The Subthalamic Nucleus Influences Visuospatial Attention in Humans

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Abstract

■ Spatial attention is a lateralized feature of the human brain. Whereas the role of cortical areas of the nondominant hemisphere on spatial attention has been investigated in detail, the impact of the BG, and more precisely the subthalamic nucleus, on signs and symptoms of spatial attention is not well understood. Here we used unilateral deep brain stimulation of the subthalamic nucleus to reversibly, specifically, and intraindividually modify the neuronal BG outflow and its consequences on signs and symptoms of visuospatial attention in patients suffering from Parkinson disease. We tested 13 patients with Parkinson disease and chronic deep brain stimulation in three stimulation settings: unilateral right and left deep brain stimulation of the subthalamic nucleus as well as bilateral deep brain stimulation of the subthalamic nucleus. In all three stimulation settings, the patients viewed a set of pictures while an eye-tracker system recorded eye movements. During the exploration of the visual stimuli, we analyzed the time spent in each visual hemispace, as well as the number, duration, amplitude, peak velocity, acceleration peak, and speed of saccades. In the unilateral left-sided stimulation setting, patients show a shorter ipsilateral exploration time of the extrapersonal space, whereas number, duration, and speed of saccades did not differ between the different stimulation settings. These results demonstrated reduced visuospatial attention toward the side contralateral to the right subthalamic nucleus that was not being stimulated in a unilateral left-sided stimulation. Turning on the right stimulator, the reduced visuospatial attention vanished. These results support the involvement of the subthalamic nucleus in modulating spatial attention. Therefore, the subthalamic nucleus is part of the subcortical network that subserves spatial attention. ■

INTRODUCTION

Hemispatial neglect is a condition that is characterized by a failure to explore the side of space contralateral to the lesion and to react or respond to stimuli or subjects located on this side (Karnath, Himmelbach, & Rorden, 2002). Persistent neglect is often the consequence of a right parietal (Mort et al., 2003) or right superior temporal lesion commonly seen after stroke (Karnath, Ferber, & Himmelbach, 2001). But neglect may also occur after lesions in other brain areas such as the frontal lobe or subcortical structures (Committeri et al., 2007; Mort et al., 2003). In chronic neglect patients, lesions restricted to the right BG or thalamus have been reported to induce neglect as well (Karnath et al., 2002). Within the BG, the right putamen and caudate nucleus have been identified to be crucial structures associated with spatial neglect (Karnath et al., 2002). But studies investigating the impact of BG on neglect demonstrate heterogeneous and even contradictory results because lesion studies on spatial neglect after stroke use different lesion-mapping techniques and the accuracy involved in investigating merely BG nuclei differs according to the mapping methods. Only a minority of studies have also mapped the integrity of white matter tracks, such as the superior longitudinal fasciculus, that takes its course adjacent to the BG (Karnath, Rennig, Johannsen, & Rorden, 2011). However, a BG lesion may also affect neighboring white matter tracts potentially involved in the neural network of spatial attention.

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is an established therapy in advanced stages of Parkinson disease (PD; Deuschl et al., 2006). Although the mechanisms of bilateral STN-DBS are not well understood, DBS is believed to interfere with increased output from the BG and thereby to improve the functions of their target structures (Bergman, Wichmann, & DeLong, 1990). Previous studies have used acute effects of STN-DBS as a tool to reversibly and intraindividually modify the activity in BG circuits (Schroeder et al., 2002). Whereas bilateral STN-DBS has been studied more frequently, unilateral stimulation can also be tested under experimental conditions by turning on one DBS electrode at a time. Under unilateral stimulation of the left STN, PD patients have shown mild but significant neglect behavior, neglecting left-sided stimuli (Witt, Kopper, Deuschl, & Krack, 2006). However, in this study, we used a motor task that measured

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RT while patients responded to visual cues in the right and left extrapersonal hemispace. Consequently, the motor domain, affected by PD and also affected by STN-DBS, was the major outcome measure. In this study, visual exploration behavior was tested using an eye-tracker system to measure spatial attention in the ocular motor system, which is less affected in PD. So we tested the hypothesis that the STN is part of the attentional system managing space orientation. If so, the laterality of hemispheric specialization with a superior function of the nondominant hemisphere on spatial orientation should also be evident in the subcortical nuclei and here, in particular, the STN that was to be manipulated in the study.

