Neuroscience Letters 500 (2011) 113–117

Contents lists available at ScienceDirect

Neuroscience Letters

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

Executive control in Parkinson's disease: Effects of dopaminergic medication and deep brain stimulation on anti-cue keypress performance

Jos J. Adam[a,b,*], Hanna van Houdt[a], Bart Scholtissen[c], Veerle Visser-Vandewalle[b,d], Ania Winogrodzka[b,e], Annelien Duits[b,f]

[a] Faculty of Health, Medicine and Life Sciences, Maastricht University, Maastricht, The Netherlands
[b] School of Mental Health and Neuroscience, Maastricht University, Maastricht, The Netherlands
[c] Faculty of Psychology and Neuroscience, Maastricht University, Maastricht, The Netherlands
[d] Department of Neurosurgery, Maastricht University Medical Centre, Maastricht, The Netherlands
[e] Department of Neurology, Maastricht University Medical Centre, Maastricht, The Netherlands
[f] Department of Psychology, Maastricht University Medical Centre, Maastricht, The Netherlands

ARTICLE INFO

Article history:
Received 8 April 2011
Received in revised form 30 May 2011
Accepted 8 June 2011

Keywords:
Deep brain stimulation
Subthalamic nucleus
Parkinson's disease
Anti-cue
Reaction time
Response selection
Executive control

ABSTRACT

Using an anti-cue keypress task, we examined executive control in Parkinson's disease (PD) patients treated with deep brain stimulation (DBS) of the subthalamic nucleus (STN) and dopaminergic medication. Across sessions, we varied stimulation (on, off) and dopaminergic medication (on, off). Reaction time (RT) results of the PD patients and their age-matched controls showed a consistent pattern of RT costs and benefits generated by anti-cues with short and long preparation intervals, respectively. This pattern was evident in all sessions, except when DBS stimulation and medication were off. In this condition PD patients showed no RT benefits. These findings are discussed in terms of an executive control process that suppresses the automatic but inappropriate response activation generated by anti-cues. In PD this mechanism is severely compromised but it can be remediated by dopaminergic medication and DBS, suggesting an essential role of the basal ganglia in the selection and suppression of competing responses.

We investigated the ability of four Parkinson's disease (PD) patients treated with deep brain stimulation (DBS) of the subthalamic nucleus (STN) and dopaminergic medication to suppress automatic response activation generated by anti-cues in a keypress task. STN stimulation (on, off) and dopaminergic medication (on, off) were orthogonally combined and implemented in five separate sessions distributed over two days. Because dopaminergic medication improves executive control of anti-saccades in PD [14], we expected patients off medication to show a smaller anti-cue reaction time (RT) benefit than patients on medication. Because stimulation of the STN facilitates inhibitory control in a stop-signal task [22], we expected a further decrease in this benefit with stimulation turned off. We examined a group of seven age-matched control subjects to establish baseline and possible learning effects.

Anti-cues differ from standard cues by promoting a motor response in the direction opposite to the location of the cue. Thus, anti-cues require the preparation and execution of a mirror-symmetrical response (i.e., contraversive behaviour). The anti-saccade task is a widely investigated type of contraversive behaviour, requiring the subject to look away from the target, not toward it [9,7]. It is well established that anti-saccades take longer to initiate than normal pro-saccades [25], and, furthermore, that they are mediated by executive functions that exert voluntary top-down inhibitory control over automatic processes [19]. Basal ganglia and frontal cortex have been implicated as contributing to the suppression of automatic behavioural tendencies [24,13]. Furthermore, Isoda and Hikosaka [15] recently demonstrated that the STN is critically involved in this type of executive control. Using single-cell recordings in macaque monkeys, they found neurons in the STN to play a key role in switching from automatic to controlled (eye movement) behaviour. Not surprisingly, then, PD patients typically show impaired performance on the anti-saccade task, suggesting a deficit in exerting executive control over oculomotor reflexes [6,23].

Converging evidence for the notion that PD is associated with an impaired ability to suppress automatic response activation comes from a study on stimulus–response compatibility effects in PD [20]. Praamstra and Plat [20] examined RT performance in a so-called Simon task and found a larger compatibility effect for PD patients compared to healthy controls. In the Simon task, the location of

* Corresponding author at: Faculty of Health, Medicine and Life Sciences, PO Box 606, 6200 MD, Maastricht, The Netherlands. Tel.: +31 43 388 1389; fax: +31 43 367 0972.
E-mail address: jos.adam@maastrichtuniversity.nl (J.J. Adam).

0304-3940/$ – see front matter © 2011 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.neulet.2011.06.016

Table 1
Patient characteristics.

Case[a]	Age	Medication	Postop	DBS parameters	UPDRS (s1)	UPDRS (s2)	UPDRS (s3)	UPDRS (s4)
1	75	L-Dopa/Benserazide 625 mg, Ropinirole 6 mg	1	L: 2.7 V; 90 μS; 180 Hz R: 2.3 V; 120 μS; 180 Hz	22	21	51	35
2	58	L-Dopa/Carbidopa 750 mg	7	L: 4.9 V; 90 μS; 130 Hz R: 4.8 V; 120 μS; 130 Hz	28	35	68	41
3	75	L-Dopa/Benserazide 187.5 mg, Pramipexol 1.625 mg	3	L: 5.3 V; 60 μS; 130 Hz R: 0.9 V; 60 μS; 130 Hz	45	49	69	51
4	67	L-Dopa/Benserazide 250 mg, Pergolide 4 mg	2	L: 1.6 V; 90 μS; 130 Hz R: 1.3 V; 90 μS; 130 Hz	34	34	41	39

