Neuroscience Letters 509 (2012) 50–55

Contents lists available at SciVerse ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet

Selective attention deficits in early and moderate stage Parkinson's disease

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ARTICLE INFO

Article history:
Received 7 February 2011
Received in revised form
13 September 2011
Accepted 22 December 2011

Keywords:
Parkinson's disease
Cognition
Attention networks
Alerting
Orienting
Executive control

ABSTRACT

Patients with Parkinson's disease (PD) often show impaired performance on visuospatial attentional tasks. The objective of the study was to examine the attentional function of PD patients performing the attentional network test (ANT). We used the ANT to compare PD patients with healthy controls with respect to the efficiency of 3 anatomically defined attentional networks: the alerting, orienting, and executive control networks. We found that PD patients showed a selective abnormality in the orienting network. Although the alerting and executive control networks apparently remained unaffected, the efficiencies of these networks in patients with PD negatively correlated with the Hoehn–Yahr stage. The results supported the idea that the orienting processes may be more dynamic in PD than in non-PD individuals.

1. Introduction

Parkinson's disease (PD), originally characterized as a motor disorder, has recently received increasing attention because of the associated cognitive deterioration. Individuals with PD display impairments in performing various cognitive tasks that primarily depend on the frontal lobes [27]. Such patients have been found to show deficits in memory, social cognition, abstract reasoning and visuospatial attention [1,23].

Accumulating evidence suggests that the level of the disruption in visuospatial attentional functions increases with disease severity [26]. In particular, PD patients show impairments in performing tasks that require switching attention between 2 perceptual dimensions [14]. Furthermore, Briand and colleagues found that reflexive attentional processes are more active in PD patients than in healthy controls [2]. Studies have also supported suggestions that patients with PD have attention disorder in task-switching experiments [37]. These findings suggest that PD manifests a deficit in different aspects of attentional function.

Posner and Petersen proposed that sources of attention could be further divided into 3 networks [33]. These networks carry out functions of alerting, orienting, and executive control. The alerting network involves the ability to tonically maintain the alert state and to phasically respond to a warning signal. Neuroimaging evidence reveals that the alerting network consists of specific frontal and parietal areas and involves the cortical projection of the norepinephrine system [8]. The orienting network involves the selection of information from among numerous sensory inputs. The temporal parietal junction, superior parietal lobe, and frontal eye fields are involved [3,28]. The blockage of cholinergic input to the superior parietal lobe influences the ability to shift attention to cues [4]. Executive control of attention is involved in conflict processing. It includes the anterior cingulate cortex and lateral prefrontal cortex and is modulated by dopamine [5,13].

The attentional network test (ANT) is a combination of the cued reaction time task and the flanker task [32]. The ANT provides a measure of the efficiency of the alerting, orienting, and executive control attentional networks [9]. The unique activation and time courses of the 3 attentional networks have also been demonstrated in recent cognitive neuroscience studies [7]. The task has deliberately been kept brief and with straightforward instructions; thus, test results can be obtained within 30 min.

Although the ANT has been used to study attentional functions in a wide range of populations, relatively little is known about the alterations of the attentional networks in PD. Therefore, in this study, ANT was used to compare the operation of these 3 networks between healthy controls and patients with PD.

2. Materials and methods

2.1. Subjects

We studied 44 patients with idiopathic PD and 28 healthy controls (HC). Patients were recruited from among outpatients who were diagnosed and regularly treated at the First Hospital of Anhui Medical University, Anhui Province, China. All patients fulfilled

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doi:10.1016/j.neulet.2011.12.049