METHODS

Patients

At the University Hospital in Kiel, we examined 13 PD patients, 3 women and 10 men, 32.5 months (range = 6–100 months) after bilateral electrode implantation in the STN for chronic DBS. All PD patients fulfilled the brain bank criteria for PD (Hughes, Daniel, Kilford, & Lees, 1992), and all patients suffered from advanced PD. Patients' data and clinical characteristics are given in Table 1. None of the patients had a diagnosis of dementia preoperatively or postoperatively, and all patients scored ≥24 points on the Mini-Mental Status Examination (Folstein, Folstein, & McHugh, 1975) screening test. Preoperatively, there was a predominance of motor symptoms on the left side for five patients and on the right side for eight patients. The neurological examination excluded strabismus and deficits in the visual field. All patients had normal vision or corrected-to-normal vision, and none of the patients complained of diplopic images. The stimulating electrodes (Medtronic, Minneapolis, MN) were implanted using stereotactic MRI-based targeting and intraoperative electrophysiology with microrecording and microstimulation as previously described (Schrader, Hamel, Weinert, & Mehdorn, 2002). For the determination of the position of the electrode contacts, we used our stereotactic targeting software (Brainlab, Feldkirchen, Germany). After placing the AC–PC line (anterior commissure and posterior commissure) on the postoperative MRI, we determined the position of the four electrode contacts by assigning the center of the corresponding artifact. The stereotactic coordinates of the active contacts in relation to the mid-AC–PC point were marked on the corresponding normalized horizontal sections of the Schaltenbrand-Wahren Atlas (Schaltenbrand & Wahren, 1977). The preoperative MRI did not show any large vessel infarction, and an MRI after surgery excluded complications such as cerebral hemorrage. Patients were tested in a dopaminergic ON state. At the time of testing, patients received an average levodopa equivalent daily dosage of 363.7 mg. The protocol was approved by the ethics committee at Christian Albrecht University Kiel, and all patients gave informed consent.

Table 1. Demographic Data and Clinical Findings of PD Patients

	PD Patients (n = 13)
Age (years)	62.13 ± 8.874 (39–71)
Male/female	10/3
Disease duration (years)	16.31 ± 6.019 (10–29)
Right-/left-sided disease onset	8/5
Stimulation duration (months)	32.54 ± 27.573 (6–100)
Hoehn & Yahr ON-ON	2.23 ± 0.484 (1.5–3)
Hoehn & Yahr OFF-OFF	3.42 ± 0.703 (2.5–5)
Levodopa equivalence dosage	363.69 ± 218.955 (54–750)
Mini Mental Status Examination	28.62 ± 2.29 (24–30)
Visual acuity test right (%)	73.85 ± 15.021 (50–100)
Visual acuity test left (%)	72.31 ± 16.909 (50–100)
Amplitude right (V)	3.02 ± 0.804 (1.1–4.1)
Amplitude left (V)	3.05 ± 0.736 (2.0–4.5)
Pulse duration (μsec)	62.31 ± 8.32 (60–90)
Frequency (Hz)	167.31 ± 27.13 (130–210)

Data are given as absolute values or mean (range) and ±*SD*.

Test Procedure

Each patient was tested in three stimulation conditions in a double-blinded design: right electrode ON and left electrode OFF (right ON/left OFF), right electrode OFF and left electrode ON (right OFF/left ON), and both electrodes ON (right ON/left ON). The order of the stimulation conditions in which the patient was tested was randomly assigned to every patient. Identical stimulation parameters as for chronic DBS were used. All patients had unipolar stimulation. The neurological motor examination (Unified Parkinson Disease Rating Scale part III, UPDRS III) and test procedure began at least 30 min after changing the stimulation condition when a stable clinical status was achieved. The examiner performing the motor evaluation and the examiner testing spatial neglect were blinded to the stimulation settings and the results of the motor evaluation, respectively. To quantify the degree of motor symptom asymmetry, the left and right score sums of the unilateral UPDRS III items (20–26) were calculated. After the motor examination, the patient was presented with a set of pictures, whereas the patient's eye position and movement were recorded by an eye-tracking system.

