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Space-based but not object-based inhibition of return is impaired in Parkinson's disease

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ABSTRACT

Impairments in certain aspects of attention have frequently been reported in Parkinson's disease (PD), including reduced inhibition of return (IOR). Recent evidence suggests that IOR can occur when attention is directed at objects or locations, but previous investigations of IOR in PD have not systematically compared these two frames of reference. The present study compared the performance of 18 nondemented patients with PD and 18 normal controls on an IOR task with two conditions. In the "object-present" condition, objects surrounded the cues and targets so that attention was cued to both a spatial location and to a specific object. In the "object-absent" condition, surrounding objects were not presented so that attention was cued only to a spatial location. When participants had to rely on space-based cues, PD patients demonstrated reduced IOR compared to controls. In contrast, when objects were present in the display and participants could use object-based cues, PD patients exhibited normal IOR. These results suggest that PD patients are impaired in inhibitory aspects of space-based attention, but are able to overcome this impairment when their attention can be directed at object-based frames of reference. This dissociation supports the view that space-based and object-based components of attention involve distinct neurocognitive processes.

Idiopathic Parkinson's disease (PD) is a progressive neurological illness defined clinically by motor symptoms that include resting tremor, bradykinesia, rigidity, and postural instability. Neuropathologically the disease is characterized by the loss of dopamine-producing cells of the substantia nigra pars compacta that project to the striatum (Agid, 1991). Cognitive impairment often occurs in PD, although only a subset of patients has dementia. In the usual case, patients with PD exhibit relatively subtle and circumscribed cognitive impairment that involves aspects of attention (Salmon & Filoteo, 2007). In particular, it has been suggested that these patients have an attention deficit that is mediated by impaired inhibitory processes (Filoteo, Rilling, & Strayer, 2002). Although nondemented PD patients often perform similarly to neurologically healthy individuals on tests that require the facilitatory aspects of orienting (Bennett, Waterman, Scarpa, & Castiello, 1995; Goldman, Baty, Buckles, Sahrmann, & Morris, 1998), they frequently are impaired when conditions promote a conflict between task-relevant and irrelevant information, such as on tests of selective attention (Filoteo, Maddox, Ing, & Song, 2007), negative priming (Mari-Beffa, Hayes, Machado, & Hindle, 2005), and set shifting (Downes et al., 1989). It should be noted, however, that PD patients can perform normally on some attention tasks that require inhibition (Grande et al., 2006; Possin, Cagigas, Strayer, & Filoteo, 2006).

Inconsistent findings regarding deficits in inhibitory aspects of attention may reflect differences in the impact of PD on object-based and space-based attention. A number of studies using space-based attention tasks have identified altered inhibitory processes in PD (Filoteo et al., 1997, 2002; Gurvich, Georgiou-Karistianis, Fitzgerald, Millist, & White, 2007; Hsieh, Lee, Hwang, & Tsai, 1997; Wright, Burns, Geffen, & Geffen, 1990; Wylie & Stout, 2002), whereas other studies using object-based tasks show normal inhibition of attention in these patients (Lee, Wild, Hollnagel, & Grafman, 1999; Possin et al., 2006). This selective deficit in attention is similar to the selective deficits PD patients display on tests of spatial working memory as compared to tests of object working memory (Owen, Iddon, Hodges, Summers, & Robbins, 1997; Possin, Filoteo, Song & Salmon, 2008; Postle, Jonides, Smith, Corkin, & Growdon, 1997). However, no study has directly compared inhibitory aspects of space-based and object-based attention in the same PD patients.

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A phenomenon that might be well-suited for comparing inhibitory processes in space-based and object-based attention in patients with PD is "inhibition of return" (IOR). Typically, when a person's visual attention is cued to a location in the periphery, stimuli in that location enjoy an immediate processing advantage over stimuli presented in other locations in the visual field. However, stimuli at the cued location are at a processing disadvantage if more than 300 ms elapses following the cue, presumably because attention has moved away and is inhibited from returning to the cued location (Maylor & Hockey, 1985; Posner & Cohen, 1984; Tipper, Driver, & Weaver, 1991). Because this 'IOR' biases attention away from previously attended locations in favor of novel locations (Klein, 2000), it is thought to be an essential component of efficient visual search (Posner & Cohen, 1984). If attention constantly returned to previously examined locations the search process would breakdown.