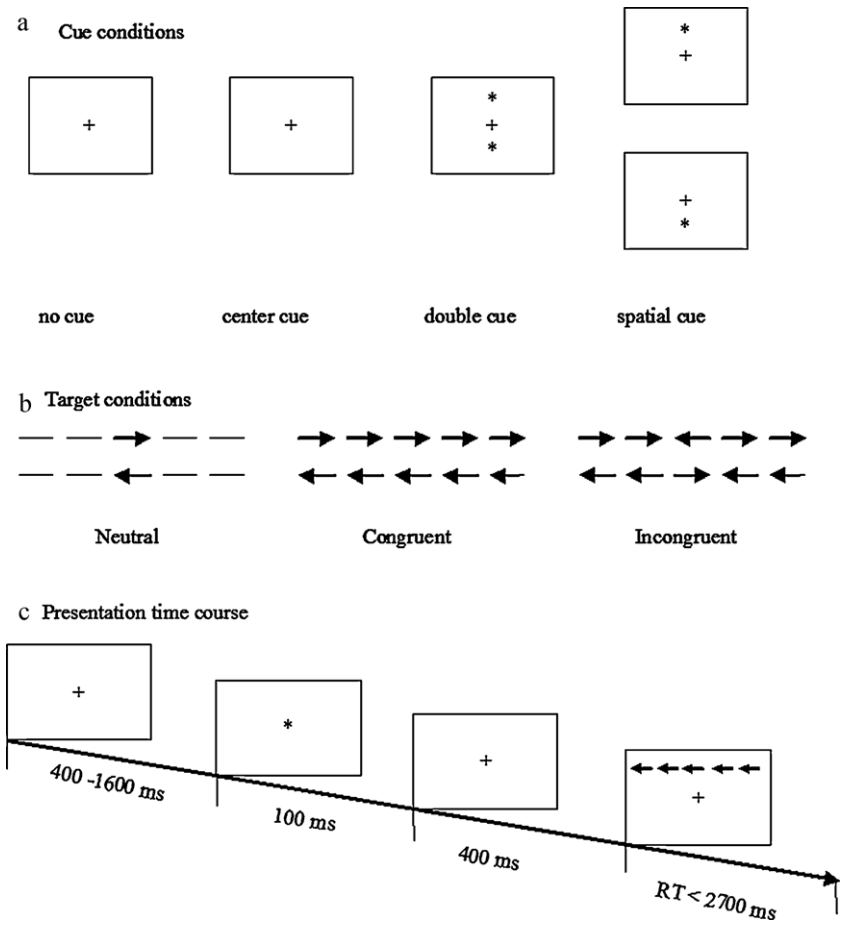

Fig. 1. Experimental paradigm of the attention network test (ANT). (a) The 4 cue conditions. (b) The 6 stimuli used in the present experiment. (c) An example of the procedure.

Parkinson's Disease Society Brain Bank clinical criteria for definite PD [18]. They were screened by neurologists, and those with a history of other neurological or psychiatric illnesses such as depression or dementia were excluded. According to criteria defined by Hoehn and Yahr, PD patients in this study were within stages I–III. All patients were being treated with levodopa, and the experiment was tested in the "on" state of medication.

In addition, 28 healthy controls, matched to patients for age, sex and intellectual level, were recruited; they received compensation for their participation.

Written informed consent was obtained from each participant. This research was complied with the Helsinki Declaration [41].

2.2. Neuropsychological background tests

The neuropsychological background tests were Mini-Mental State Examination (MMSE), verbal fluency test (VFT), and digit span (DS). The Zung Self-Rating Depression Scale (SDS) was also administered to evaluate possible depressive state.

2.3. Attentional network test

The ANT was programmed using E-Prime (Version 1.1, Psychology Software Tools, Pittsburgh, PA). Participants viewed the stimuli on a computer screen and responses were collected via two response buttons. Stimuli consisted of a row of five horizontal black lines, with arrowheads pointing leftward or rightward, against a gray background. The target was a leftward or rightward pointing arrowhead flanked on either side by two arrows pointing in the same direction (congruent condition), or in the opposite direction (incongruent condition), or by lines without arrowheads (neutral condition). Target location was always uncertain except when spatial cue was presented. Participants were instructed to fixate on a centrally located cross for the duration of the task, and to respond as quickly and accurately as possible (see Fig. 1). Participants were asked to identify the direction of the center arrow by pressing a button to identify left facing arrows with the index finger of the left hand and another button for right facing arrows with the index finger of the right hand. The maximum target display duration was 2700 ms. Cues consisted of an asterisk presented for 100 ms with an onset 400 ms prior to the target. There were four cue conditions: (1) no-cue, in which only the central fixation cross was presented throughout the 100 ms interval during which a cue would normally be presented; (2) central-cue, in which a single cue was presented at the location of the central fixation cross; (3) double-cue, in which cues were presented simultaneously at each possible target location (both above and below the fixation point); (4) spatial-cue, in which a single cue predicted the location of the target (either above, below the central fixation point). The ANT consisted of a 24-trial practice block and three experimental blocks of trials. Each experimental block consisted of 96 trials (48 conditions: 4 cue types $\times$ 2 target locations $\times$ 2 target directions $\times$ 3 congruencies, with two repetitions). The order of presentation of trials was randomized. Fig. 1 illustrates the task.

2.4. Calculation of attention network efficiencies

The ANT uses differences in reaction times (RT) derived from the different experimental conditions to measure the alerting, orienting, and executive control networks. The alerting effect was

Table 1
Demographic and neuropsychological information of participants.

