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The role of the basal ganglia in the control of automatic visuospatial attention

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Abstract

Cognitive impairments in patients with basal ganglia dysfunction are primarily revealed where performance relies on internal, voluntary control processes. Evidence suggests that this also extends to impaired control of more automatic processes, including visuospatial attention. The present study used a non-predictive peripheral cueing paradigm to compare and contrast visuospatial deficits in patients with Parkinson's disease (PD) with those previously revealed in patients with Huntington's disease (HD) (Fielding et al., 2006a). Compared to age-matched controls, both PD and HD patients exhibited increased distractibility or poor fixation, however only PD patients responded erroneously to cue stimuli more frequently than control subjects. All subjects demonstrated initial facilitation for valid *versus* invalid cues following the shorter stimulus-onset asynchronies (SOAs) and a performance decrement at the longer SOAs (inhibition of return), although there was a clear differentiation between these groups for immediate SOAs. Unlike both control and PD subjects, where IOR manifested between 350 and 1000 msec, IOR was evident as early as 150 msec for HD patients. Further, for PD patients, spatially valid cues resulted in hyper-reflexivity following 150 msec SOAs, with saccadic latencies shorter than those generated in response to un-cued targets. Thus contrasting deficits were revealed in PD and HD, emphasizing the important contribution of the basal ganglia in the control of more automatic behaviors (*JINS*, 2006, *12*, 657–667.)

Keywords: Parkinson's disease, Huntington's disease, basal ganglia disorders, saccades, attention, inhibition.

INTRODUCTION

Parkinson's (PD) and Huntington's (HD) diseases are both neurodegenerative disorders, manifesting not only in profound motor dysfunction, but a range of non-motor deficits, which parallel this decline (McPherson & Cummings, 1996; Shoulson, 1990). Principally implicating structures comprising, and connected to, the basal ganglia (BG), PD is characterized by the loss of neurons within the substantia nigra pars compacta (SNc), (Marsden, 1984), resulting in a reduction in BG output. Conversely, in HD, neuronal loss and astrocytosis are most prominent in the GABAergic output neurons of the striatum (Vonsattel, 1999), resulting in disinhibition of BG output. Given that the BG receive input from, and project to, virtually the entire cerebral cortex and brain stem motor areas, they play a significant role in the control of a host of behaviors, motor, affective, and cognitive. But, rather than implementing any particular behavior, the BG appear primarily concerned with focusing neural resources *via* context-dependent facilitation/amplification or inhibition of neural activity (McAuley, 2003) influencing the selection and suppression of competing responses (Seiss & Praamstra, 2004).

Accordingly, both PD and HD result in a loss or impairment of function over a range of behaviors, including poor attentional control, postulated to underlie more organizational and executive aspects of behavior (Ivory et al., 1999). In PD, pronounced difficulty is experienced initiating and facilitating wanted behavior, and inhibiting more reflexive behaviors. A range of paradigms investigating attentional control in PD have consistently demonstrated abnormally rapidly disengagement or impaired maintenance of attention (Bradshaw et al., 1993; Filoteo et al., 1994; Filoteo et al., 1997; Pollux & Robertson, 2001; Wright et al., 1990;

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Yamaguchi & Kobayashi, 1998). Conversely, HD manifests in distractibility (difficulty inhibiting extraneous activity) and perseverative behavior, revealed in a number of set-shifting tasks whereby patients persist with a response set, which is no longer appropriate to the task (Georgiou et al., 1995; Georgiou et al., 1996; Josiassen et al., 1983; Lawrence et al., 1996; Sprengelmeyer et al., 1995).

These studies support the suggestion that impairments in the cognitive control of behavior in these disorders are primarily revealed where performance relies on internal, *voluntary* control processes (Brown & Marsden, 1990). However an important aspect of control is the inhibition of more *automatic* or reflexive operations (Crawford et al., 2002). Not surprisingly, there is growing evidence of impairment to the control of more automatic processes in PD and HD, including automatic visuospatial attention.

Automatic visuospatial attention, a stimulus-driven, *bottom-up* process, is conventionally investigated using cue-target tasks, in which spatially compatible, or incompatible, cue and target stimuli are presented successively (Posner, 1980). The presentation of an exogenous cue, or a salient visual event, necessarily results in response conflict, given that it initiates both facilitatory and inhibitory neural processes, which must be modulated according to a desired behavior (Tipper & Weaver, 1998). The former process is relatively automatic and prepares a host of ocular motor or attentional structures and networks for action, the latter is a more deliberate process, which inhibits the activation of these regions where inappropriate.

These competing processes normally result in differential effects for short and long delays, or stimulus onset asynchronies (SOA), between cue and target presentation. Typically short SOAs manifest in a facilitation of responses to targets presented in the same location as the cue, relative to those presented in other locations. Longer SOAs result in a relative slowing of response to a target presented in the same location as the previous stimulus (Posner & Cohen, 1984). The latter phenomenon, known as inhibition of return (IOR), has been the subject of intensive investigation, with various theoretical and neural accounts proposed.

Attentional theories attribute the source of IOR to the orienting of attention towards a particular location, and the subsequent removal of this attention, discouraging re-inspection of an already attended-to location (Klein, 1988; Posner & Cohen, 1984; Sapir et al., 1999). It has also been proposed that IOR is simply a consequence of the activation of the ocular motor system, resulting from the inhibitory modulation of a motor program generated towards a previously cued location (Tassinari et al., 1987; Taylor & Klein, 1998). However, as Ro et al. (2003) suggest, these accounts are not necessarily mutually exclusive, and may simply represent different manifestations of the same underlying process.

Exact neural mechanisms underlying IOR are also unclear, however, the involvement of the midbrain structure superior colliculus (SC) (Danziger et al., 1997; Sapir et al., 1999; Tipper et al., 1997) has been proposed by both sensory-attentional and ocular motor theories, (Rafal et al., 1988; Sparks & Hartwich-Young, 1989), with modulation of activity consistent with the time-course of IOR over a range of modalities (Spence et al., 2000). However, the associated reduction in facilitatory activity over the SC appears to reflect a signal reduction that has taken place cortically (Dorris et al., 2002; Mayer et al., 2004; Wascher & Tipper, 2004). Ro et al. (2003), for example, have demonstrated that the frontal eye fields (FEF), which are heavily interconnected with the SC, play a crucial role in generating IOR. Transcranial magnetic stimulation applied over the FEFs resulted in the elimination of the slowed response to cued targets (Ro et al., 2003). This suggests that the inhibitory component of the IOR may emanate from the FEF. Further, it has been proposed that this temporary inhibitory link set up between stimuli at inhibited locations and their responses, may derive from the posterior parietal cortex (Fuentes, 2004). Thus IOR may be characterized as the relative precedence of inhibitory activity, *versus* facilitatory activity, over the SC, which is determined cortically by structures commonly involved in both eye movement and attention (Corbetta et al., 1998; Kustov & Robinson, 1996).

The BG comprise an important component of attentional networks, primarily concerned with the focusing of neural resources *via* selectively facilitating or inhibiting neural activity (McAuley, 2003). Significantly, the SC is normally gated by tonic inhibitory input from the BG output structure substantia nigra pars reticula (SNr) (Hikosaka et al., 1993; Hikosaka et al., 2000). Thus the BG may well influence SC activity, particularly under conditions that promote competing processes, including situations that generate IOR.

