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Horizontal and vertical attentional orienting in Parkinson's disease

Gudrun M.S. Nys [a,*], Patrick Santens [b], Guy Vingerhoets [a]

[a] Laboratory for Neuropsychology, Department of Neurology, Ghent University, De Pintelaan 185 (4K3) 9000 Gent, Belgium
[b] Department of Neurology, Ghent University Hospital, De Pintelaan 185 (1K12) 9000 Gent, Belgium

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ABSTRACT

Patients with Parkinson's disease (PD) typically suffer from an asymmetric degeneration of dopaminergic cells in the substantia nigra, resulting in right-sided (RPD) or left-sided (LPD) predominance of motor symptomatology. As the dopaminergic system is also involved in attention, we examined horizontal and vertical orienting of attention in LPD ($N = 10$), RPD ($N = 9$) and controls ($N = 10$). Four LPD patients demonstrated left neglect and three LPD patients demonstrated neglect for the upper visual field. LPD patients demonstrated a slower performance in detecting targets in the left hemifield and did not demonstrate a validity effect, unlike RPD patients and controls. RPD patients performed similar to controls, with the exception of one patient showing left and another showing right neglect, and two RPD patients demonstrated lower neglect. In sum, horizontal and vertical orienting of attention can be affected in Parkinson's disease – particularly in LPD – from very subtle slowing to clinically detectable horizontal and/or vertical neglect.

1. Introduction

Parkinson's disease (PD) is a common neurodegenerative disorder which is classically characterized by well-known motor symptoms. These include bradykinesia, rigidity, resting tremor and postural changes. The onset and course of motor symptoms is typically asymmetric, resulting in right-sided (RPD) or left-sided (LPD) predominance of symptomatology. This motor asymmetry, which is almost pathognomonic for PD, is related to asymmetric degeneration of dopaminergic cells in the substantia nigra pars compacta and the subsequent asymmetric dysfunction of the nigrostriatal pathway. Functional neuroimaging studies of presynaptic dopaminergic function, such as fluorine-18-labelled fluorodopa (^{18}F-dopa) PET-scan or DAT-SPECT scan have demonstrated reduced tracer uptake in the posterior putamen, contralateral to the predominantly affected limb (Djaldetti, Ziv, & Melamed, 2006). These alterations are accompanied by an upregulation of postsynaptic striatal dopaminergic receptors in the same areas, as is indicated by a number of radioligand studies (Djaldetti et al., 2006).

The posterior putamen is considered the sensorimotor part of the striatum. However, dopaminergic deficiency also occurs in more anterior and ventral parts of the striatum, which are known as the associative and limbic striatum, as well as in cortical brain areas, reflecting the progressive neurodegeneration in the mesolimbic and mesocortical dopamine pathways. Indeed, it is well-known that the dopaminergic system contributes to cognition, particularly executive function and attention (Kaasinen & Rinne, 2002). Executive functions consist of the ability to plan, organize and regulate goal-directed behaviour. Deficits of executive functions have been repeatedly demonstrated in non-demented patients with Parkinson's disease. Commonly used tests of executive functions include the Wisconsin Card Sorting Test and Trail Making Test (mental flexibility), the Tower of London task (planning) and verbal fluency (executive memory) (Kaasinen & Rinne, 2002). Disorders of attention in PD include impairment in divided attention, selective attention, sustained attention, and the orienting of visuospatial attention. With respect to attentional asymmetry, there are several reports demonstrating subtle signs of left-sided neglect in LPD on visual exploration behaviour (Ebersbach et al., 1996), line bisection (Lee, Harris, Atkinson, & Fowler, 2001; Starkstein, Leiguarda, Gershanik, & Berthier, 1987), size estimation (Harris, Atkinson, Lee, Nithi, & Fowler, 2003) and even in daily life behaviour, e.g. bumping into the left side of doorways (Davidsdottir, Cronin-Golomb, & Lee, 2005).