Characteristic	PD patients	Healthy controls
Number of participants	44	28
Sex (F/M)	19/25	8/20
Age, years, mean ± SD (range)	58.1 ± 10.8 (34–75)	57.3 ± 12.7 (26–79)
Educational level (range)	9.05 ± 4.28 (0–16)	10.2 ± 4.2 (0–15)
SDS, mean ± SD (range)	33.8 ± 5.2 (24–43)	30.6 ± 4.2 (21–37)
MMSE, mean ± SD (range)	28.3 ± 1.5 (24–30)	28.8 ± 1.1 (24–30)
DS, mean ± SD (range)	6.3 ± 1.0 (5–8)	6.4 ± 1.2 (4–8)
VFT, mean ± SD (range)	11.5 ± 2.5 (7–18)	11.4 ± 3.0 (7–16)
Duration of disease, years, mean ± SD (range)	2.45 ± 1.54 (0.25–6)	
Hoehn–Yahr stage (number of patients)		
1	15	
1.5	11	
2	12	
3	6	
Antiparkinson therapy	L-DOPA	

Table 2a
Means (and standard deviation) of RTs and error rates (%) under each condition in PD and healthy controls groups.

Group	Flanker	Cue type			
		Center	Double	None	Spatial
Mean RTs (ms) and standard deviations					
PD	Congruent	876 (202)	869 (194)	915 (200)	807 (186)
	Incongruent	973 (225)	987 (245)	1015 (217)	905 (245)
	Neutral	870 (196)	866 (201)	901 (191)	806 (187)
Health controls	Congruent	827 (128)	841 (138)	874 (117)	786 (131)
	Incongruent	912 (130)	921 (135)	978 (135)	859 (138)
	Neutral	817 (113)	822 (122)	865 (109)	782 (108)
Error rates (%) and standard deviations					
PD	Congruent	1.5 (2.6)	0.9 (2.3)	0.9 (2.4)	0.8 (1.9)
	Incongruent	2.0 (4.4)	2.0 (4.3)	2.3 (4.4)	1.2 (2.5)
	Neutral	1.3 (2.9)	1.6 (3.1)	1.4 (2.5)	0.8 (1.9)
Health controls	Congruent	0.6 (1.5)	0.3 (1.1)	0.6 (1.5)	0.3 (1.1)
	Incongruent	1.3 (2.5)	1.9 (3.5)	0.9 (1.7)	0.7 (1.6)
	Neutral	1.3 (3.0)	0.15 (0.8)	1.0 (1.8)	0.3 (1.1)

Table 2b
Attention network scores (in RT and ratio score) of PD patients and matched healthy controls groups.

	PD patients		Healthy controls	
	M	*SE*	*M*	*SE*
Alerting (ms)	37.2	5.82	44.7	6.74
Ratio	0.040	0.007	0.052	0.008
Orienting (ms)	67.5*	4.30	43.5	6.11
Ratio	0.075*	0.005	0.051	0.007
Executive (ms)	103.1	8.68	85.4	5.49
Ratio	0.115	0.010	0.100	0.006
Mean RT (ms)	899.4	30.6	856.9	22.6
Accuracy (%)	98.6*	0.002	99.2	0.002

* Indicate statistically significant differences.

calculated by subtracting the mean RTs of the conditions with double cues from the mean RTs of the conditions with no cue. The orienting effect was calculated by subtracting the mean RTs of the conditions with spatial cues from the mean RTs of the conditions with center cues. The executive effect was calculated by subtracting the mean RTs of the conditions with congruent flankers from the mean RTs of the conditions with incongruent flankers.

Independent-sample of *t*-test was used to examine the demographic and neuropsychological background data of the two groups. One-way analysis of variance (ANOVA) was used to examine the three attentional network scores and ratio scores of the two study groups. Associations between the ANT scores and the Hoehn–Yahr stage were analyzed by Pearson correlation.

3. Results

The means and standard deviations of the demographic and clinical characteristics of PD patients and HC are summarized in Table 1. There were no significant differences in age, gender, educational level, SDS, MMSE, DS, or VFT between the 2 groups (Table 1).