Given the anatomical and functional links between the BG and the SC, compromised performance may be anticipated in patients with BG dysfunction. Indeed, altered performance has been demonstrated in our own investigations of saccadic behavior in HD, revealing accelerated onset of IOR, but appropriate suppression of cue-related activity (Fielding et al., 2006). This was considered attributable to either distractibility, resulting in removal of facilitatory activity from a non-informative cue location, or the greater involvement of cortical inhibitory control mechanisms to gate intruding and inappropriate responses. Persistence of an attentional set strongly biased against responding to cue stimuli, or perseveration, is consistent with HD neuropathology. Each of these scenarios results in relatively strong and persistent inhibitory activity over the area of the SC motor map encoding the region of space occupied by the cue/target. A saccade to a non-inhibited spatial region does not require the removal of this inhibitory activity in SC regions representing the cue, thus the balance of activity over the SC motor map might be altered relatively quickly, and the threshold for release of a saccade might be reached relatively earlier on.

However, in PD, findings are varied and widely discrepant. Whereas earliest studies report normal cueing effects

in PD (Posner et al., 1985), subsequent studies have revealed evidence of hyper-reflexivity, or more rapid disengagement of attention, at shorter SOAs (Briand et al., 2001; Pollux & Robertson, 2001). Over longer SOAs, reports include normal onset of inhibition (IOR), as early as 288 ms (Kingstone et al., 2002) and more persistent facilitation following valid cues with 500 and 800 ms SOAs (Yamaguchi & Kobayashi, 1998). Rapid decay of attentional inhibition with 1000 ms SOAs (J.V. Filoteo et al., 1997), reduced or eliminated IOR for 1400 and 1800 ms SOAs (Poliakoff et al., 2003), and no effect of cueing at 600 ms (Pollux & Robertson, 2001), have also been proposed and may well reflect methodological inconsistencies between the various studies (Poliakoff et al., 2003). In the single study, which has addressed IOR in PD within the context of eye movement, an increased magnitude in the IOR was found to correspond with disease stage (Briand et al., 2001). These authors attributed this to over-active reflexive attentional processes in PD.

This study sought to investigate the role of the BG in the control of automatic visuospatial attention, by examining the nature of deficits in PD using a saccadic paradigm similar to that of Briand et al. (2001). As an extension of this earlier work, we also evaluated the effects of valid and invalid cueing separately, by ascertaining a baseline measure of performance for comparison. This enabled us to contrast behaviors revealed in our previous investigation in HD. Notably, ocular motor deficits in both PD and HD parallel those found for other motor systems. Although in PD this equates to increased latencies for more volitional saccades, for more reflexive saccades, latencies are often shorter than normal (i.e., hyper-reflexive), and patients tend to respond erroneously to non-target stimuli with greater frequency (Armstrong et al., 2002; Crevits & De Ridder, 1997; Kingstone et al., 2002; Muller et al., 1994; Rascol et al., 1989; Rottach et al., 1996; White et al., 1983). As such, it was hypothesized that, in contrast to the findings in HD of accelerated onset of IOR and appropriate response suppression (Fielding et al., 2006a), PD patients would experience difficulty inhibiting erroneous responses to cue stimuli, and that onset of IOR would be delayed, consistent with a reduction in the inhibitory output of SNr neurons to regions of the SC motor map encoding non-target or cue stimuli. Temporal exploration of spatial cueing in these patient groups might help elucidate both the impact and time-course of facilitatory and inhibitory processes, in turn leading to a greater understanding of the IOR.

Importantly, cost/benefit analyses were conducted by comparing latencies of valid and invalidly cued saccades with latencies of un-cued saccades. Although latencies following neutral or bi-directional cues are more conventionally used for this type of analysis, we considered that the response conflict inherent in the presentation of two competing visual stimuli (i.e., discrete modulation of activity over a range of ocular motor structures) may be inappropriate as a baseline measure of performance for patients who exhibit impaired conflict resolution.

METHODS

Participants

Twelve patients with mild to moderate PD participated voluntarily in this study. All were clinically diagnosed with PD by a neurologist, with motor disabilities responsive to anti-Parkinsonian medication (O.W). Ages varied between 46 and 75 years (M = 62.58 yrs, SD = 9.23 yrs). Clinical manifestations of the disease were evident from 1 to 17 years. Disease severity was evaluated using the motor subscale of the Unified Parkinson's Disease Rating Scale. Clinical data for this group are shown in Table 1.

An equivalent number of neurologically healthy, control subjects also participated in this study. These participants were aged between 46 and 76 years (M = 62.25 yrs, SD = 10.01 yrs), with no significant difference in age between control and patient groups.

No participant demonstrated visual impairment, other than refractive error, or gross clinical ocular motor pathology. Participants were screened for cognitive decline using the mini-mental state examination (MMSE) (Folstein et al., 1975). Scores <22 out of 30 were considered indicative of dementia or abnormal cognitive functioning. No scores for either group were below 25, with no significant difference found between PD patients (M = 28.67, SD = 1.67) and controls (M = 29.25, SD = 1.48). Depressive symptoms were evaluated using the Beck Depression Inventory (BDI) (Beck et al., 1961), revealing a significant difference between patient (M = 8.79, SD = 3.20) and control (M = 3.92, SD = 3.42) groups, $t(22) = 3.60$, $p < .05$. Although most participants' scores fell within what is considered a normal range overall (0–9) (Beck & Steer, 1991), 5 PD subjects exhibited moderate symptoms of depressive illness (10–18), consistent with previous literature (Schrag et al., 2000). The digit span task (DS), a component of the Wechsler Adult Intelligences Scale (Wechsler, 1955), was administered to ascertain recall of an increasing number of digits both forwards and backwards; these tasks are considered to reflect attention to a given task and short term working memory. No significant difference was found between groups in scores scaled for age effects.

Apparatus

Apparatus and procedure, including analyses, are identical to those reported by Fielding et al., 2006. Horizontal displacement of the eye was recorded using an IRIS infrared eye tracking system, which has a resolution of >0.5°, with output sampled at 1kHz. Screen based stimuli were generated using E-Prime software and displayed on an LCD monitor. Data were analyzed off-line using interactive Matlab software. Participants were seated with their heads positioned on a stable chin rest directly in front of the screen. The stimulus display comprised a white centrally positioned fixation cross on a black background, flanked by two white boxes (53 × 53 mm) positioned such that their cen-

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Table 1. Clinical data for Parkinson's disease (PD) patients

Participant	Age (yrs)	Disease duration (yrs)	MMSE	BDI	DS (scaled)	UPDRS motor subscale	Medication
1	66	7	30	7.5	7	24	Levodopa/Carbidopa, Cabergoline
2	49	4	30	8	8	8	Cabergoline
3	59	10	28	10	11	2	Levodopa/Carbidopa Pergolide Mesylate
4	70	10	28	8	2	10	Levodopa/Benserazide Entacapone, Zolpidem tartrate
5	67	4	29	13	8	10	Cabergoline, Fluvoxamine
6	46	10.5	29	8	9	13	Levodopa/Carbidopa Entacapone, Domperidone Levodopa/Benserazide
7	70	1	30	12	14	29	Levodopa/Benserazide
8	54	17	30	4	14	11	Cabergoline
9	67	8	29	12	14	23	Levodopa/Carbidopa Benzhexol, Entacapone
10	70	2.5	30	7	15	16	Levodopa/Benserazide
11	75	7	26	7	10	27	Levodopa/Benserazide
12	58	15	25	13	10	N/Av	Levodopa/Carbidopa Domperidone, Amantadine Levodopa/Benserazide

Note. MMSE = Mini Mental State examination (max score 30); BDI = Beck Depression Inventory (0–9 = normal, 10–18 = mild-moderate, 19–29 = mod-severe, 30–63 = severe); DS = Digit Span (Wechsler Adult Intelligences Scale—scaled for age); UPDRS = Unified Parkinson's Disease Rating Scale (motor subscale); N/AV = not available

ters were 10° (115 mm) to either side of fixation with respect to the participant's dominant eye. Target stimuli were green crosses measuring 17 × 17 mm, which appeared in the centre of one of the two flanking boxes, or at center to signify the conclusion a trial. Output from the eye tracker was displayed alongside a control signal generated by E-Prime, which indicated stimulus change. A photodiode was placed directly over a non-visible portion of the screen to concurrently record stimulus change in real time.