Stimulus Material

Forty-two visual stimuli were selected from the International Affective Picture System (IAPS; Lang, Bradley, & Cuthbert,

2008). The visual stimuli were complex pictures representing objects, people, landscapes, and scenes of life. The pleasure level ranged from 4.5 to 5.5, and the level of arousal was varied from 1 to 9 to increase patients' alertness. We selected an additional 21 landscape pictures from private material. These were reflected vertically in the middle of the picture (mirrored pictures). Using all 63 pictures, we created three picture sets consisting of 21 randomly assigned pictures, each of which 7 were mirrored and 14 were derived from IAPS. Every patient saw each of these three randomly ordered picture sets only once and presented in a pseudorandom order with regard to the three different stimulation conditions, that is, some patients began by viewing picture set 1 in the condition right ON/left OFF and other patients began with picture set 1 in the condition right OFF/left ON. By avoiding a fixed order of picture sets, we minimized the risk that the results were affected by the pictures themselves that might have had asymmetrical eye-catching regions. Pictures were displayed on a color monitor (24 in., resolution 1024 × 760, vertical refresh 70 Hz). The patients sat 87 cm in front of the monitor (corresponding to vertical angle of vision of 28.05° and a horizontal angle of vision of 21.5°) in a dimly illuminated room. The monitor was connected to a personal computer equipped with E-Prime presentation software (Psychological Software Tools, Inc., Sharpsburg, PA) triggered by the eye-tracking system.

Eye-tracking Recordings

The head position was stabilized with the eye-tracker inbuilt chin and forehead rest. In every stimulation setting, the system was recalibrated with a 13-point grid. Fixation and eye movements were recorded monocularly from the left eye with an infrared video-based eye tracker (IView-X Hi-Speed 1250, SMI GmbH, Munich, Germany) at a sampling rate of 500 Hz and an instrument spatial resolution of 0.01° while patients viewed the pictures binocularly. Patients started each 21-picture session by fixating on a cross at the center of the screen for calibration. However, after this, patients were told that they were free to look anywhere on the screen at the beginning of every subsequent picture to evaluate the pictures afterwards. Instantaneous eye position was tracked by an apparatus-mounted camera (sensomotoric instruments) close to the patient's left eye. The patient's gaze position was shown on the experimenter's screen to monitor the patient's status and the quality of the data. Each visual stimulus was on the screen for 10 sec, so viewing one picture set took 210 sec. After observation of each picture, patients rated emotional valence and arousal using the 9-point Self-assessment Manikin Scale (Lang et al., 2008). This task served as motivation for detailed observation of the picture.

Eye recordings were classified into three categories. "Fixation duration" was defined as the time between two saccades with a minimal 80-msec rest of eye movements. "Saccades" were defined as any movements of the eye, and "blinks" were defined as the time duration that no eye data were available. For analysis, the computer screen was divided into 32 vertical areas of interest (AOIs), and sequential numbers were assigned to these from left to right (Figure 1). The fixation duration was summed for each AOI. In addition, we subtracted the fixation duration of each AOI of the stimulation right ON/left OFF and right OFF/left ON from the "baseline condition" right ON/left ON and summed up these differences for the right and left hemispaces. Saccades were analyzed for the number of saccades, saccade amplitude, duration, peak velocity, and acceleration peak. This was carried out separately for left- and right-sided saccades at every stimulation setting.

Statistical Analysis

The Wilcoxon signed-rank test was used to determine the stimulation settings (stimulation voltage, frequency pulse width and amplitude of the right versus left electrodes). UPDRS total and subscores were analyzed using Kruskal–Wallis tests on account of the nonparametric distribution of the data. Given significant differences between stimulation settings, Mann–Whitney U tests were performed for a pairwise comparison between specific stimulation settings. Recording times of the eye-tracking experiment were analyzed using a repeated-measures ANOVA with the within-subject factor Stimulation Setting. The fixation duration recorded by the eye-tracker was summed for the left (AOI 1–16) and right (AOI 17–32) hemispace for each stimulation setting separately and then compared using t tests for dependent samples. For a more detailed analysis of the fixation duration in relation to each AOI, we tested the relevance of the changes in fixation duration caused

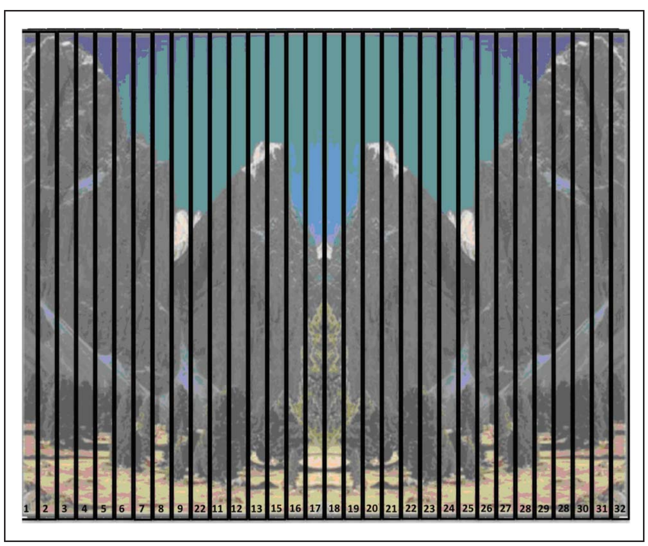

Figure 1. For analysis, the computer screen was divided into 32 vertical AOIs, and sequential numbers were assigned to these from left to right.