Whereas studies of uni*lateral* neglect abound, vertical neglect has been relatively unexplored in spite of the fact that a significant vertical component to neglect may be evident in the performance of patients. In patients with left neglect after stroke, targets in the lower half of the display of cancellation tasks are missed, indicating inferior neglect (Halligan & Marshall, 1989). Ladavas and coworkers (Ladavas, Carletti, & Gori, 1994) demonstrated impaired orienting in the lower visual field in neglect patients when a peripheral luminance increment was used to summon attention

* Corresponding author. Address: Laboratory for Neuropsychology, Ghent University Hospital, De Pintelaan 185 (4K3), B-9000 Ghent, Belgium. Fax: +32 (0) 93324555.
E-mail address: gudrun.nys@ugent.be (G.M.S. Nys).

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automatically. Posterior parietal damage associated with horizontal neglect thus tends to produce neglect of lower visual space (Halligan & Marshall, 1989; Ladavas et al., 1994; Pitzalis, Spinelli, & Zoccolotti, 1997). From the available literature on neglect, it follows that upper visual neglect is rarer than lower neglect. In contrast with neglect after stroke, two studies have recently shown that patients with LPD tend to underestimate the *upper* visual field with respect to line bisection (Lee, Harris, Atkinson, Nithi, & Fowler, 2002) and size matching of two rectangles in the superior and inferior visual field (Harris et al., 2003). In a seminal review, Previc (1998) suggested that dopamine is an important neurotransmitter in the brain which represents the upper visual field. For example, animal research has shown that destruction of the dopamine-rich substantia nigra results in nose-diving during a descent from a higher place; on the other hand, dopamine agonists have been shown to result in upward turning (Previc, 1998).

At present, it is still unclear whether there are impairments in horizontal and/or vertical orienting of attention in patients with lateralised Parkinson's disease. The present study will compare the orienting of attention in four quadrants of the visual field between patients with LPD, RPD and healthy controls by employing a variant of the well-known Posner paradigm (Posner, 1980). Orienting of attention in this paradigm is assessed using a central (e.g. an arrow) or a peripheral cue (e.g. a luminance increase) followed by a peripheral target at the cued (valid trial) or uncued location (invalid trial) requiring a simple detection response. The subject is instructed to press a button in response to the detection of the target, while maintaining fixation on a centrally located stimulus (i.e. *covert* attention). Typically, short stimulus onset asynchronies (SOAs) between cue and target presentation manifest in a facilitation of responses to valid targets, relative to invalid targets. Most studies investigating voluntary shifts of attention (central cues) in PD have found that the magnitude of the cueing effect is reduced in PD patients (Filoteo et al., 1997; Pollux & Robertson, 2001; Wright, Burns, Geffen, & Geffen, 1990; Yamada, Izyuuinn, Schulzer, & Hirayama, 1990; Yamaguchi & Kobayashi, 1998) and that the cueing effect declines as symptom severity increases (Yamada et al., 1990). Effects of PD on automatic shifts of attention in response to peripheral visual cues have been investigated in fewer studies. Moreover, these studies frequently employed a suboptimal procedure to assess reflexive spatial attention, using exogenous cues that were predictive of target location, thus conflating reflexive ('bottom-up') and voluntary ('top-down') attentional effects. That is, targets appeared more often at cued than at uncued spatial locations. Failure to prevent the involvement of voluntary attentional processes (that are already thought to be deficient in PD) may have obscured true performance in automatic orienting (but see Briand, Hening, Poizner, & Sereno, 2001; Danziger, Kingstone, & Rafal, 1998; Friedrich, Egly, Rafal, & Beck, 1998; Ladavas et al., 1994) for designs assessing pure exogenous orienting of attention).

Attentional side differences between left and right hemifields have also largely been ignored. Previous studies in neglect patients have demonstrated longer RTs at contralesional locations for valid targets, and dramatic increases in RTs for invalid trials when attention has to be de-coupled (i.e., 'disengaged') from an *ipsilesional* location towards a *contralesional* target (Losier & Klein, 2001; Posner, Walker, Friedrich, & Rafal, 1987). This so-called "disengagement deficit" has been shown to be most pronounced following right parietal damage compared to left parietal damage and to be particularly related to the neglect syndrome, even when *clinical* signs of neglect are no longer present (Losier & Klein, 2001).