Procedure

Ethics approval was granted by the North Western Behavioral and Psychiatric Research and Ethics Committee. All participants gave their informed consent prior to inclusion in the study, in accordance with the Helsinki declaration. All participants continued with their normal medication regime. Each was tested in a series of blocks of 52 trials, presented in a single session, using a modified version of the IOR paradigm described by Posner and Cohen (1984) (see Fig. 1). Appropriate breaks were provided to counter fatigue effects.

Participants were required to fixate upon the white fixation cross at the commencement of each trial, and to maintain fixation during presentation of a visual cue in either the left or right hemifield. This visual cue comprised displacement and altered luminance of one or both peripheral boxes for a period of 50 ms. Target presentation followed a further fixation period of 17, 100, 300, or 950 ms, resulting in effective stimulus onset asynchronies (SOAs) between cue and target of 67, 150, 350, and 1000 ms. Participants were instructed to make a saccade to the target as soon as it appeared, and to maintain fixation until it was extinguished. The target was presented for 2000 ms, after which time gaze was redirected to the center of the screen by the appearance of a green cross at the center of the screen for 1000 ms. The white fixation cross was then presented for a period of 1000 ms, signifying the onset of another trial.

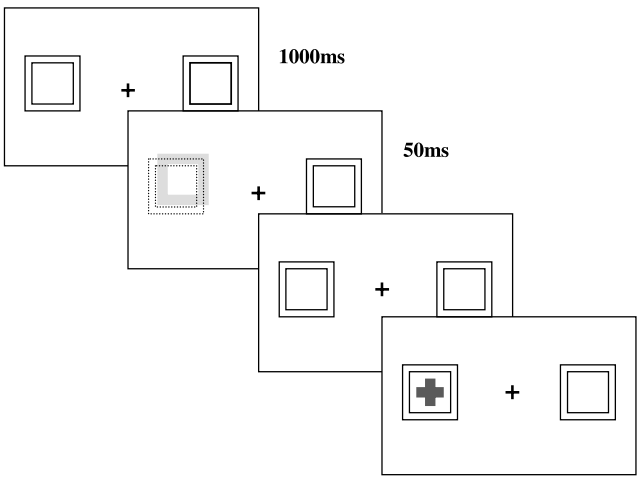

Fig. 1. Schematic diagram of a validly cued trial.

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Trial type was determined by the type of cue preceding target onset.

1. no-cue trial—target only
2. valid trial—comprised cue and target presented in the same hemifield
3. invalid trial—comprised cue and target presented in opposite hemifield
4. catch trial—presentation of a cue but no subsequent target, to reduce the likelihood of anticipatory responses.

Although neutral or bi-directional trials were presented to participants, these were not subsequently evaluated and so shall not be included for discussion.

Valid and invalid trials occurred with equal probability, ensuring that cues were unpredictive of subsequent target location. Trials were presented randomly in blocks of 52 trials (4 trials for each cued trial and 4 catch trials) until a statistically appropriate number of error-free responses were generated for each SOA/cue type combination (approximately 6.5 blocks, similar to our previous HD study). Because automatic trial replacement was not available to the experimenter, the number of trials presented for each subject was determined subjectively, by on-line visual inspection of performance.

Data Analysis

Saccadic latency was determined for each trial, reflecting the stimulus-saccadic response-time differential. Stimulus onset was calculated using a real-time trace of on-screen presentation (diode), and saccade onset using a position trace. Although ultimately determined manually for each trial and reflected in a visually evident departure from baseline, the beginning and the end of a saccade corresponded respectively to a peak and trough in acceleration of movement.

Trials excluded consisted of those that were corrupted by:

1. blinks,
2. poor fixation between cue and target presentation
3. erroneous responses to cue (>90 ms), prior to target presentation, irrespective of amplitude.

Poor fixation referred to inappropriate movement of the eye following cue onset, which (1) bears no directional relationship to the cue and (2) is generated within 90 msec following target presentation. This time constraint represents a physiologically impossible time course for a saccade to be generated to the target stimulus, and thus includes anticipations.

Trials exhibiting poor fixation were excluded from analysis of means and analyzed separately using a χ^2 for independence, to determine frequency as a proportion of total trials analyzed. Erroneous responses to the cue were also excluded and analyzed separately. The "distribution" of erroneous responses was analyzed using 2-way ANOVA with the between-subjects factor of Group (PD *vs* Control) and the within-subject factors of SOA (67, 150, 350, 1000 ms, and catch trials). Post-hoc ANOVA was also conducted for each SOA. Means and standard deviations were calculated for saccadic latencies over all remaining trials.

Average saccadic latencies for these remaining trials were submitted to 3-way ANOVA with the between-subjects factor Group (PD *vs* Controls), and the within-subject factors of cue (valid, invalid) and SOA (67, 150, 350, 1000 ms). Post-hoc ANOVA determined the effect of cue for each SOA. Cost/benefit analyses were performed deriving "benefit" of cueing scores by subtracting the average latencies of validly cued trials from no-cue trials prior to analysis, and deriving "costs" by subtracting latencies of no-cue trials from invalidly cued trials. These cost and benefit ANOVAs featured between-subjects factor Group (PD *vs* Controls), and within-subject factor SOA (67, 150, 350, 1000 ms). All post-hoc ANOVA or pair-wise analyses were adjusted for underestimation of error using Bonferroni type adjustments.

A series of Pearson's product moment correlations were also performed between UPDRS scores, as an indicator of disease severity, and a range of performance indices over all SOAs including proportion of erroneous responses and cueing effects.

RESULTS

A significantly larger proportion of trials were corrupted by anticipations or instances of poor fixation by PD patients (8.4%) compared to control subjects (3.2%), $\chi^2(1, n = 6038) = 70.44$, $p < .05$. PD patients also generated a significantly larger proportion of erroneous responses to the cue, or saccades to the cue (15.9%), than control subjects (9.0%), $\chi^2(1, n = 5674) = 61.82$, $p < .05$. ANOVA of distribution of erroneous responses to the cue (Group × SOA) revealed a main effect of SOA ($F(4,88) = 41.94$, $p < .05$). Proportionately fewer erroneous responses were made in response to trials with 67 ms SOAs ($M = 2.59$) and 150 ms SOAs ($M = 6.62$), than those with 350 ms and 1000 ms SOAs and catch trials ($M = 14.99$, 16.62, and 17.45 respectively). No differences were found overall in the proportion of erroneous responses to the cue made in response to trials with SOAs of 350 ms, 1000 ms, and catch trials.