The original evidence for IOR comes from a simple cueing task developed by Posner and Cohen (1984). A cue, in this case a brief increase in luminance at the cued location, is presented in one of two squares that are located equidistant from a central fixation point. Although the cue does not predict the location of the subsequent target and participants are instructed to ignore it, attention is automatically drawn there. Following the cue, attention is brought back to fixation by increasing the luminance of the fixation point. Next, a target is presented either in the cued square or the uncued square. When there is at least 300 ms between the offset of the cue and the onset of the target, detection of the target is slower when it is presented in the cued square as compared to the uncued square. This difference in detection time is thought to reflect IOR of attention within a space-based frame of reference (i.e., where the cue is located in space).

Subsequent studies with neurologically healthy individuals have shown that IOR also occurs when attention is mediated by object-based frames of reference (i.e., which object is associated with the location of the cue; Abrams & Dobkin, 1994; Jordan & Tipper, 1998, 1999; Leek, Reppa, & Tipper, 2003; List & Robertson, 2007; Tipper et al., 1991; Tipper, Jordan, & Weaver, 1999; Tipper, Weaver, Jerreat, & Burak, 1994; Weaver, Lupianez, & Watson, 1998). For example, attention is inhibited from returning to a cued object even if the object moves to a new location (Tipper et al., 1991), IOR is greater to a location when irrelevant objects surround cues and targets than when objects are absent from the display, and inhibition can spread across an object's surface to a non-cued location (Jordan & Tipper, 1999; Leek et al., 2003).

Previous studies of IOR in patients with PD have shown both reduced (Filoteo et al., 1997; Poliakoff et al., 2003; Yamaguchi & Kobayashi, 1998) and normal IOR (Briand, Hening, Poizner, & Sereno, 2001; Fielding, Georgiou-Karistianis, & White, 2006; Grande et al., 2006), but all of these studies confounded space-based and object-based attention by presenting cues and targets within squares. Thus, it remains unknown whether or not PD differentially affects inhibitory aspects of attention in space-based and object-based conditions. The present study was designed to address this issue using an attention cueing task developed by Leek et al. (2003). This task assesses IOR in two conditions: an "object-present" condition in which objects surround the cues and targets, and an "object-absent" condition in which surrounding objects are not presented with the cues and targets. Because the conditions are otherwise identical, the effect of objects in the display on PD patients' attention processes can be directly tested. The object-absent condition is thought to engage only space-based IOR because the subject's attention is cued solely to spatial location. In contrast, the object-present condition engages a combination of both space-based and object-based IOR because the subject's attention is cued to both a spatial location and a specific object. By comparing the two conditions, any differential effects of PD on IOR in space-based and object-based attention can be determined. Based on previous studies, it was anticipated that the PD patients would show decreased IOR in the object-absent (i.e., space-based) condition, but normal IOR in the object-present condition.

1. Method

1.1. Participants

Eighteen nondemented patients with PD (11 men and 7 women) and 18 normal controls (9 men and 9 women) participated in the study. Participants gave written informed consent, and the study was approved by the University of California, San Diego Institutional Review Board. The patients with PD were recruited from the Movement Disorders Clinics at the San Diego VA Health Care System and the University of California, San Diego. All patients were diagnosed by a board-certified neurologist with specialty training in movement disorders, and the diagnosis was based on the presence of at least two of the following symptoms: (1) resting tremor, (2) rigidity, or (3) bradykinesia and the absence of atypical symptoms. The patients had been diagnosed an average of 5.4 years (range = 2–17, SD = 3.8), and the patients were evenly split as to whether their symptoms started on the right or left side of their body. Motor functioning was assessed using Hoehn and Yahr's rating scale (Hoehn & Yahr, 1967) and the Unified Parkinson's Disease Rating Scale Part III (Fahn, Elton, & the UPDRS Development Committee, 1987). According to the Hoehn and Yahr and the UPDRS motor examination rating scales, all patients exhibited mild to moderate motor impairments (Hoehn and Yahr: $M = 2.12$, range = 1–3, SD = 0.57; UPDRS motor examination: $M = 23.22$, range = 9–46, SD = 11.73).

The patients were treated with their normal regimen of dopaminergic agents at the time of testing (see Table 1) and were tested at the time of day when they felt cognitively more alert. No patients were taking anticholinergic or antipsychotic medication. Normal control participants were recruited from relatives of patients and from newspaper advertisements. All participants were screened for a history of significant neurological disease (other than PD), serious psychiatric illness (major affective disorder or schizophrenia), and substance abuse. In addition, participants were excluded if they scored below 132 on the Dementia Rating Scale (DRS; Mattis, 1976) or worse than 20/50 on the Rosenbaum Pocket Vision Screener.