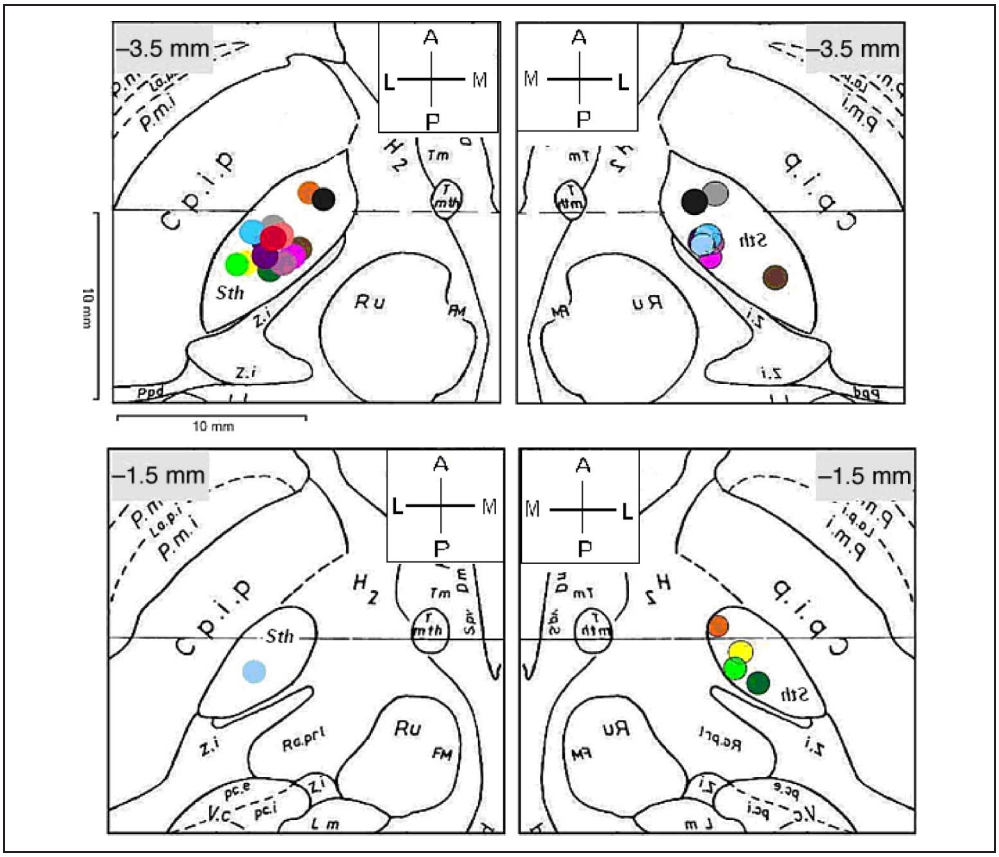

Figure 2. Schematic representation of the location of active electrode contacts used for stimulation during the study over a series of two axial sections of the Schaltenbtand and Wahren atlas (A = anterior; M = medial; P = posterior; L = lateral). Left, left brain contacts; right, right brain contacts. Negative numbers on the graphs represent millimeters inferior from the midcommissural point. Cp.i.p. = Crus posterior of the internal capsula; RU = nucleus ruber or red nucleus; Ra. pr1 = preleminiscal radiation; Sth = subthalamic nucleus; V.c. = nucleus ventrocaudalis; z.i. = zona incerta.

by changes in the stimulation setting using the reliable change index (RCI) in every AOI. The fixation duration in each AOI of the three conditions was summed up. The fixation duration of each AOI was compared between stimulation settings. The RCI for the stimulation condition right ON/left OFF was calculated using the formula RCI = (fixation duration in the right ON/left OFF stimulation setting − fixation duration in the right ON/left ON stimulation setting)/SD_{diff}, where SD_{diff} is the standard error of the difference score (Frerichs & Tuokko, 2006). In analogy, RCI of the right OFF/left ON stimulation setting was calculated for each AOI. Upper and lower cutoff values of

Table 2. Results of the Neurological Examination (UPDRS Total and Subscores) in Three Stimulation Settings