A main effect of Group was also revealed, with PD patients generating significantly more erroneous responses to the cue overall (PD = 14.53, Controls = 8.78) $F(1,22) = 5.55$, $p < .05$, as well as a significant Group by SOA interaction ($F(4,88) = 4.84$, $p < .05$). Although the pattern of erroneous responses similar for both PD patients and controls, post-hoc ANOVA revealed significantly larger differences between groups for trials with 350 ms SOAs ($p < .05$) and 1000 ms SOAs ($p < .01$), with considerably larger, although non-significant differences found for catch trials. Thus the longer the SOA, the larger the differences found between groups, with PD patients generating progressively more erro-

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neous responses to the cue than controls over time. This finding forms the basis of the interaction reported earlier (see Fig. 2a), and contrasts with relatively normal inhibitory control found in patients with HD (see Fig. 2b).

Three-way ANOVA of mean saccadic latency (Group × SOA × Cue) revealed a main effect of cue, ($F(1,22) = 21.16$, $p < .001$), a main effect of SOA ($F(3,66) = 22.59$, $p < .001$), and a significant Cue × SOA interaction ($F(3,66) = 38.96$, $p < .001$). No significant group effects were revealed. Overall, latencies following valid cues were relatively shorter than those following invalid cues with 67 ms SOAs ($D = -2$ ms, $p < .001$), 150 ms SOAs ($D = -59$ ms, $p < .001$), and 350 ms SOAs ($D = -11$ms, $p > .05$). Post-hoc ANOVA of cue for each SOA revealed that IOR was clearly evident with 1000 msec SOAs, with valid cues resulting in relatively longer latencies than invalid cues ($D = 48$ ms, $p < .001$). This difference failed to reach significance with 350 ms SOAs, approximating the crossover region between facilitation and inhibition (IOR) for both groups (see Fig. 3a). This contrasts with results by HD patients, which demonstrated onset of IOR as early as 150 ms (see Fig. 3b).

Two-way ANOVA of *cost* (invalid cue minus no cue) revealed a main effect of SOA ($F(3,66) = 5.65$, $p < .001$), although no main effect of Group, and no Group/SOA interaction. Saccadic latencies following invalid cues were elevated over all SOAs relative to the no-cue condition. However, pair-wise SOA comparisons revealed significant differences between trials with SOAs of 350 ms and 1000 ms ($p < .001$), with the latency differential (effect of an invalid cue) greatest at 350 ms SOAs.

Although a 2-way ANOVA of *benefit* (no cue minus valid cue) showed no main effect of Group, a main effect of SOA ($F(3,66) = 55.05$, $p < .001$) and a significant Group × SOA interaction ($F(3,66) = 2.89$, $p < .05$) were revealed. Pair-wise SOA comparisons revealed that the "benefit" of cueing following 67 ms and 150 ms SOA trials was comparable ($p > .05$), although "smaller" for both 350 ms and 1000 ms SOA trials ($p < .05$).

Fig. 4a and b demonstrate that for control subjects, all cued trials resulted in increased response times relative to the provision of no cue, with the larger the SOA, the longer the response time. However, for PD patients this relative increase in response times following a visual cue applied only to 350 ms and 1000 ms SOA trials. At 150 ms SOAs, response times were almost identical to those demonstrated using no prior cue, and for 67 ms SOAs response times were actually quicker, relative to the provision of no cue;

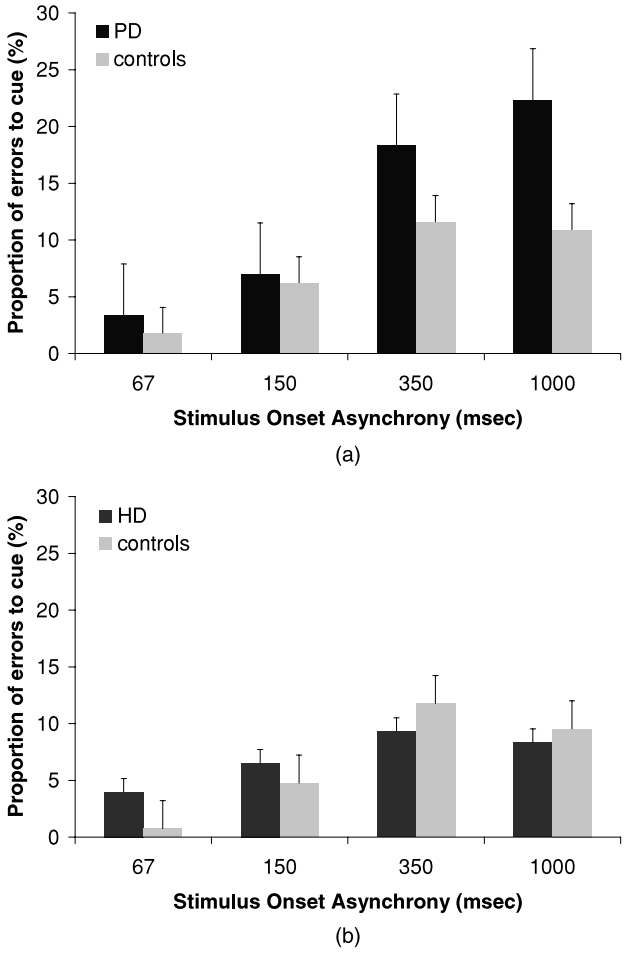

Fig. 2. a, b. Erroneous responses to the cue as a proportion of total trials, for PD and HD patients.

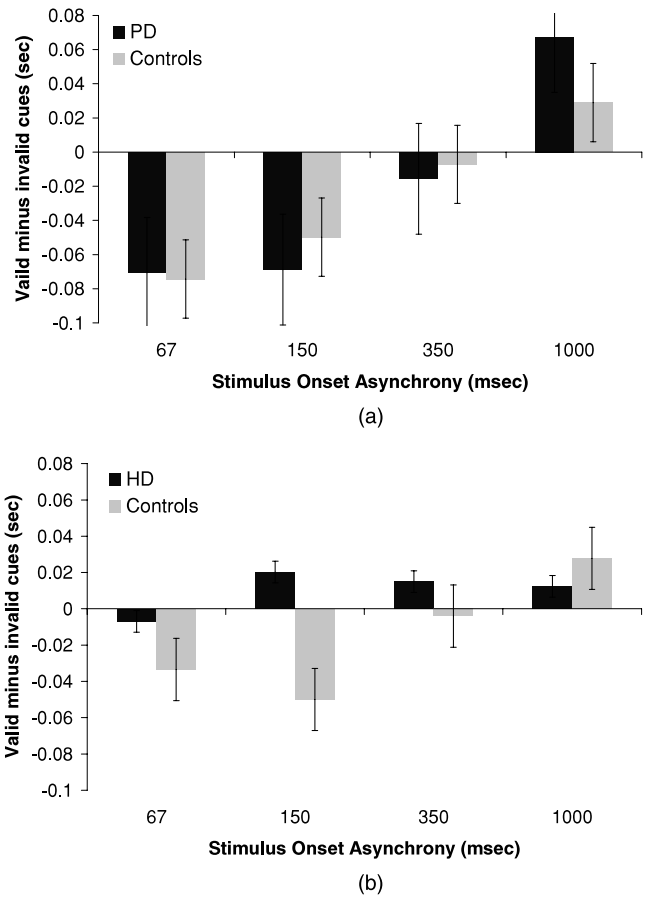

Fig. 3. a, b. Latencies for valid minus invalid cues for PD and HD patients.