The PD patients did not differ significantly from the controls in age, $t(34) = 0.88$, $p = 0.39$, years of education, $t(34) = -0.15$, $p = 0.88$, DRS scores, $t(33) = -1.18$, $p = 0.25$, or Geriatric Depression Scale (GDS) scores, $t(31) = 1.95$, $p = 0.06$ (see Table 2). Although there was a trend for the PD patients to have higher GDS scores than the controls, none of the patients met DSM-IV criteria for depression.

1.2. Apparatus and stimuli

Stimuli were presented on a 50.8 cm monitor. Randomization and presentation of stimuli, and recording of response reaction time and accuracy, were executed by Eprime software, version 1.1.

The stimuli and procedures used in the IOR experiment were modified from those used by Leek et al. (2003). The experiment was composed of two conditions: "object-present" and "object-absent." Illustrations of the four possible target locations and "filler" trials for the object-present condition can be seen in Fig. 1. In both conditions, the cue consisted of a white outline square, and the target consisted of a white filled square. The conditions differed only by the presence of L-shaped figures surrounding the cues and targets in the object-present condition. More specifically, segmented, black outlined, L-shaped figures were presented in two possible orientations: tilted 45° in either direction from the vertical meridian (figures presented in Fig. 1 are in the −45° orientation). These figures were composed of two rectangles of equal width but differing in length. The cue could appear in the center of either rectangular figure (the target locations presented in Fig. 1 are based on a cue positioned in the center of the left rectangle). The cue and target locations used in the object-absent condition were identical, but no surrounding objects were present (i.e., no rectangles were presented).

Participants were seated such that their line of sight was perpendicular to the center of the stimulus display, and their viewing distance was 43 cm. The longer rectangles subtended 10.8° × 2.5° and the shorter rectangles 4.6° × 2.5° of visual angle. The cue was a white outlined square and the target was a filled white square, and they each subtended 2° × 2° of visual angle. The fixation cross was black and subtended 0.6° of visual angle. The distance between the center of cues and targets for Locations 2, 3, and 4 was always 5.9°. The dimensions of the entire display were 19.2° × 15.9°. The stimuli were presented against a gray background. In the object-absent condition, the cues, targets, and fixation cross were identical to those in the object-present condition.

1.3. Procedure

Following is the trial procedure for the object-present condition, which is illustrated in Fig. 2. Each trial began with the presentation of the fixation cross. After 1000 ms, two L-shaped figures appeared on either side of the central black fixation cross. After 1000 ms, the cue was presented for 90 ms in the middle of one of the L-shaped figures. Following either a short delay (300 ms) or a long delay (500 ms)

Table 1
Characteristics of the Parkinsonian patients.

No.	Age	Disease duration[a]	H & Y stage	UPDRS motor exam	Antiparkinsonian medication, daily dose (mg)[b]
1	67	17.4	2	17	LeCa 800/200, Se 5, En 800, Pr 1
2	67	3.9	2.5	33	LeCa 600/150, Pr 5, Am 100
3	63	4.5	2.5	28	Se 10, Ro 5
4	64	4.3	1	16	LeCa 600/150, Pr 2
5	58	4.8	2	9	LeCa 200/50, Pr 2, Se 5
6	73	11.6	2	13	LeCa 300/75, Pr 2, Am 100, En 400
7	65	5.5	2.5	46	Pr 5, LdCaEn 300
8	82	3.8	3	32	LeCa 600/150
9	54	2.2	1	12	Pr 3
10	68	4.0	1.5	11	LeCa 200/50
11	55	7.0	2.5	24	LeCa 400/100
12	75	3.6	2.5	45	LeCa 800/200, En 800
13	79	3.7	2	26	LeCa 800/200, Se 5
14	64	3.1	2	22	Se 1
15	79	4.6	2	31	Ro 15, LeCaEn 300, Se 10
16	56	1.7	3	32	Unmedicated
17	64	8.8	2	9	LeCa 900/225, Pr 2, Am 200
18	63	2.8	2	12	LeCa 300/75, Am 300

[a] Age and disease duration in years.
[b] LeCa, levodopa-carbidopa; En, entacapone; Pr, pramipexole; Am, amantadine; Ro, ropinirole; Se, selegiline; Ca, carbidopa; LdCaEn, levodopa-carbidopa-entacapone.

