was a larger difference in the magnitude of IOR between the cue-target and target-target tasks at 1400 ms than at 1800 ms, implying that, as with young subjects, response inhibition exerts a greater influence at shorter intervals (Poliakoff et al., 2002a). Response inhibition might also explain why, in the cue-target task, the control group produced significantly larger IOR for right hand than left hand targets only at an SOA of 1400 ms. Stimuli to the right hand might be expected to automatically activate the right foot response more strongly, due to stimulus–response compatibility effects (Aglioti and Tomaiaiuolo, 2000), and thus require greater response inhibition, which plays a greater role at 1400 ms. The side of the responding hand has been found to interact with cueing effects in previous studies (Possamaï, 1991; Ivanoff and Klein, 2001).

It is important, however, to consider the other possibility; namely, could IOR in PD be underestimated in the target-target task? One argument is that the motor demands of responding twice in quick succession in the target-target task may have differentially affected RTs to the second target in the PD group and thus influenced IOR. However, the same motor response was required to all stimuli, so the motor demands were the same for trials in which the two successive stimuli were presented to the same or opposite hands. Secondly, PD patients did not make significantly more errors than controls in the target-target task, as would be expected if they found it more demanding, nor were their overall RTs significantly different from those of controls in either task. Thirdly, IOR was not observed in the PD patients over the longer SOAs between trials. In this case, patients had more than 4 s to prepare their next response, suggesting that a motor refractory period could not be responsible. The target-target task also involved twice as many responses across the session, so it was possible that fatigue or practice affected the PD and control groups differentially. However, when IOR
scores were calculated for the first and the second half of the target-target task, there was no main effect of order \( F(1,44) = 0.091, \ P = 0.764 \), nor did order interact with any other factors. In addition, overall RTs for the first and the second half were not significantly different for either the PD \( t(23) = 0.518, \ P = 0.609 \) or control groups \( t(23) = 0.836, \ P = 0.412 \).

We conclude, therefore, that the magnitude of genuine IOR, which is independent of response inhibition (Tassinari et al., 2002), is smaller in PD patients than in controls. Cue-target tasks were used in all previous studies of IOR in PD, so response inhibition could therefore account for the observations of ‘IOR’ in these studies. Furthermore, the variation in motor demands of the cue-target tasks used could explain why reduced IOR among PD patients has been observed in some studies but not others. Indeed, differing response demands are thought to have produced divergent results in two recent studies of negative priming in PD patients (Stout et al., 2002). An important question concerns how general our findings might be. We should predict that if IOR does reflect a truly supramodal system (Spence et al., 2000; Spence, 2001; Eimer, 2003), our findings using tactile stimuli will generalize to target-target tasks involving visual, auditory and multisensory stimuli. Secondly, the effects of medication need to be investigated, as patients were tested only ‘ON’ medication, so it is possible that the observed changes in IOR were, at least to some extent, secondary to the effects of medication.

Comparison with the findings of Poliakoff et al. (2002a) suggests that response inhibition may be larger in older subjects than in young subjects. This could explain the observations of normal (Hartley and Kieley, 1995; Faust and Balota, 1997; Metzler, 1999) or increased (Woods, 1992; Tipper et al., 1997) IOR in older subjects, despite a reduction in inhibitory attentional mechanisms (for a review see McDowd et al., 1994). If inhibitory mechanisms do decline with age, then more inhibition would be required to prevent a response being made to the cue in older subjects, and thus IOR measured using a cue-target task would be larger.

**What cognitive mechanisms might underlie reduced IOR in PD?**

It is possible that IOR *per se* is not affected by PD, but patients remain more strongly oriented to the cued location, so that facilitation masks IOR. This cannot be ruled out completely by the present findings, but in previous studies involving informative central arrow cues, PD patients exhibited reduced cueing effects at longer SOAs (Sharpe, 1990; Wright et al., 1990, 1993; Filoteo et al., 1997; Yamaguchi and Kobayashi, 1998; Pollux and Robertson, 2001; although see Kingstone et al., 2002). Thus, patients were, if anything, faster to reorient their attention to the uncued location. In addition, the task used in our experiment was designed to minimize facilitation. The same reasoning suggests that the reduced IOR in PD is not secondary to another deficit causing patients to disengage their attention more slowly from the cued location, such as perseveration.
(Partiot et al., 1996) or the switching of attention (Hayes et al., 1998).

We now consider two explanations for the reduction of IOR in PD patients. First, inhibitory processes are impaired in PD (Filoteo et al., 1997) and, secondly, PD patients are hyper-reflexive (Jackson and Houghton, 1995; Briand et al., 2001; Kingstone et al., 2002). According to the former explanation, specific inhibitory processes that prevent the return of attention to the cued location are impaired, while according to the latter, orienting to a salient, external stimulus is stronger than the bias introduced by IOR. While different, the two explanations may not be mutually exclusive and the latter may also involve inhibition. Both hypotheses can also explain the findings with central predictive cues (Jackson and Lees, 1993).