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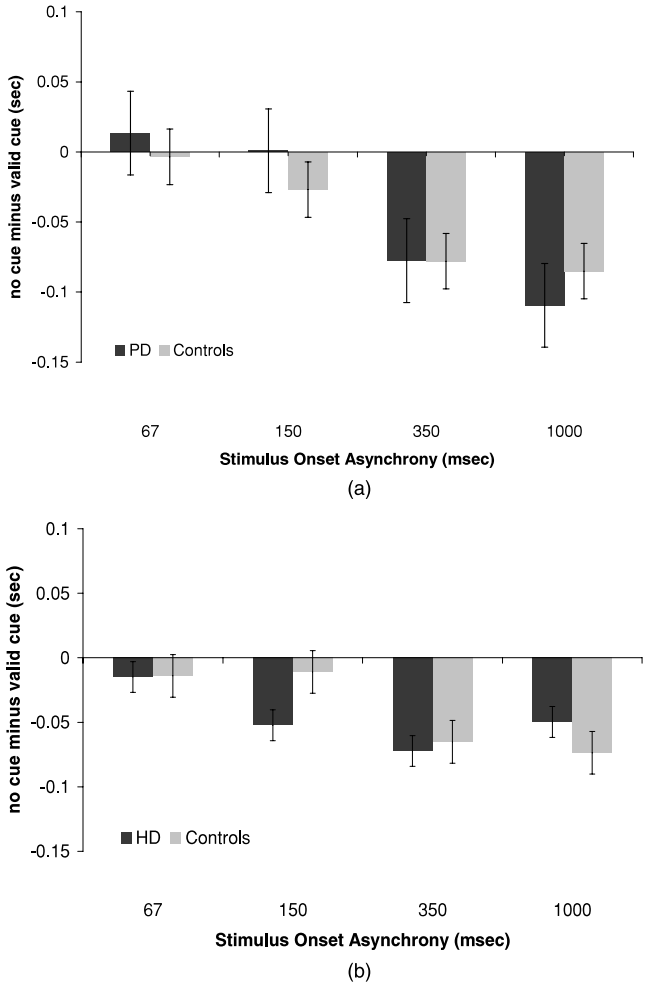

Fig. 4. a, b. Benefit of valid cueing for PD and HD patients.

suggesting hyper-reflexivity or rapid disengagement of attention in PD. Further, the benefit of a value cue was clearly evident for HD subjects by 150 msec, unlike control subjects, where significant increases were only evident over 350 msec.

DISCUSSION

This study used a non-predictive peripheral cueing paradigm to evaluate visuospatial deficits in patients with PD. Specifically, it sought to investigate the effect of attentional manipulation using a saccadic paradigm, by presenting spatially valid and invalid visual cues over a range of SOAs. Results are compared and contrasted to those from a previously published study with HD patients. Although PD patients exhibited poor fixation prior to target presentation, similar to those with HD, they also responded erroneously to cue stimuli more frequently than control subjects, unlike HD patients. Whereas accelerated onset of IOR has been reported in HD, cueing effects were comparable for PD and control subjects. However, disinhibition of stimulus-driven, or automatic responses resulting in hyper-reflexivity at short SOAs, was also revealed in PD, which we attribute to the presentation of a spatially valid cue.

The pivotal role of the SC in both the representation of IOR and saccade programming has been identified by a range of studies, as discussed. Importantly this structure shares anatomical and functional links with the BG and is subject to inhibitory modulation by the BG output structure SNr (Hikosaka et al., 2000). Because PD and HD chiefly compromise BG output, these results may well reflect impaired modulation of activity over the SC motor map, where the direction and amplitude of any saccade is a direct function of the site of stimulation (Munoz & Wurtz, 1993, 1995). Importantly, this cueing task evokes facilitation and inhibition of a response, each representing dynamically interacting functions that activate a host of cortical regions, both in a bottom-up stimulus driven manner and in top-down signals from cortex. Whereas the sudden appearance of a cue stimulus transiently increases activity in sensory and motor SC regions, the shaping of an independent motor plan, consistent with the required movement, recruits projections from not only the SNr but cortical regions including the FEF, posterior parietal cortex (PPC), and striate cortex (V1) (Corbetta et al., 2002; Munoz, 2002; Munoz & Istvan, 1998).

Several studies propose an anterior processing stream, which appears to constitute the basis for intentional action selection (Corbetta et al., 2000; Gitelman et al., 1999; Hopfinger et al., 2000; Kastner & Pinsk, 2004; Nobre et al., 1997; Perry & Zeki, 2000; Wojciulik & Kanwisher, 1999). Frontal and (pre)frontal regions, incorporating the anterior cingulate gyrus and supplementary and frontal eye fields (Kaneko, 1996), may project a context-dependent feedback signal backwards to the PPC inhibiting automatic capture of attention and subsequent motor activation (Small et al., 2003). A second network, incorporating a range of frontal and parietal regions, is activated only when a response is made to stimuli that appear in inhibited locations (Mayer et al., 2004). Notably, these networks are consistent with those implicated in oculomotor control and proposed attentional networks. Activation of the superior parietal lobe, anterior cingulate, and thalamus accords with regions traditionally associated with shifting, engaging and response preparation operations of attention (Mesulam et al., 2001; Posner & Petersen, 1990). Similarly, the involvement of the posterior parietal lobe and superior and middle temporal gyri corresponds with a number of studies, which suggest that these regions mediate maintenance and shifting of attention (Corbetta et al., 2000; Friedrich et al., 1998; Gitelman et al., 1999; Hopfinger et al., 2000). Post and pre-central gyrus and occipital lobes, also activated, are traditional visual and motor areas responsible for the exploratory component of visuospatial attention (Gitelman et al., 1999) and target response (Hopfinger et al., 2000).

The IOR phenomenon appears to reflect the precedence of inhibitory activity over the SC motor map encoding the overlapping cue and target region. In HD, it was suggested that accelerated onset of IOR may reflect either premature

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disengagement of activity from a non-informative cue location (distractibility) or perseveration of attention set, a function of the requirement to inhibit a response to cue stimuli (Fielding et al., 2006). Presumably inhibitory activity is derived cortically, *via* the aforementioned networks. However, PD patients demonstrated relatively normal onset of IOR. As predicted by the IOR phenomenon, valid cues resulted in shorter saccadic latencies to subsequent targets than invalid cues with SOAs of 67, 150, or 350 ms but longer saccadic latencies at SOAs of 1000 ms.

Relative to *un-cued* visually guided saccades, saccadic latencies following presentation of invalid cues were relatively consistent over time and between groups. However, saccadic latencies following presentation of *valid* cues reveal differences both over time (SOA) and group. For control subjects, all validly cued trials resulted in increased response times relative to the provision of no cue, with the larger the SOA, the longer the response time. This may represent a build up of IOR. For PD patients, the relative increase in response times following presentation of a valid cue applied only to the longer SOA trials. At 150 ms SOAs, PD response times were almost identical to uncued visually guided saccades and for 67 ms SOAs response times were actually quicker, relative to the provision of no cue. This finding suggests hyper-reflexivity in PD, with visual cues seemingly accelerating subsequent sensory-motor transformations over short periods of time (i.e., 67 and 150 ms). This is consistent with a growing number of studies, including that of Briand et al. (2001), highlighting the significance of inhibitory dysfunction in PD and represents an important feature of voluntary control over behavior.