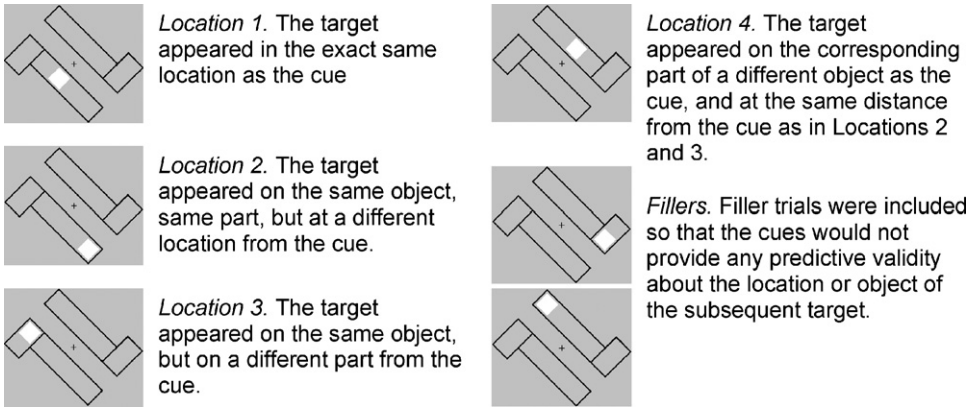

Fig. 1. An illustration of possible target locations based on a cue location in the same position as the target depicted in Location 1. The display orientation depicted here is −45° from vertical. Cue and target positions for the object-present and object-absent conditions are identical.

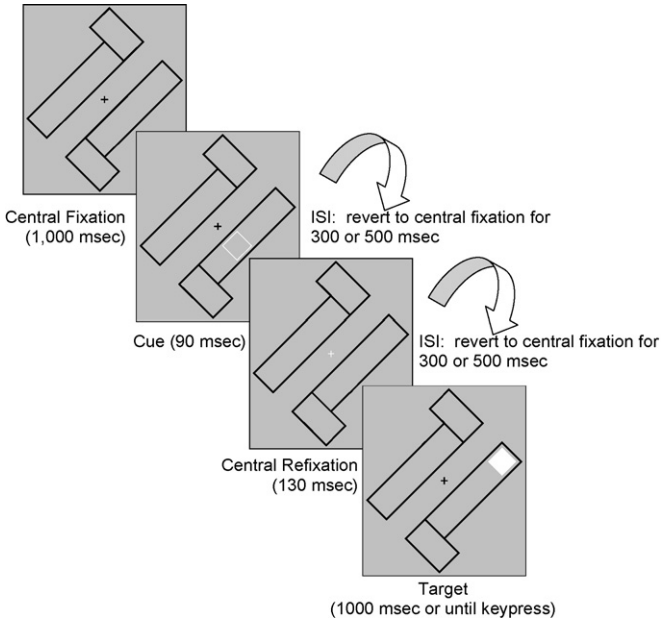

Fig. 2. Schematic diagram of a single trial of object-present condition. In this example, the figures are presented at +45° from vertical and location 2 is illustrated. A fixation point appeared for 1000 ms between each trial.

from cue offset, the fixation cross changed to white for a period of 130 ms, and then reverted back to black. Following another delay of the same length (300 or 500 ms), the target was presented at one of the six possible locations. In this design, stimulus onset asynchrony (SOA) had two levels: 820 ms and 1220 ms. The target remained on the screen until the participant responded by pressing the spacebar or for 1000 ms. If the participant did not press the spacebar after 1000 ms, the computer produced a buzz sound. In addition to the trials with targets, there were also "catch" trials, which were composed of an identical procedure but did not have a target. If the participant pressed the spacebar during a catch trial, a buzz sound was produced. These catch trials were included so as to reduce anticipatory responses. The trial procedure for the object-absent condition was identical to the procedure for the object-present condition, except for the absence of the L-shaped figures.

Participants were informed that the white outline square did not predict the location of the subsequent filled square. They were instructed to press the spacebar as quickly as possible after they detected the filled square, and to withhold their response when no filled square appeared. The importance of maintaining their gaze at the fixation cross throughout the experiment was stressed before and after the practice trials.

Table 2
Demographic characteristics of patients and normal controls.

	Age[a]	Education[a]	Proportion male	DRS	GDS	Rosenbaum
PD	67.0 (8.3)	16.6 (2.2)	0.6	139.6 (3.3)	5.9 (4.7)	20/27.2 (6.3)
NC	69.4 (8.2)	16.4 (2.2)	0.5	140.8 (2.8)	2.9 (4.2)	20/24.7 (4.8)

Values represent mean (SD).
[a] Age and disease duration in years.