Postop, years since implantation; DBS, deep brain stimulation; UPDRS, Unified Parkinson's Disease Rating Scale, scores on part III have been shown representing motor function; s, session; L, left; R, right; DBS parameters are provided in: amplitude in V, pulse width in ms and frequency in Hz; medication is given in total daily doses.
[a] All patients except case 2 were female.

the stimulus is irrelevant and a non-spatial attribute (e.g., color or identity) carries the relevant information. For instance, a colored light occurs either to the left or right of a central fixation point and participants have to press a right key when the color is red and left key when the color is green. The typical finding in this paradigm is that responses are faster and more accurate when the stimulus location and response location correspond (i.e., compatible condition) than when they do not (i.e., incompatible condition). Most accounts of the Simon effect attribute it to the automatic activation of the response on the side of the stimulus location [17]. On compatible trials, the automatic activation supports the selection of the required response, thus facilitating RT. In contrast, on incompatible trials, the stimulus automatically activates the wrong response, which must be inhibited, thereby lengthening RT. Praamstra and Plat [20] interpreted the greater Simon effect in PD patients as a deficit in executive control, in particular, an impairment to inhibit automatic visuomotor activation.

In the present study, we tested the hypothesis that dopaminergic medication and DBS of the STN mediate performance on an anti-cue keypress task that requires a speeded finger response. The reason for using an anti-cue keypress task rather than an anti-cue saccade task [11] was the fact that finger keypress responses are much easier to measure than eye movements, making the anti-cue keypress task potentially an appealing clinical instrument for the exploration and assessment of basal-ganglia deficits in PD.[1]

To trace the time course of response inhibition processes, we manipulated the cue-target interval. If participants are successful in inhibiting the activated responses on the side of the anti-cue, a RT *benefit* should be observed. However, if participants are not able to do this then a RT *cost* might emerge. As explained earlier, this is because left and right cues automatically activate left and right hand finger responses, respectively [8,3], which in the case of anti-cues are the wrong responses. Hence, in the anti-cue keypress task, participants need to suppress the initial but erroneous activation of the ipsi-lateral hand and redirect it to the contra-lateral hand. This is an effortful, time-consuming executive control process. Hence, short cue-target intervals might be expected to generate RT costs, whereas longer cue-target intervals might be expected to generate RT benefits.

This study included 4 right-handed patients with advanced PD (3 women, 1 man; mean age 68.0 ± 8.0 years) treated with DBS of the STN. See Table 1 for the characteristics of the patients. The anti-cue keypress task was added to a standard postoperative evaluation during a two-day stay in our university hospital, so that ethical approval was waived. All patients gave written informed consent to perform the additional task and to retrieve data from their medical records. The standard evaluation included assessment of clinical symptoms in four sessions, distributed over two days: (1) both medication and stimulation on; (2) medication off and stimulation on; (3) both medication and stimulation off; and (4) medication on and stimulation off. In an additional session (session 5) only the anti-cue keypress task was administered with both medication and stimulation on. See Table 1 for the respective assessments of the motor symptoms, using the Unified Parkinson's Disease Rating Scale (UPDRS), part III. Seven age-matched control subjects participated in this study with an average age of 67.0 ± 13.4 years (4 women, 3 men).

A row of four empty boxes (35 mm × 35 mm), separated by 25 mm (between adjacent sides), was continuously visible as squares in orange-brown outline on a black background. At the start of each trial, a visual warning signal was presented as a small red square (10 mm × 10 mm) midway between the two inner boxes. It flickered three times during an interval of 750 ms, after which it disappeared. Then, after an additional period of 750 ms, either all four boxes turned red (neutral cue) or the two leftmost or the two rightmost boxes turned red (anti-cue). After a cue-target (or preparation) interval of 100 ms, 250 ms, 500 ms, 750 ms, or 1000 ms, the target was presented by making one box green. Thus, cues and targets were presented as boxes that were colored in. Participants were instructed to indicate the location of the target as quickly and accurately as possible by pressing the corresponding response key, after which all boxes became empty again. Responses were made by pressing one of the four keys with the index and middle fingers of both hands. When pressing an incorrect response key, an error message was briefly displayed on the screen.

Participants were explicitly told to take advantage of the anti-cue by preparing the fingers on the opposite hand (i.e., the mirror-symmetrical responses: i.e., left side cue = prepare right hand responses; right side cue = prepare left hand responses).

All PD patients performed the anti-cue task at five different moments in time (T) corresponding to the five sessions of the two-day clinical evaluation. The first test was at day one approximately at 10 a.m. (T_1), when the patients had their stimulators on and were on regular dopaminergic medication (see Table 1). Patients were instructed to take their medication before 7.00 a.m. The next test was at the same day at 4 p.m. (T_2), about 9 h after their last medication intake (this is the "medication off" condition). Immediately after this second session, the stimulator was switched off and the test was repeated the following day at 9 a.m. (T_3). Immediately after this third session, patients received soluble levodopa (*Madopar Dispers*, 125 mg). After 1 h, the fourth test was performed (T_4). Finally, at 1 p.m. that second day, the stimulator was switched on and the test was repeated for the last time (T_5). The control subjects per-

[1] In the terminology of Fischer and Weber, the present anti-cue keypress task is an anti-cue pro-keypress task [11]: it presents a lateralized cue signal which directs attention and motor preparation to the opposite side (anti-cue) where the target signal will appear and the response has to be produced after a certain cue-target interval. The keypress task is to press the key associated with the position of the target (pro-keypress).