Inhibitory mechanisms, represented over the SC motor map, would normally prevent direct visuomotor execution in response to the cue stimulus, with overrepresentation, as suggested in HD, resulted in accelerated onset of IOR. In PD, impaired inhibitory mechanisms are likely to result in greater activation of saccadic neurons, bringing them closer to threshold than in neurologically healthy individuals. Target related activity, represented neurally by an overlapping population of neurons with the cue, is already close to threshold for release at short SOAs. Thus a saccade to the target may be initiated more quickly. Hyperactive attentional orienting may even underlie motor symptoms such as freezing, with attention conceivably captured by the edges of a doorway. More strongly affected by task-irrelevant spatial properties of stimuli, patients benefit from visual cues over various movement tasks.

These results enable differentiation, temporally, of the effects of valid *versus* invalid cues and suggest that the IOR phenomenon may be most closely related to either declining response preparation or increasing inhibition to a valid cue. However, even though our hypothesis of delayed onset of IOR in PD was not supported, the exact time course of this phenomenon could not be determined for either PD patients or control subjects. Theoretically for both groups it could be anywhere between 350 ms and 1000 ms. Certainly previous investigations of the effect of spatial cueing in PD lack consistency in task presentation, and the impact that numerous task-related features have on the time course of features like initial facilitation and IOR, may explain discrepant results. The time course of facilitation and inhibition following valid cues, in particular, remains uncertain and worthy of further investigation if we are to fully understand the role of the BG in this phenomenon.

Significantly, unlike HD patients, PD patients generated a larger proportion of erroneous responses to the cue, prior to the onset of the target. Although for both PD patients and control subjects longer SOAs resulted in proportionately more of these errors than shorter SOAs, PD patients generated progressively more errors than controls with longer SOAs. Thus the reduction in the inhibitory function of the BG appears to manifest in a temporal decay, with patients experiencing difficulty maintaining a suitable level of activation of pause neurons to keep competing motor neuron activation below threshold. Certainly inappropriate responses to irrelevant stimuli have been demonstrated previously in PD (Oostenveld et al., 2001), with enhanced attention-related potentials above motor cortex believed to reflect poor inhibition of direct, stimulus-driven visuomotor activation. This is consistent with results in HD, which suggest that cortical inhibitory mechanisms are not subject to this decay and reflect the opposite nature of dysfunction in PD and HD.

Finally, for both PD and HD patients, a significantly larger proportion of trials were corrupted by anticipations or instances of poor fixation, relative to trials preceded by appropriate fixation, 8.4% and 7.1%, respectively. In HD, it was proposed that the disinhibition of BG activity may result in difficulty gating extraneous noise over the SC motor map and the subsequent generation of unwanted saccades. This is consistent with irrelevant saccadic intrusions reported by other authors (Lasker & Zee, 1997; Leigh et al., 1983). Clearly, this is ameliorated by the added inhibitory input by cortex with the establishment and implementation of attentional set, where task demands require screening of spatially defined stimuli. However, in PD, steady fixation is often disrupted by saccadic intrusions or square wave jerks (Rascol et al., 1991; White et al., 1983). Hafed and Clark (2002) provide an interesting account of the possible link between microsaccades, including square wave jerks, which occur during gaze fixation and covert shifts of attention (Hafed & Clark, 2002). They propose that square wave jerks may be a result of subliminal activation of the ocular motor system, reflecting attention shifts to a visual cue and back to fixation. In PD, deterioration of the dopaminergic nigro-striatal system compromises the role of the BG in sufficiently inhibiting extraneous saccades by a reduction in strength of excitatory signals projecting to pause neurons, which must be silenced to prevent spurious burst activity (Armstrong et al., 2002). The constant presentation of peripheral stimuli throughout this paradigm potentially provides a source of distraction, thereby exacerbating attentional capture, even in the absence of a relevant visual target. Maintaining attention, as previously mentioned, is invari-

ably compromised in PD (Bradshaw et al., 1993; Filoteo et al., 1994; Filoteo et al., 1997; Pollux & Robertson, 2001; Wright et al., 1990; Yamaguchi & Kobayashi, 1998).

In summary, the altered inhibitory output of the BG in both PD and HD resulted in two distinct deficit profiles. Whereas disinhibition of BG activity in HD manifested in the relative early precedence of cortical inhibitory activity (accelerated onset of IOR) and appropriate screening out of non-target stimuli (Fielding et al., 2006), reduced BG output in PD resulted in hyper-reflexivity and difficulty withholding an erroneous response to non-target stimuli. These contrasting deficits, in disorders which are simplistically opposite in terms of BG dysfunction, have the potential to inform us about the quality of control of more reflexive behaviours by the BG, particularly where both facilitatory and inhibitory processes vie for dominance.

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REFERENCES

Armstrong, I.T., Chan, F., Riopelle, R.J., & Munoz, D.P. (2002). Control of saccades in Parkinson's disease. *Brain and Cognition*, *49*, 198–201.

Beck, A. & Steer, R.A. (1991). *The Beck Depression Inventory (Manual)*. New York: Psychological Corporation.

Beck, A., Ward, C., Mendelson, M., Mock, J., & Erbaugh, J. (1961). An inventory for measuring depression. *Archives of General Psychiatry*, *4*, 53–63.

Bradshaw, J., Waterfall, M.L., Phillips, J.G., Iansek, R., Mattingley, J.L., & Bradshaw, J.A. (1993). Re-orientation of attention in Parkinson's disease: An extension to the vibrotactile modality. *Neuropsychologia*, *31*, 51–66.

Briand, K.A., Hening, W., Poizner, H., & Sereno, A.B. (2001). Automatic orienting of visuospatial attention in Parkinson's disease. *Neuropsychologia*, *39*, 1240–1249.

Brown, D.L. & Marsden, C.D. (1990). Cognitive function in Parkinson's disease: From description to theory. *Trends in Neuroscience*, *13*, 21–28.

Corbetta, M., Akbudak, E., Conturo, T.E., Snyder, A.Z., Ollinger, J.M., Drury, H.A., Linenweber, M.R., Petersen, S.E., Raichle, M.E., Van Essen, D.C., & Shulman, G.L. (1998). A common network of functional areas for attention and eye movements. *Neuron*, *21*, 761–773.

Corbetta, M., Kincade, J.M., Ollinger, J.M., McAvoy, M.P., & Shulman, G.L. (2000). Voluntary orienting is dissociated from target detection in human posterior parietal cortex. *Nature Neuroscience*, *3*, 292–297.

Corbetta, M., Kincade, J.M., & Shulman, G.L. (2002). Neural systems for visual orienting and their relationships to spatial working memory. *Journal of Cognitive Neuroscience*, *14*, 508–523.

Crawford, T.J., Bennett, D., Lekwuwa, G.U., Shaunak, S., & Deakin, J.F.W. (2002). Cognition and the inhibitory control of saccades in schizophrenia and Parkinson's disease. *Progress in Brain Research*, *140*, 449–466.

Crevits, L. & De Ridder, K. (1997). Disturbed striatoprefrontal mediated visual behaviour in moderate to severe parkinsonian patients. *Journal of Neurology, Neurosurgery and Psychiatry*, *63*, 296–299.