Table 3
Reaction time (ms) as a function of group, condition, target location, and stimulus onset asynchrony.

	Object-present condition		Object-absent condition	
	820 ms	1220 ms	820 ms	1220 ms
Controls				
Location 1	485 (68)	472 (79)	452 (86)	450 (85)
Location 2	468 (86)	450 (78)	441 (83)	442 (72)
Location 3	470 (72)	461 (80)	432 (90)	430 (82)
Location 4	431 (75)	433 (80)	410 (80)	425 (75)
PD group				
Location 1	509 (81)	501 (74)	481 (78)	464 (74)
Location 2	482 (88)	469 (75)	459 (83)	463 (74)
Location 3	493 (83)	480 (79)	468 (80)	453 (68)
Location 4	458 (88)	443 (78)	466 (86)	455 (78)

Values represent mean (SD).

The object-present and object-absent conditions each consisted of 12 trials for each location within each SOA, with half of these trials presented in each orientation. In this design, the cues do not provide any predictive validity about the location or object of the subsequent target because the locations are equiprobable and random, and because of the inclusion of filler trials. In addition, 48 "catch" trials (i.e., when no target is presented) were included in each condition. The total number of trials within each condition was 192. The order of the conditions was counterbalanced within each group, and administration of the conditions was separated by a minimum of 30 min.[1]

2. Results

Only trials based on Locations 1 through 4 were included in the analyses. Trials where no responses were made were excluded from the data, which comprised 1.7% of the data for the controls, and 4.0% of the data for the patients. In addition, trials with reaction times greater than 800 ms (slow), or reaction times less than 200 ms (anticipatory), were discarded from the data. These exclusions made up an additional 1.1% of the data for the controls, and 1.7% for the patients. An ANOVA was conducted to evaluate whether the total number of trials excluded differed by group or condition. The main effect of group, $F(1, 34) = 1.96$, $p = 0.17$, $\eta_p^2 = 0.06$, main effect of condition, $F(1, 34) = 0.01$, $p = 0.94$, $\eta_p^2 < 0.001$, and the interaction effect, $F(1, 34) = .22$, $p = 0.64$, $\eta_p^2 = 0.01$, were all not significant. Mean reaction times by group, condition, location, and SOA are presented in Table 3.

2.1. Inhibition of return effects

IOR effects were calculated within each condition by subtracting the mean reaction time for Location 4 from the mean reaction times for Locations 1, 2, and 3, which is the same method used in the study by Leek et al. (2003). IOR effects by group, condition, and location are presented in Fig. 3. Greater values in Fig. 3 indicate greater IOR. A 2 (group) by 2 (condition) by 3 (location) by 2 (SOA) ANOVA was performed, with IOR effects as the dependent measure. The group by condition interaction was significant, $F(1, 34) = 7.76$, $p < 0.01$, $\eta_p^2 = 0.19$. There was also a significant condition by location interaction, $F(2, 68) = 3.31$, $p = 0.04$, $\eta_p^2 = 0.09$. None of the other interactions were significant, including group by condition by SOA, $F(1, 34) = 0.002$, $p = 0.96$, $\eta_p^2 < 0.001$, group by condition by location, $F(2, 34) = 0.53$, $p = 0.59$, $\eta_p^2 = 0.02$, or group by condition by location by SOA, $F(2, 68) = 0.28$, $p = 0.76$, $\eta_p^2 = 0.01$. The main effect of condition was significant in that IOR was greater in the object-present condition than the object-absent condition, $F(1, 34) = 32.28$, $p < 0.01$, $\eta_p^2 = 0.49$. The main effect of location was significant, $F(2, 68) = 19.82$, $p < 0.001$, $\eta_p^2 = 0.37$, such that greater IOR was observed for Location 1 than for Locations 2 or 3. The main effect of group was not significant, $F(1, 34) = 1.98$, $p = 0.17$, $\eta_p^2 = 0.06$.

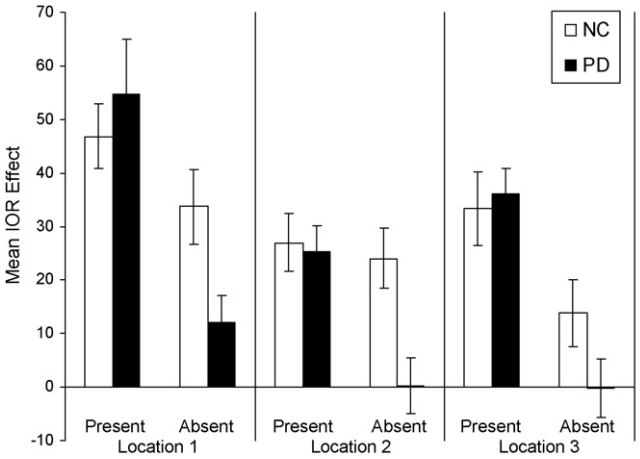

Fig. 3. Mean inhibition of return (IOR) by group, location, and object-present or object-absent condition. Bars represent SEM.