	Right ON/Left ON (n = 13)	*Right ON/Left OFF (n = 13)*	*Right OFF/Left ON (n = 13)*	χ^2	*p*
UPDRS III Total	26.31 ± 6.54	33.62 ± 7.38	33.08 ± 8.85	5.36	.068
UPDRS, right[a]	5.77 ± 2.62	11.77 ± 3.94[b]	7.23 ± 3.06[b]	12.71	.002
UPDRS, left[a]	6.77 ± 3.06	8.69 ± 4.84[b]	12.92 ± 5.22[b]	10.51	.005
UPDRS axial	13.62 ± 4.07	13.46 ± 3.15	12.92 ± 3.84	0.50	.78
UPDRS tremor	0.77 ± 1.36	2.92 ± 3.55	2.92 ± 2.96	4.73	.094
UPDRS rigor	0.77 ± 1.09[c]	3.92 ± 2.57	3.85 ± 2.08[c]	17.32	<.001
UPDRS akinesia	14.08 ± 5.41	16.31 ± 5.48	15.77 ± 5.31	0.96	.62
UPDRS bradykinesia	2.00 ± 0.91	2.00 ± 0.71	2.00 ± 0.71	0.05	.97
UPDRS postural instability	6.54 ± 2.96	6.54 ± 1.85	6.46 ± 2.40	0.12	.94

Data are given in mean ± *SD*.

[a]Sum of unilateral items of the UPDRS (Items 20–26).

[b]Significant differences between stimulation setting right ON/left OFF and right OFF/left ON ($p < .03$).

[c]Significant differences between stimulation setting right ON/left ON and right OFF/left ON: $p < .0001$.

1.645 or −1.645, respectively, indicated reliable change. To avoid multiple testing, only AOIs showing a reliable change triggered a separate t test between stimulation settings. In addition, we subtracted the fixation duration of each AOI of the stimulation right ON/left OFF and right OFF/left ON from the "baseline condition" right ON/left ON and summed up these differences for the right and left hemispaces.

RESULTS

There was no significant difference between the stimulation settings when comparing the right and left electrodes with regard to stimulation voltage, frequency, and pulse width (Table 1). Figure 2 shows the position of the active electrode contacts.

Motor Score

Total UPDRS motor scores significantly improved under STN stimulation. The unilateral items showed significant changes in the degree of symptom asymmetry ($p < .03$). The stimulation setting right ON/left OFF significantly improved left-sided motor functions, and the stimulation setting right OFF/left ON significantly improved right-sided motor functions (see Table 2).

Analysis of the Eye Recordings

Average total recording times per patient and stimulation setting did not significantly differ between stimulation settings (right ON/left ON: 182.3 sec; right ON/left OFF: 171.4 sec; and right OFF/left ON: 173.9 sec; one-way ANOVA: $p > .4$). Fixation durations of each stimulation setting are displayed in Figure 3A. An ANOVA for repeated-measures including the within-subject factor Time Spent in the right or left hemispace and the within-subject factor Stimulation Setting showed significant interaction effect ($F = 3.6$, $p = .038$). In the stimulation setting right OFF/left ON, patients significantly fixated on the left side of the hemispace for shorter periods of time (67.3 sec, $SD = 44.4$ sec [area under the curve AOI 1–16]; Figure 3A) compared with the stimulation setting right ON/left ON (107.0 sec, $SD = 40.1$, $t = 2.4$, $p = .023$) and the stimulation setting right ON/left OFF (106.4 sec, $t = 2.5$, $p = .019$). There was a trend for longer fixation duration in the stimulation setting right OFF/left ON for the right hemispace (106.6 sec, $SD = 60.2$ [area under the curve AOI 17–32]; Figure 3A) compared with the stimulation setting right ON/left OFF (65.0 sec, $SD = 47.8$, $t = -1.9$, $p = .06$) and no significant differences compared with the right ON/left ON setting (75.3 sec, $SD = 52.4$, $p > .2$). RCIs greater than 1.6 existed only in the comparison between the stimulation settings right ON/left ON and right OFF/left ON in AOI 11, 20, 21, and 22. Post hoc analysis demonstrated significantly shorter fixation duration in AOI 11 for the right OFF/left ON setting and significantly longer fixation duration in AOI 20, 21, and 22 compared with the right ON/left ON stimulation setting ($p < .05$ for all comparisons; see Figure 3A). Further analysis of the hemispace of fixation duration on