The aim of this study is twofold. First, we will examine whether certain patients with LPD or RPD demonstrate clinical horizontal and/or vertical neglect as assessed by standard neglect cancellation. In addition, we will compare orienting of attention in horizontal and vertical space between patients with LPD, patients with RPD, and healthy controls. In particular, we will examine whether PD patients with primarily left-sided symptoms also demonstrate covert attentional asymmetries and/or a disengagement deficit for invalidly cued left targets.

Table 1
Comparison variables of included participants.

	LPD	RPD	Co	*p*
Demographics				
Age (years)[a]	64.1 (7.9)	61.1 (11.0)	64.9 (1.7)	.67
Sex ratio (men:women)	7:3	6:3	6:4	.89
Education (years)[a]	12.2 (3.0)	13.3 (3.4)	12.0 (3.3)	.66
PD variables				
Disease duration (years)[a]	9	6.5	–	.16
Hoehn and Yahr stage[b]	2 [1–3]	1.5 [1.5–4]	–	.61
UPDRS motor[b]	14 [9–43]	12.5 [8–46]	–	.96
UPDRS left motor[b]	7 [3–19]	0.5 [0–15]	–	.01*
UPDRS right motor[b]	2 [0–14]	6 [0–19]	–	.08
Cognitive variables				
MMSE[a]	27.5 (1.7)	28.4 (1.2)	28.5 (1.7)	.31
NART IQ[a]	101.5 (27.9)	109.1 (22.2)	111.6 (15.9)	.61

Significant values ($p < 0.05$) are indicated with an asterisk.
[a] Values are expressed as mean (SD).
[b] Values are expressed as median (range). UPDRS Motor: motor scale of the Unified Parkinson Disease Rating Scale. MMSE: Mini-Mental State Examination. NART IQ: National Adult Reading Test IQ.

2. Methods

2.1. Participants

Patients with idiopathic PD were recruited between July 2007 and May 2008 at the Movement Disorders Unit of the Ghent University Hospital (Belgium). Diagnosis of PD was made by an experienced Movement Disorder neurologist (P.S.) according to the clinical criteria as described by Gelb, Oliver, and Gilman (1999). The total sample consisted of 10 healthy controls and 19 PD patients. A summary of participant characteristics is presented in Table 1.

The PD patients were generally in the early stages of their disease (Hoehn and Yahr stages 1 or 2) (Hoehn & Yahr, 1967). Right- and left-sided motor composite scores were created by summing the individual motor items of tremor (items 20 and 21), rigidity (item 22), finger taps (item 23), hand grips (item 24), alternating hand movements (item 25), and leg agility (item 26) from the UPDRS Part III. We used a minimum of a two-point difference between right and left symptoms on the UPDRS motor scale to identify the side of predominant symptoms (see also Cooper et al., 2009). This approach resulted in a categorisation of 10 LPD patients and 9 RPD patients (see Table 1 for median lateralised UPDRS scores). Staging and severity indices were obtained on the same day as the experimental task session, and scores were obtained in the "on" medication state. All patients were treated with levodopa (mean dosage 627 mg, range 150–1350 mg), 16 had additional treatment with dopamine receptor agonists (mean levodopa equivalent dosage 310 mg, range 125–500 mg)[1].

Exclusion criteria for patients and controls were age >80, premorbid neurological or psychiatric history, dementia [Mini-Mental State Examination (MMSE) < 25], and for patients a history of deep brain stimulation or continuous enteral levodopa, and structural

[1] Levodopa dosage was calculated taking into account a multiplication with 1.5 if COMT inhibitors (tolcapone, entacapone) were administered in addition to levodopa. Levodopa equivalent dose of dopamine receptor agonists was calculated using 1 mg of pergolide = 1.5 mg pramipexole = 5 mg ropinirole = 100 mg levodopa.