To further examine the group by condition interaction, independent samples *t*-tests were performed to compare the IOR effects of the groups within each condition, collapsed across IOR effect type and SOA. Within the object-present condition, the groups did not differ in the magnitude of IOR, $t(34) = -0.38$, $p = 0.71$, $d = 0.13$. However, as predicted, the PD patients demonstrated smaller IOR effects than the controls when the objects were absent from the display, $t(34) = 2.96$, $p < 0.01$, $d = -0.99$. In fact, while the controls demonstrated significant IOR in the object-absent condition, $t(17) = 4.35$, $p < 0.01$, $d = 1.03$, the IOR effects of the PD patients were not significantly different from zero, $t(17) = 1.03$, $p = 0.32$, $d = 0.24$.[2]

The significant condition by location interaction was further examined by performing paired samples *t*-tests to compare the magnitude of IOR associated with the different locations within each condition, collapsed across the two groups and SOA. In the object-present condition, IOR was significantly greater in Location 1 than both Location 2, $t(35) = 4.65$, $p < 0.01$, $d = 0.84$, and Location 3, $t(35) = 3.28$, $p < 0.01$, $d = 0.52$. In addition, IOR was significantly greater in Location 3 than Location 2, $t(35) = 2.51$, $p = 0.02$, $d = 0.36$. In the object-absent condition, IOR was significantly greater in Location 1 than in both Location 2, $t(35) = 2.59$, $p = 0.01$, $d = 0.40$, and Location 3, $t(35) = 3.85$, $p < 0.01$, $d = 0.60$. The magnitude of IOR associated with Locations 2 and 3 did not differ significantly, $t(35) = 1.33$, $p = 0.19$, $d = 0.21$. Although IOR was reduced for Locations 2 and 3, significant IOR was observed for these conditions in controls (both $ps < 0.05$).

2.2. Space-based IOR and motor symptoms

To determine whether the impairment in space-based IOR was associated with overall motor symptom severity and with the specific motor symptoms of resting tremor, rigidity, or bradykinesia, the IOR effect associated with Location 1 in the object-absent condi-

[1] The order in which the conditions were administered did not have an effect on any of the main findings discussed below.

[2] The group by condition interaction was also examined using mean reaction time in each of the four locations, rather than IOR effects, to determine whether general reaction time may have modulated this effect. For the object-present condition, the group by location interaction was not significant, $F(3, 32) = 0.37$, $p = 0.76$, $\eta_p^2 = 0.01$. For the object-absent condition, the group by location interaction was significant, $F(3, 32) = 3.42$, $p = 0.02$, $\eta_p^2 = 0.09$. Tests of simple within-subjects contrasts indicated that the reaction time differences were smaller for the patients between Location 4 and Location 1, $F(1, 34) = 6.26$, $p = 0.02$, $\eta_p^2 = 0.16$, Location 2, $F(1, 34) = 9.53$, $p < 0.01$, $\eta_p^2 = 0.22$, and there was a trend for location 3, $F(1, 34) = 2.90$, $p < 0.10$, $\eta_p^2 = 0.08$.

tion was correlated with the UPDRS motor examination total score and with previously derived UPDRS factor scores corresponding to tremor, rigidity, and bradykinesia (Stebbins & Goetz, 1998). The IOR effect associated with Location 1 was chosen because this is the best measure of space-based IOR, given that the target appears in the exact cued Location. There was a trend for reduced space-based IOR to be associated with greater overall motor symptom severity, $r = -0.44$, $p = 0.07$, and also with bradykinesia, $r = -0.43$, $p = 0.07$. Space-based IOR did not significantly correlate with tremor, $r = -0.25$, $p = 0.33$, or rigidity, $r = -0.21$, $p = 0.40$.

3. Discussion

As predicted, PD patients demonstrated a significant reduction in IOR relative to controls when objects were absent from the display and attention was directed by only space-based processes. In direct contrast, the patients demonstrated virtually identical IOR effects to those of the control participants when attention could be directed by both space-based and object-based processes (i.e., in the object-present condition). This pattern of results indicates that PD patients are selectively impaired in space-based IOR, and are able to overcome this impairment when they can direct their attention to objects.