Danziger, S., Fendrich, R., & Rafal, R.D. (1997). Inhibitory tagging of locations in the blind field of hemianopic patients. *Consciousness and Cognition*, *6*, 291–307.

Dorris, M.C., Klein, C., Everling, S., & Munoz, D.P. (2002). Contribution of the primate superior colliculus to inhibition of return. *Journal of Cognitive Neuroscience*, *14*, 1256–1263.

Fielding, J., Georgiou-Karistianis, N., Bradshaw, J., Millist, L., Churchyard, A., & White, O. (2006). Accelerated time-course of inhibition of return in Huntington's disease. *Behavioural Brain Research*, *166*, 211–219.

Filoteo, J.V., Delis, D.C., Demadura, T., Salmon, D.P., Roman, M.J., & Shults, C.W. (1994). Abnormally rapid disengagement of attention to global and local stimulus levels may underlie the visuoperceptual impairments in Parkinson's patients. *Neuropsychology*, *8*, 210–217.

Filoteo, J.V., Delis, D.C., Salmon, D.P., Demadura, T., Roman, M.J., & Schults, C.W. (1997). An examination of the nature of attentional deficits in patients with Parkinson's disease: Evidence from a spatial orienting task. *Journal of the International Neuropsychological Society*, *3*, 337–347.

Folstein, M.F., Folstein, S.E., & McHugh, P.R. (1975). Mini-Mental State. A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, *12*, 189–198.

Friedrich, F.J., Beck, D., Egly, R., & Rafal, R.D. (1998). Spatial attention deficits in humans: A comparison of superior parietal and temporo-parietal junction lesions. *Neuropsychology*, *12*, 193–207.

Fuentes, L.J. (2004). Inhibitory processing in the attentional networks. In M.I. Posner (Ed.), *Cognitive Neuroscience of Attention*, (pp. 45–55). New York: Guilford Press.

Georgiou, N., Bradshaw, J.L., Phillips, J.G., Bradshaw, J.A., & Chiu, E. (1995). The Simon effect and attention deficits in Gilles de la Tourette's syndrome and Huntington's disease. *Brain*, *118*(Pt 5), 1305–1318.

Georgiou, N., Bradshaw, J.L., Phillips, J.G., & Chiu, E. (1996). The effect of Huntington's disease and Gilles de la Tourette's syndrome on the ability to hold and shift attention. *Neuropsychologia*, *34*, 843–851.

Gitelman, D., Nobre, A.C., Parrish, T.B., LaBar, K.S., Kim, Y.H., Meyer, J.R., & Mesulam, M. (1999). A large-scale distributed network for covert spatial attention: Further anatomical delineation based on stringent behavioural and cognitive controls. *Brain*, *122*, 1093–1106.

Hafed, Z.M. & Clark, J.J. (2002). Microsaccades as an overt measure of covert attention shifts. *Vision Research*, *42*, 2533–2545.

Hikosaka, O., Matsumura, M., Kojima, J., & Gardiner, T.W. (1993). Role of basal ganglia in initiation and suppression of saccadic eye movements. In N. Mano, I. Hamada & M.R. DeLong (Eds.), *Role of the Cerebellum and the Basal Ganglia in Voluntary Movement*, (pp. 213–219). Amsterdam: Excerpta Medica.

Hikosaka, O., Takikawa, Y., & Kawagoe, R. (2000). Role of the basal ganglia in the control of purposive saccadic eye movements. *Physiological Reviews*, *80*, 953–978.

Hopfinger, J.B., Buonocore, M.H., & Mangun, G.R. (2000). The neural mechanisms of top-down attentional control. *Nature Neuroscience*, *3*, 284–291.

Ivory, S.J., Knight, R.G., Longmore, B.E., & Caradoc-Davies, T. (1999). Verbal memory in non-demented patients with idiopathic Parkinson's disease. *Neuropsychologia*, *37*, 817–828.

Josiassen, R.C., Curry, L.M., & Mancall, E.L. (1983). Development of neuropsychological deficits in Huntington's disease. *Archives of Neurology*, *40*, 791–796.

Kaneko, C.R.S. (1996). Effect of obotenic acid lesions of the omnipause neurons on saccadic eye movements in rhesus macaques. *Journal of Neurophysiology*, *75*, 2229–2242.

Kastner, S. & Pinsk, M.A. (2004). Visual attention as a multilevel selection process. *Cognitive, Affective, and Behavioral Neuroscience*, *4*, 483–500.

Kingstone, A., Klein, R.M., Morein-Zamir, S., Hunt, A., Fisk, J., & Maxner, C. (2002). Orienting attention in aging and Parkinson's disease: Distinguishing modes of control. *Journal of Clinical & Experimental Neuropsychology*, *24*, 951–967.

Klein, R.M. (1988). Inhibitory tagging system facilitates visual search. *Nature*, *334*, 430–431.

Kustov, A.A. & Robinson, D.L. (1996). Shared neural control of attentional shifts and eye movements. *Nature*, *384*, 74–77.

Lasker, A.G. & Zee, D.S. (1997). Ocular motor abnormalities in Huntington's disease. *Vision Research*, *37*, 3639–3645.

Lawrence, A.D., Sahakian, B.J., Hodges, J.R., Rosser, A.E., Lange, K.W., & Robbins, T.W. (1996). Executive and mnemonic functions in early Huntington's disease. *Brain*, *119*, 1633–1645.

Leigh, R.J., Newman, S.A., Folstein, S.E., Lasker, A.G., & Jensen, B.A. (1983). Abnormal ocular motor control in Huntington's disease. *Neurology*, *33*, 1268–1275.

Marsden, C.D. (1984). The pathophysiology of movement disorders. *Neurologic Clinics*, *2*, 435–459.

Mayer, A.R., Seidenberg, M., Dorflinger, J.M., & Rao, S.C. (2004). Event-related fMRI study of exogenous orienting: Supporting evidence for the cortical basis of inhibition of return. *Journal of Cognitive Neuroscience*, *161*, 262–1271.

McAuley, J.H. (2003). The physiological basis of clinical deficits in Parkinson's disease. *Progress in Neurobiology*, *69*, 27–48.

McPherson, S. & Cummings, J.L. (1996). Neuropsychological aspects of Parkinson's disease and parkinsonism. In I. Grant & K.M. Adams (Eds.), *Neuropsychological aspects of neuropsychological disorders*, (pp. 288–311). New York: Oxford University Press.

Mesulam, M., Nobre, A.C., Kim, Y.H., Parrish, T.B., & Gitelman, D.R. (2001). Heterogeneity of cingulate contributions to spatial attention. *NeuroImage*, *13*, 1065–1072.

Muller, C., Wenger, S., Fertl, L., & E., A. (1994). Initiation of visual-guided random saccades in parkinsonian patients with severe motor fluctuations. *Journal of Neural Transmission*, *7*, 101–108.

Munoz, D.P. (2002). Saccadic eye movements: Overview of neural circuitry. *Progress in Brain Research*, *140*, 89–96.

Munoz, D.P. & Istvan, P.J. (1998). Lateral inhibitory interactions in the intermediate layers of the monkey superior colliculus. *Journal of Neurophysiology*, *79*, 1193–1209.

Munoz, D.P. & Wurtz, R.H. (1993). Fixation cells in monkey superior colliculus. II. Reversible activation and deactivation. *Journal of Neurophysiology*, *70*, 576–589.