3.1. Efficiencies of the 3 networks

Mean raw RTs and error rates for each cue condition in the 2 groups are summarized in Table 2a, while the mean scores and standard error (*SE*) for each of the attentional networks, mean RT, and global accuracy for PD patients and healthy controls are summarized in Table 2b. The data showed that the orienting network effect was significantly higher [F (1, 70) = 10.579, $p < 0.05$] in PD patients (67.5 ms) than in healthy controls (43.5 ms). The differences between the groups for alerting and executive control network scores were non-significant [F (1, 70) = 0.695, F (1, 70) = 2.054, respectively, $p > 0.05$]. No differences were detected in overall mean RT [F (1, 70) = 1.001, $p > 0.05$] and accuracy [F (1, 70) = 3.285, $p > 0.05$] between the 2 groups.

However, since RTs were generally longer for the PD patients, we thought it useful to use ratios to examine specific effects that are not influenced by overall reaction time. Ratio score transformations have proven effective in uncovering group effects in processes, in a manner that is independent of global slowing [10]. Consequently, we calculated a ratio score transformation for each participant by dividing the mean RT, determined under each condition, by the

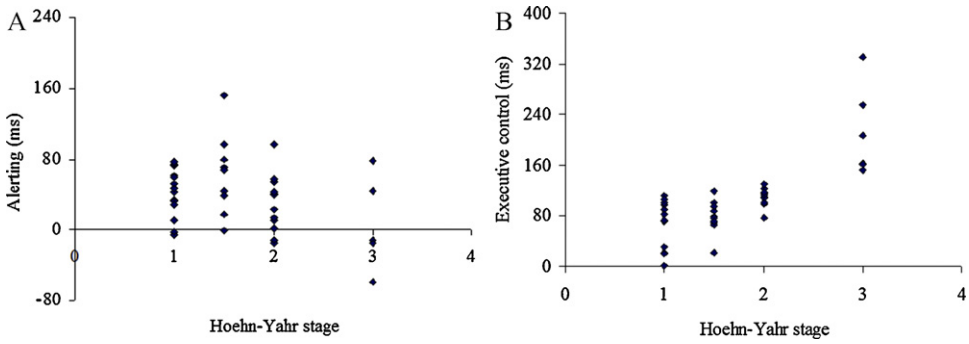

Fig. 2. (A) Negative correlation between the scores of the alerting network and the Hoehn–Yahr stage in patients with Parkinson's disease (PD). (B) Positive correlation between the conflict scores of the executive control network and the Hoehn–Yahr stage in patients with PD.

participant's overall RT (Table 2b) for each of the 3 attentional networks.

There was a statistically significant difference in the orienting effect [F (1, 70) = 8.785, $p < 0.05$] between the 2 groups, but the difference between PD patients and controls for the alerting and executive effects, based on the ratio score, were insignificant non-significant [$F(1, 70) = 1.343$, $F(1, 70) = 1.345$, respectively, $p > 0.05$]. These results demonstrate that the PD group has a selective abnormality of the orienting networks while the alerting and executive control networks remain unaffected.

3.2. Correlations between attentional network and Hoehn–Yahr stage

We also found that there was a negative correlation between the Hoehn–Yahr stage and the alerting network score ($r = -0.357$, $p < 0.05$) (Fig. 2A), and a positive correlation with the executive network score ($r = 0.761$, $p < 0.001$) (Fig. 2B). No relationship was found between the Hoehn–Yahr stage and the orienting network score. Moreover, Hoehn–Yahr stage was positively correlated with overall RT ($r = 0.475$, $p < 0.05$). There was no effect of age on PD alerting, orienting, and executive control attention networks ($r = -0.032$, $r = 0.202$, $r = 0.116$, respectively; $p > 0.05$).

4. Discussion

The results of our study add to the literature that describes deficits in specific attentional networks associated with various neurological and psychiatric disorders [11,39]. Specifically, the current study demonstrated that patients with PD had a selective abnormality in the orienting network, while differences in alerting and executive control network scores between PD patients and healthy controls were not significantly different. However, the efficiencies of these networks in PD patients were negatively correlated with Hoehn–Yahr stage. The orienting effect was also significantly higher in PD patients (67.5 ms) than in healthy controls (43.5 ms), indicating that patients benefited from spatially informative cues to a greater degree than healthy controls, in terms of RT.

The main finding of the study is that the orienting network is affected by PD. The results are in line with previous studies that indicated that orienting processes may be more dynamic. For instance, Mari-Beffa et al., using a negative priming paradigm, reported that PD patients demonstrated a robust effect of positive priming from distractor words [25]. Henik et al. examined facilitatory and interference effects by using a computerized version of the Stroop test, and found that PD patients presented an augmented facilitatory effect [17]. They suggested that the augmented facilitatory effect reflected a decline in cortical inhibitory processes and reflect a decline in cortical inhibitory processes. In both tasks, PD patients were faster than controls at processing previously ignored stimulus attributes, suggesting that they were less efficient at inhibiting their processing in the first place. That is, the inhibitory processes that prevent the return of attention to the cued location are impaired [31].