These results suggest that PD specifically impacts the neural network underlying space-based IOR. It is widely understood that the superior colliculus (SC) plays a critical role in IOR (Berger & Henik, 2000; Dorris, Klein, Everling, & Munoz, 2002; Fecteau, Bell, & Munoz, 2004; Rafal, Calabresi, Brennan, & Sciolto, 1989; Rafal, Posner, Friedman, Inhoff, & Bernstein, 1988; Sapir, Soroker, Berger, & Henik, 1999; Sereno, Briand, Amador, & Szapiel, 2006), and recent evidence suggests that the SC expresses inhibition that is generated or modulated by upstream brain areas such as the posterior parietal cortex and the frontal eye fields (Corbetta & Shulman, 2002; Dorris et al., 2002; Fielding, Georgiou-Karistianis, Bradshaw, et al., 2006; Mayer, Seidenberg, Dorflinger, & Rao, 2004; Rosen et al., 1999; Vivas, Humphreys, & Fuentes, 2003). The present results suggest that the caudate nucleus and associated cortical-subcortical circuits affected by PD may also play a key role in space-based IOR, because (1) dopamine depletion of the caudate nucleus and its effects on associated neural circuits are thought to mediate the cognitive sequelae of nondemented PD (DeLong & Wichmann, 2007; Marie et al., 1999; Owen, 2004; Sawamoto et al., 2008), and (2) we observed a tendency for reduced space-based IOR to be associated with motor symptoms (e.g., bradykinesia) mediated by dopamine loss in the striatum (Bernheimer, Birkmayer, Hornykiewicz, Jellinger, & Seitelberger, 1973; Brucke et al., 1997; Grafton, 2004; Otsuka et al., 1996). In addition, the caudate nucleus has been shown to modulate SC functioning through inhibitory afferent connections via the substantia nigra pars reticulata (Hikosaka, Sakamoto, & Miyashita, 1993; Hikosaka & Wurtz, 1983; Joseph & Boussaoud, 1985). Specifically, the caudate nucleus sends phasic inhibitory signals to the substantia nigra pars reticulata which periodically releases the SC from the tonic inhibitory effect of that nucleus (Hikosaka, Takikawa, & Kawagoe, 2000). Because the caudate nucleus is a major input station in the basal ganglia that receives input from association cortices involved in visual processing (Hikosaka et al., 2000), the generation of these inhibitory signals may be based on visual reference frames provided by association cortex.

Although the present results suggest that caudate dysfunction in PD might contribute to the observed deficits in IOR, PD patients were unimpaired in object-based IOR. This dissociation may arise because different regions of the caudate nucleus receive input from diverse cortical structures and may be differentially affected by the disease. In particular, the dorsal and ventral cortical streams involved in visual processing demonstrate remarkable segregation in their connections to the caudate nucleus. Dorsal stream regions that are important for space-based visual processing (including posterior parietal cortex and dorsolateral prefrontal cortex subsuming the frontal eye fields) connect preferentially to anterior and dorsal regions of the caudate, whereas ventral stream regions that are important for object-based visual processing (including inferior temporal cortex and ventral prefrontal cortex) connect preferentially to posterior or ventral caudate nucleus (Alexander, DeLong, & Strick, 1986; Baizer, Desimone, & Ungerleider, 1993; Leh, Ptito, Chakravarty, & Strafella, 2007; Yeterian & Pandya, 1991, 1993). There is also evidence that material-specific functional segregation occurs within the caudate nucleus, where the dorsal head of the caudate is more involved in spatial working memory and posterior and ventral regions are more involved in object working memory (Cohen, 1972; Divac, Rosvold, & Szwarcbart, 1967; Iverson, 1979; Levy, Friedman, Davachi, & Goldman-Rakic, 1997; Postle & D'Esposito, 1999).

In light of this segregation of function in the caudate nucleus and its connections, it is important to note that dopamine depletion in the caudate nucleus of PD patients appears to follow both a rostral/caudal and dorsolateral/ventromedial gradient. Dopamine depletion is greatest in the anterodorsal extent of the head of the caudate nucleus (Kish, Shannak, & Hornykiewicz, 1988) and dopamine uptake sites are most reduced dorsally (Joyce, 1993; Kaufman & Madras, 1991; Piggott et al., 1999). This suggests that space-based IOR may be most dependent upon circuits that involve the dorsal head of the caudate nucleus and the dorsal stream of cortex that are most impacted by PD, whereas object-based IOR may be mediated by circuits that involve more ventral and caudal regions of the caudate nucleus and ventral stream cortical regions that are less impacted by PD. Some preliminary support for this dorsal/ventral stream interpretation of space-based and object-based IOR is provided by a recent fMRI study that compared IOR to location and color cues (Zhou & Chen, 2008). While both tasks activated a common network involving bilateral precentral gyrus and lateral occipital cortex, spatial cueing uniquely activated the superior portion of posterior parietal cortex bilaterally, whereas color cueing uniquely activated ventrolateral prefrontal cortex.