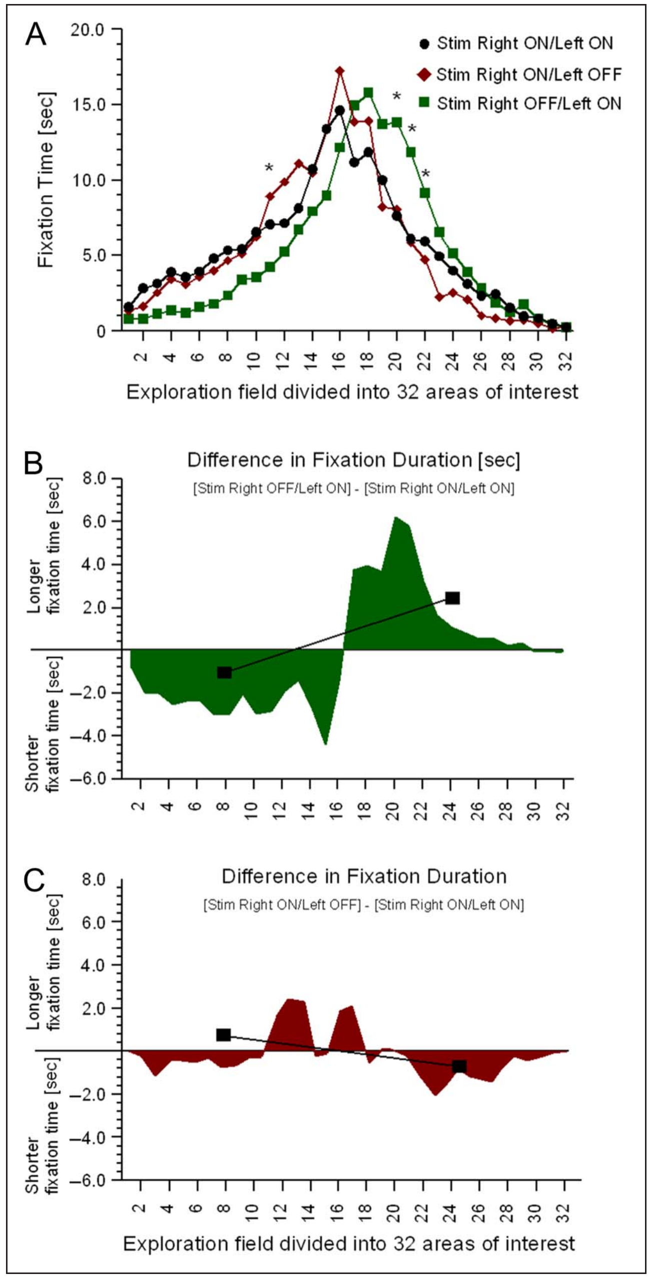

Figure 3. (A) Fixation durations are illustrated for each stimulation setting (● = right ON/left ON stimulation; ♦ = right ON/left OFF stimulation; ■ = right OFF/left ON stimulation). The exploration field is separated into 32 vertical ROIs (* displays significant differences between unilateral right-side stimulation and unilateral left-side stimulation). Bilateral symmetrical stimulation (right ON/left ON stimulation) was used as the baseline condition. (B) The difference in fixation duration between stimulation right OFF/left ON and stimulation right ON/left ON. (C) The difference in fixation duration between right ON/left OFF and stimulation right ON/left ON. The gray bar indicates the difference in interaction effect of unilateral stimulation in comparison with bilateral stimulation.

nonmirrored and mirrored pictures did not reveal any significant differences and no RCIs more or less than 1.6. In conclusion, patients spent less time in the left hemispace in the right OFF/left ON stimulation condition and demonstrated a trend toward longer fixation duration in the right OFF/left ON condition to the right-sided hemispace compared with the right ON/left OFF stimulation condition. Using the bilateral stimulation setting right ON/left ON as a baseline condition, both AOIs of the right ON/left OFF and the AOI of the right OFF/left ON condition were subtracted from the AOI of this baseline condition (Figure 3B and C). An ANOVA including the within-subject factor "time spent in the right or left hemispace" and the "within-subject factor stimulation setting" (changes from right ON/left ON to right OFF/left ON and right ON/left OFF) showed a significant interaction ($F = 3.98$, $p = .048$; Figure 3B and C). A t test demonstrated significantly longer exploration of the right hemispace in the right OFF/left ON stimulation setting ($T = 3.75$, $p = .03$), but a nonsignificant t test in the right ON/left OFF stimulation setting demonstrated no significant changes from baseline (right ON/left ON). To explore the effect of motor symptom asymmetry on visual exploration, patients were divided into groups of patients with a right-lateralized or a left-lateralized symptom. An ANOVA analysis included the Onset Side as between-subject variable and the Stimulation Condition as within-subject variable revealed no significant effect of the factor Onset Side. Single significant differences were found between right and left-lateralized onset of PD motor symptoms.