Munoz, D.P. & Wurtz, R.H. (1995). Saccade-related activity in monkey superior colliculus. I. Characteristics of burst and buildup cells. *Journal of Neurophysiology*, *73*, 2313–2333.

Nobre, A., Sebestyen, G.N., Gitelman, D.R., Mesulam, M., Frackowiak, R.S., & Frith, C. (1997). Functional localisation of the system for visuospatial attention using positron emission tomography. *Brain*, *120*, 515–533.

Oostenveld, R., Praamstra, P., Stegeman, D.F., & Van Oosterom, A. (2001). Overlap of attention and movement-related activity in lateralised event-related brain potentials. *Clinical Neurophysiology*, *112*, 477–484.

Perry, R.J. & Zeki, S. (2000). The neurology of saccades and covert shifts in spatial attention: An event-related fMRI study. *Brain*, *123*, 2273–2288.

Poliakoff, E., O'Boyle, D.J., Moore, A.P., McGlone, F.P., Cody, F.W.J., & Spence, C. (2003). Orienting of attention and Parkinson's disease: Tactile inhibition of return and response inhibition. *Brain*, *126*(Pt 9), 2081–2092.

Pollux, P.M. & Robertson, C. (2001). Voluntary and automatic visual spatial shifts of attention in Parkinson's disease: An analysis of costs and benefits. *Journal of Clinical & Experimental Neuropsychology*, *23*, 662–670.

Posner, M.I. (1980). Orienting of attention. *Quarterly Journal of Experimental Psychology*, *32*, 3–25.

Posner, M.I. & Cohen, Y. (1984). Components of visual orienting. In H. Bouma & D.G. Bouwhuis (Eds.), *Attention and Performance*. New Jersey: Erlbaum.

Posner, M.I. & Petersen, S.E. (1990). The attention system of the human brain. *Annual Review of Neuroscience*, *13*, 25–42.

Posner, M.I., Rafal, R.D., Choate, L.S., & Vaughan, J. (1985). Inhibition of return: Neural basis and function. *Cognitive Neuropsychology*, *2*, 211–228.

Rafal, R.D., Posner, M.I., Friedman, H.H., Inhoff, A.W., & Bernstein, E. (1988). Orienting of visual attention in progressive supranuclear palsy. *Brain*, *111*, 267–280.

Rascol, O., Clanet, M., Montastruc, J.L., Simonetta, M., Soulier-Esteve, M.J., Doyon, B., & Rascol, A. (1989). Abnormal ocular movements in Parkinson's disease: Evidence for involvement of dopaminergic systems. *Brain*, *112*, 1193–1214.

Rascol, O., Sabatini, U., Simonetta-Moreau, M., Montastruc, J.L., Rascol, A., & Clanet, M. (1991). Square wave jerks in Parkinsonian syndromes. *Journal of Neurology, Neurosurgery and Psychiatry*, *54*, 599–602.

Ro, T., Farne, A. & Chang, E. (2003). Inhibition of return and the human frontal eye fields. *Experimental Brain Research*, *150*, 290–296.

Rottach, K.G., Riley, D.E., DiScenna, A.O., Zivotofsky, A.Z., & Leigh, J.R. (1996). Dynamic properties of horizontal and vertical eye movements in parkinsonian syndromes. *Annals of Neurology*, *39*, 368–377.

Sapir, A., Soroker, N., Berger, A., & Nenik, A. (1999). Inhibition of return in spatial attention: Direct evidence for collicular generation. *Nature Neuroscience*, *2*, 1053–1054.

Schrag, A., Jahanshahi, M., & Quin, N. (2000). What contributes to quality of life in patients with Parkinson's disease. *Journal of Neurology Neurosurgery and Psychiatry*, *69*, 308–312.

Seiss, E. & Praamstra, P. (2004). The basal ganglia and inhibitory mechanisms in response selection: Evidence from subliminal priming of motor responses in Parkinson's disease. *Brain*, *127*, 330–339.

Shoulson, I. (1990). Huntington's disease: Cognitive and psychi-

atric features. *Neuropsychiatry, Neuropsychology, and Behavioural Neurology*, *3*, 15–22.

Small, D.M., Gitelman, D.R., Gregory, M.D., Nobre, A.C., Parrish, T.B., & Mesulam, M. (2003). The posterior cingulate and medial prefrontal cortex mediate the anticipatory allocation of spatial attention. *NeuroImage*, *18*, 633–641.

Sparks, D.L. & Hartwich-Young, R. (1989). The deep layers of the superior colliculus. In R.H. Wurtz & M.E. Goldberg (Eds.), *The Neurobiology of Saccadic Eye Movements*, Vol. 89 (pp. 213–255). Amsterdam: Elsevier.

Spence, C., Lloyd, D., McGlone, F.P., Nicholls, M.E., & Driver, J. (2000). Inhibition of return is supramodal: A demonstration between all possible pairings of vision, touch, and audition. *Experiment Brain Research*, *134*, 42–48.

Sprengelmeyer, R., Lange, H., & Homberg, V. (1995). The pattern of attentional deficits in Huntington's disease. *Brain*, *118*, 145–152.

Tassinari, G., Aglioti, S., Chelazzi, L., Marzi, C.A., & Berlucchi, G. (1987). Distribution in the visual field of the costs of voluntarily allocated attention and of the inhibitory after-effects of covert orienting. *Neuropsychologia*, *25*, 55–71.

Taylor, T.L. & Klein, R.M. (1998). On the causes and effects of inhibition of return. *Psychonomic Bulletin & Review*, *5*, 625–643.

Tipper, S.P., Howard, L.A., & Jackson, S.J. (1997). Selective reaching to grasp: Evidence for distractor interference effects. *Vision and Cognition*, *4*, 1–38.

Tipper, S.P. & Weaver, B. (1998). The medium of attention: Location-based, object-centred, or scene-based? In R.D. Wright (Ed.), *Visual Attention*, (pp. 77–107). New York: Oxford University Press.

Vonsattel, J.P. (1999). Huntington's disease neuropathology. In A.B. Joseph & R.R. Young (Eds.), *Movement Disorders in Neurology and Neuropsychiatry*, (pp. 161–170). Massachusetts: Blackwell Science, Inc.

Wascher, E. & Tipper, S.P. (2004). Revealing effects of noninformative spatial cues: An EEG study of inhibition of return. *Psychophysiology*, *41*, 716–728.

Wechsler, D. (1955). *Wechsler Adult Intelligence Scale Manual*. New York: Psychological Corp.

White, O.B., Saint-Cyr, J.A., & Sharpe, J.A. (1983). Ocular motor deficits in Parkinson's disease. II. Control of the saccadic and smooth pursuit systems. *Brain*, *106*, 571–587.

Wojciulik, E. & Kanwisher, N.G. (1999). The generality of parietal involvement in visual attention. *Neuron*, *23*, 747–764.

Wright, M.J., Burns, R.J., Geffen, G.M., & Geffen, L.B. (1990). Covert orientation of visual attention in Parkinson's disease: An impairment in the maintenance of attention. *Neuropsychologia*, *28*, 151–159.

Yamaguchi, S. & Kobayashi, S. (1998). Contributions of the dopaminergic system to voluntary and automatic orienting of visuospatial attention. *Journal of Neuroscience*, *18*, 1869–1878.