Consistent with the present results and interpretation, patients with PD show a similar dissociation on tests of visual working memory with working memory for spatial information more impaired than for object information (Postle et al., 1997). Although the relationship between space-based IOR and spatial working memory is not well understood, they appear to involve a shared process (Castel, Pratt, & Craik, 2003; Chou & Yeh, 2008). We recently demonstrated that patients with PD have a selective spatial (versus object) working memory impairment that is specific to the encoding stage and does not involve spatial working memory maintenance (Possin et al., 2008). During the encoding stage of working memory, transient perceptual representations are brought into a more durable working memory store so they will be available in the absence of information from the environment (Jolicoeur & Dell'Acqua, 1998; Ranganath, DeGutis, & D'Esposito, 2004; Woodman & Vogel, 2005). Like spatial working memory encoding, space-based IOR requires encoding of locations so that the cues can guide behavior beyond the duration of perceptual representations (Dodd & Pratt, 2007; Samuel & Kat, 2003). PD may selectively disrupt this spatial encoding process that is important for both spatial working memory and space-based IOR.

When objects were absent from the display, participants responded more slowly to Locations 2 and 3 than to Location 4, which may be somewhat surprising considering that the targets in all three of these locations are equidistant from the cue. Indeed, significant IOR was demonstrated by the controls for Locations 2 and 3 in the present study, as well as by the young adult participants in the study by Leek et al. (2003), suggesting that the inhibition did not decay based on distance alone. Several studies have demonstrated that IOR spreads only within the cued hemifield (Maylor & Hockey,

1985; Tassinari, Aglioti, Chelazzi, Marzi, & Berlucchi, 1987; Weger, Al-Aidroos, & Pratt, 2008). As argued by Weger et al. (2008), by switching our attention to the previously uncued and less attended side, we maximize our overall grasp of a scene. This mechanism may be an important component of visual search and gestalt processing. In the present study, Locations 2 and 3 were always within either the same vertical or horizontal hemifield as the cue, whereas Location 4 was in the opposite hemifield. Further, the space between the cue and Location 4 was interrupted by the fixation cross (see Fig. 1). The presence of this cross and the alignment of the squares may have divided the visual field diagonally into hemifields on which attention could operate, and within which IOR could spread to Locations 2 and 3. Unlike the controls, the PD patients did not show any evidence of space-based inhibition spreading within these hemifields. Thus, not only were PD patients impaired at inhibiting attention to a specific cued location (Location 1), but they were unable to distribute space-based inhibition beyond the cued location to bias their attention away from the cued hemifield. This distribution of attention underlies the space-based IOR effect in neurologically healthy individuals, and may be an important component of spatial attention deficits in PD.

When interpreting the results of this study it is important to consider that the patients were on dopamine replacement therapy at the time of testing. Dopamine replacement can have beneficial effects on some aspects of cognition and detrimental effects on others in PD (Cools, 2006). Grande and colleagues (Grande et al., 2006) examined the effects of dopaminergic medications on IOR in PD and showed that patients' performance did not change depending on whether they were on or off medication. However, this study did not disentangle space-based and object-based frames of reference, so it is not clear if dopamine replacement therapy impacted space-based and object-based IOR in different ways. Cools (2006) suggested that dopamine replacement therapy affects cognition in PD by remediating dopamine levels in the severely depleted dorsal striatum, and 'overdosing' the relatively intact ventral striatum, so it is conceivable that dopamine replacement therapy will improve certain space-based functions and impair object-based functions. Thus, it is not clear how dopaminergic medications may impact space-based and object-based IOR in PD, but it is unlikely that the medications induced the selective spatial impairment observed in the present study.

In conclusion, patients with PD exhibit reduced IOR when their attention is directed to locations, but normal IOR when they can overcome this impairment by directing their attention to objects. These findings suggest that the caudate nucleus and associated spatial information processing circuits disrupted in PD play a role in space-based IOR, and that object-based and space-based attention processes can be dissociated.

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