The Kolmogorov–Smirnov test showed a normal distribution of saccadic eye parameters (number of saccades, saccade amplitude, duration, peak velocity, acceleration peak). Right- and left-sided saccadic parameters were tested using ANOVA, including the between-subject factor Stimulation Setting. Statistical analysis did not reveal any significant differences ($p > .11$ for all comparisons; Figure 4). We furthermore correlated the changes in the UPDRS score and changes in eye recordings (saccade duration, amplitude, and peak velocity) and did not find significant correlations. Furthermore, the analysis of the subjective arousal ratings of the IAPS picture set showed no significant differences of arousal scores related to stimulation conditions ($p > .78$).

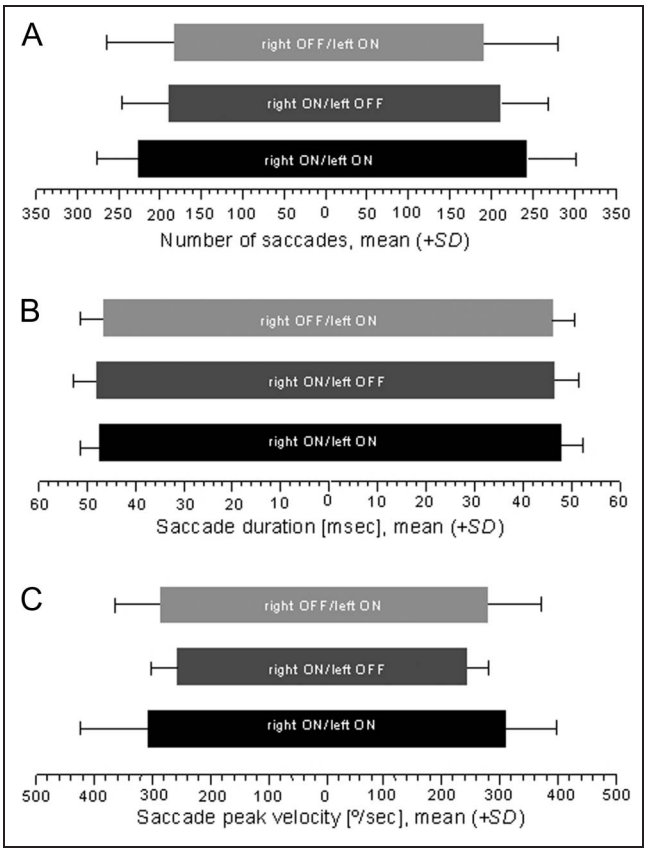

Figure 4. Saccade parameters are shown for right- and left-sided saccades: (A) number of saccades, (B) saccade duration, and (C) peak velocity. Data are given in mean (±*SD*).

DISCUSSION

Our patients showed a shift of spatial attention in the right OFF/left ON stimulation setting compared with the other stimulation settings. This imbalance in attentional recourses in this stimulation setting includes an increase in attention of right-sided stimuli and a reduced attention of left-sided stimuli. This imbalance in attentional resources is also seen in patients suffering from neglect after right hemispheral lesions (Karnath, Niemeier, & Dichgans, 1998). However, the magnitude of this shift is much smaller in our patients. These results support the role of the STN in modulating spatial attention. The right OFF/left ON stimulation setting resembles the situation of a unilateral nigrostriatal lesion on the right side at the level of the BG. Switching off STN stimulation on the right side increases BG outflow on the right and inhibits cortical projections of the corticosubcortical loops (Limousin et al., 1997). In parallel, the Parkinsonian signs worsened on the left side of the body. The left-sided STN stimulation inhibits the influence of the indirect BG pathway and consecutively releases cortical activation. This stimulation setting clinically resembles a left-sided hemiparkinsonism with an imbalance in BG tone. The net effect of an increased activation of the STN in the indirect pathway (the so-called no-go way) is an inhibition of movements and also cognitive aspects (Frank, Samanta, Moustafa, & Sherman, 2007; Frank, 2006). The inhibitory effect of electric stimulation of the STN inhibits the net effect of the indirect pathway (Ballanger et al., 2009), so the direct BG pathway that provides the "global go" is more influential (Volkmann, Daniels, & Witt, 2010). Switching off one side of the bilateral stimulation (e.g., right OFF/left ON), the stimulation ON condition of the left side partially restores BG function and the OFF condition on the right side does not influence the pathological changes of the BG circuits