Evidence for impaired inhibitory processes in PD has been found using negative priming tasks (Downes et al., 1991; Filoteo and Rilling, 2002; although see Wylie and Stout, 2002) and a modified Stroop task (Henik et al., 1993). In both tasks, PD patients were faster than controls at processing previously ignored stimulus attributes, suggesting that they were less efficient at inhibiting their processing in the first place. However, these tasks involve inhibition as a component of selective attention. Furthermore, our results indicate that PD patients were able to exert sufficient response inhibition to avoid responding in the cue-target task, and although IOR did not affect the subsequent response, this form of response inhibition did.

There is some evidence of hyper-reflexivity in PD patients. Praamstra et al. (1998) observed an earlier lateralized readiness potential in PD patients, reflecting preparation to move one hand rather than the other in response to a visual stimulus. When responding to a stimulus on the left with the right hand, the spatially compatible response must be inhibited (Simon et al., 1981). In PD, this inhibition does not affect subsequent responses, which suggests that PD patients fail to suppress the automatic response tendency as strongly as controls (Praamstra and Plat, 2001). This notion is supported by two studies of motor control. First, PD patients ‘OFF’ medication experience greater interference than controls while reaching for a target object in the presence of a distractor object requiring a different grip type (Castiello et al., 2000). Secondly, PD patients, but not controls, exhibit interference in a force production task while carrying out an RT task with the other hand (Caligiuri et al., 1992). Hyper-reflexivity has also been observed in studies of saccadic eye movements (for a review see Briand et al., 1999): patients perform as well, if not faster, than controls when required to make reflexive saccades (i.e. move their eyes to a visual stimulus; Roll et al., 1996; Armstrong et al., 2002; Kingstone et al., 2002), but are impaired when required to make memory-guided or predictive saccades (Kennard and Lueck, 1989; Briand et al., 1999). Furthermore, in antisaccade tasks, PD patients made more errors in which they failed to inhibit the saccade to the target location (Crevits and De Ridder, 1997; Briand et al., 1999; Armstrong et al., 2002; although see Kingstone et al., 2002). It has been proposed that the voluntary attention system tonically inhibits the reflexive attention system (Sereno, 1996). Thus, the hyper-reflexivity in PD may reflect disinhibition from an underactive voluntary attention system (Briand et al., 1999).

In summary, the reduction of IOR reported here could be due to impaired inhibitory processes or to hyper-reflexivity. Furthermore, inappropriate orienting to environmental stimuli may underlie certain motor symptoms in PD. For example, many patients experience ‘freezing’ when walking through narrow doorways, which may be due to attentional capture by the edges of the doorway (McDowell and Harris, 1997). In addition, the beneficial effects that visual cues can have on movement (Morris et al., 1996) may be produced by attentional capture.

**What neurobiological mechanisms might underlie reduced IOR in PD?**

Assuming that the reduced IOR is not secondary to the effects of medication, the functional changes in dopaminergic cells and the BG in PD might contribute to a reduction in the magnitude of tactile IOR in several ways. First, PD might interfere with the generation of IOR. Secondly, the inhibitory tag might be generated, but overridden by hyper-reflexivity to the cued location. There are somatotopic inputs from the somatosensory cortex to the BG in the primate brain (Graziano and Gross, 1993, 1996), whereby information regarding the location of a tactile stimulus reaches these structures.

PD might disrupt IOR at several levels. First, over-inhibitory outputs from BG to the superior colliculus might affect orienting (McDowell and Harris, 1997) and IOR. Secondly, specific descending frontal or parietal cortical inputs may be lost in PD due either to changes in the BG (Maddox et al., 1996) or to dopamine depletion in the cortical areas themselves (Stam et al., 1989; McDowell and Harris, 1997). However, changes in IOR are not typically observed in patients with frontal or parietal lesions (Posner et al., 1985; Metzler, 1999), suggesting that such signals are not essential for IOR. Thirdly, integration of sensory and contextual information within the BG (Redgrave et al., 1999a) may be necessary for IOR. The BG may act as a gain control, amplifying those stimuli that match expectations and inhibiting those that do not (Jackson and Houghton, 1995; Redgrave et al., 1999a). Fourthly, short-latency dopamine response of cells in the midbrain may play a role in the orienting of attention to novel relevant stimuli (Redgrave et al., 1999b), so attentional changes in PD could be more directly related to the depletion of these cells.

The second hypothesis is that IOR might be generated, but is overridden by hyper-reflexive orienting to external stimuli. Lidsky et al. (1985) suggested that the BG gate the access of sensory information to motor areas of the brain. This gating might influence ascending sensory inputs (Rothblat and...
Schneider, 1993) or cortical areas themselves (Bennett et al., 1995). Hyper-reflexivity would be predicted if the BG act as a gain control in selection: rather than the weights of competing stimuli being modulated by endogenous contextual inputs in the BG (Redgrave et al., 1999a), their weights would bear a stronger relation to the actual stimulus strength derived from projections by-passing the BG or from unmodulated signals from the BG; that is, the presence of a stimulus would override previous expectations.

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