Furthermore, there is some evidence of hyper-reflexivity in PD patients. PD patients show faster RT when cued to the center position, because their hyper-reflexive attentional dysfunction may be characterized by reduced response time following invalid cues (Table 2a). This is compatible with some researches. Briand et al. tested Parkinson's disease patients in a task that measures reflexive orienting of spatial attention. Seven patients with idiopathic PD and eight control subjects performed a covert orienting task where spatial attention was directed by means of exogenous cues with no predictive validity for target position. Patients with PD were significantly faster than control subjects on this reflexive visual-orienting task and showed greater IOR than control subjects. These findings are consistent with the possibility that reflexive attentional processes in PD patients may be more active [2]. Sampaio et al. found that PD subjects showed impaired psychophysical performance enhancement by valid attentional cues [35]. Moreover, hyper-reflexivity has also been observed in studies of saccadic eye movements by Kingstone et al. [20]. They examined the attentional orienting of PD patients and controls on five different tasks and found that patients were faster to reorient their attention to the uncue location. Thus, the abnormality in the orienting network may reflect impaired inhibitory processes or hyper-reflexive orienting in patients with PD.

Evidence of abnormality in orienting attention may serve as a guide to the anatomical substrates and neuromodulators affected by PD [16]. Imbalance of neurotransmitters impairs the ability of the cortex to adapt quickly to changing external conditions and contributes to the development of cognitive decline [15,36]. The abnormality of the orienting network in patients with PD may therefore also be related to impairment of neurotransmitter systems.

Another interesting result of the study is that the executive control network seemed to remain unchanged across PD patients. It appears that flankers did not interfere with RTs of the PD patients more than that of the normal controls. This result is consistent with previous studies [6,22,34,42]. Some studies have shown that interference effects were found in medication-withdrawn PD patients [34,42]. However, the reverse result was found in other studies using the flanker task [6,22] in medicated PD patients. Our results were in line with the latter observations, in which the executive control function seemed to remain unaffected; this may have been related to the medications that our participants with PD were taking. Some neuropsychological findings indicate that PD patients perform better on executive function tasks under dopaminergic medication, relative to the unmedicated state, for instance in

working memory tasks [24], in the perseveration condition of set-shifting tasks [30], and in planning tasks [21]. The present data support that a dopaminergic deficit is associated with brain dysfunction and that it is partially normalized by dopa-therapy.

Moreover, disease severity may partially explain why our study yielded no significant differences in the executive control network between PD patients and controls. Our results did show that the Hoehn–Yahr stage is positively correlated with the executive control network score, and that severe deficits in executive control function can be observed at the Hoehn–Yahr stage III (Fig. 2B). Executive dysfunctions in patients with PD are well known [2,23]. In a study of 20 non-demented PD individuals, Brand et al. and found that patients exhibited inappropriate decision-making function on executive tasks [1]. Similarly, Weintraub et al. evaluated PD patients using executive function tests and found that that they demonstrated impaired executive function [40]. Overall, our study supports that PD patients show dysfunction in the executive control network of attention in the more severe stages of the disease.

Our research also showed that the Hoehn–Yahr stage is negatively correlated with the alerting network score (Fig. 2A). A deficit in the alerting network was found to be more severe during advanced stages of PD. A possible interpretation of the decreased alerting effect is that decreased cortical levels of norepinephrine commonly occur in PD [38]. There are few reports investigating alerting in PD; however, alerting, as measured by the ANT, has been shown to decline with age in some studies [12,19]. Experimental evidence indicates that reduced levels of noradrenalin in the brain causes lowering of the magnitude of the alerting effect [29]; therefore, noradrenergic deficits may cause a decline of the alerting effect in PD patients.

5. Conclusions

In conclusion, our study represents a step towards understanding attentional deficits in Parkinson's disease. Specifically, the study showed that orienting network scores of patients with PD were abnormal and that the efficiency of the executive control network was negatively correlated with the Hoehn–Yahr stage. Future studies comparing medicated and unmedicated PD patients and those in "on" and "off" stages of their treatment are needed to exclude the confounding effects of PD treatment on such studies.

Acknowledgments

We thank the participants in this study for their involvement and support. This work was supported by National Natural Science Foundation of China (30670706, 30870766) to Kai Wang.

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