(neglecting a small lesion effect of the electrode in the STN area; Mann et al., 2009). The result of a decrease in exploration time of the left hemispace in the right OFF/left ON condition can be interpreted in such a way that switching off the right stimulator critically affects the attentional system of the right hemisphere. So the stimulated left side might be less important for this bias in exploration. The reduced visuospatial attention of left-sided space in the unilateral left-sided stimulation setting is in line with previous studies demonstrating mild signs and symptoms of reduced visuospatial attention in left-sided hemiparkinson patients and, hence, in patients with a pathology in the right BG (Ebersbach et al., 1996). Our results further show that by switching on the stimulation of the right STN, symptoms of reduced visuospatial attention vanished. This finding indicates that the right STN is part of the network subserving spatial attention.

Signs and symptoms of neglect can be found after right and left hemispheric damage, but right-sided neglect after left hemispheric damage is often mild and lasts only a short time, which might explain the lack of reduced visuospatial attention after unilateral right-sided STN stimulation in our eye-tracking experiment. The right hemispheric dominance of the attentional system might be the consequence of hemispheric specialization after language development.

An STN lesion might influence spatial orientation in two principal ways: The STN has efferents to the putamen and the head of the caudate nucleus, which are subcortical structures that are involved in perceptual spatial orientation in humans (Karnath et al., 2002). Damage to these structures in the right hemisphere can lead to considerable signs and symptoms of neglect. Furthermore, the STN might influence spatial orientation via projections to the ACC of the right hemisphere. Imaging studies examining visual attention showed an activation of the right anterior cingulate gyrus, the intraparietal sulcus of the right posterior parietal cortex, and the mesial and lateral premotor cortices (Nobre et al., 1997). The STN is connected to the ACC by means of subcortico-cortical circuits (Hamani, Saint-Cyr, Fraser, Kaplitt, & Lozano, 2004). STN-DBS seems to modulate ACC activity in a task-specific manner (Schroeder et al., 2002; Limousin et al., 1997).

Apart from an influence on motor function and spatial orientation, the STN, as the BG in general, also has an impact on oculomotor functions, as animal studies have revealed (Nambu, Takada, Inase, & Tokuno, 1996). The clinical relevance is that PD patients have deficits in the initiation of voluntary saccades, their memory-guided saccades are hypometric, and latencies and error rates of antisaccades are increased (Vermersch et al., 1994). STN-DBS can positively influence the initiation of both reflexive and volitional saccades in PD (Yugeta et al., 2010). Furthermore, unilateral right or left STN-DBS has been known to induce contralateral gaze deviation (Sauleau et al., 2008). However, three facts argue against the assumption that our results are the effect of an alteration in the oculomotor system. First, conjungate eye deviations after unilateral STN stimulation were not detected in our patients on clinical evaluation in the different stimulation settings. Second, the analysis of the number, duration, amplitude, peak velocity, and acceleration peak of saccades did not reveal any significant differences between the stimulation settings. Third, we did not find any significant correlation between the changes in the UPDRS scores and changes in eye recordings. Moreover, if unilateral right or left STN stimulation produced an imbalance in the oculomotor system leading to a contralateral ocular deviation, a change in visual exploration behavior should be detectable in both the right OFF/left ON and in the rightON/left OFF stimulation setting. In our patients, however, an asymmetry in visual attention was detected after left-sided stimulation. Testing patients in an ON medication condition, we also have to discuss possible masking effects that might explain differences between oculomotor changes as reported by others (Yugeta et al., 2010). However, previous studies examined the oculomotor changes after unilateral STN-DBS using a memory-guided saccade design, whereas our study examined free exploration of pictures, which might also explain the differences between our results and the results of previous studies.

There are two major limitations in our study. Patients were not tested in a stimulation condition in which both electrodes were turned off (right OFF/left OFF) as a control situation. Nor were they tested after a withdrawal of dopaminergic medication. Both conditions would have been very difficult for the patients to tolerate because of severe motor symptoms. Consequently, it would not only have limited recruitment but also have influenced the results because most patients would not have been able to finish the test battery. However, these limitations do not attenuate the gist of our study, demonstrating the impact of the STN on space orientation.

In conclusion, our results prove earlier assumptions that unilateral STN-DBS leads to a disturbance in the exploratory component of spatial orientation and therefore changes exploration behavior in space. These changes in visuospatial attention are rather small but detectable when analyzing visual exploration behavior.

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