Pedunculopontine and Subthalamic Nucleus Stimulation Effect on Saccades in Parkinson Disease

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BACKGROUND: **Deep brain stimulation (DBS) of the pedunculopontine nucleus (PPN) has been explored as a target to treat axial motor symptoms of advanced Parkinson disease (PD). The aim of this study was to consider relative effects of bilateral subthalamic nucleus (STN) and PPN DBS on both initiation and inhibition of saccades in advanced PD.**

METHODS: **Five patients with advanced PD performed 2 different oculomotor tasks off stimulation, with bilateral STN DBS, with bilateral PPN DBS, and with simultaneous bilateral STN and PPN DBS. The first task involved visually guided saccades, and the second task involved antisaccades (ASs). Saccadic latency, accuracy, and velocity were recorded for both the visually guided saccade and AS tasks, and prosaccades were measured for the AS task alone. Control subjects included patients with advanced PD without DBS, age-matched healthy subjects, and young healthy subjects ($n = 12$ in each group).**

RESULTS: **Simultaneous bilateral STN and PPN DBS produced the greatest improvement in mean latencies, velocities, and accuracies for visually guided saccades and ASs compared with DBS off ($P < 0.001$). Bilateral STN and PPN DBS caused a significant additional improvement compared with STN DBS alone by reducing the number of prosaccades ($P < 0.01$).**

CONCLUSIONS: **It is known that the frontal lobe is involved in saccadic inhibition during AS tasks. Hence, our novel finding of an improvement in the AS task suggests an ascending, frontally mediated effect of PPN DBS. This implies that there may be PPN-to-frontal lobe connections that may partly explain the benefits of PPN DBS in axial motor function.**

INTRODUCTION

Parkinson disease (PD) is a progressive neurodegenerative disease with loss of dopaminergic neurons in the basal ganglia (BG) that is characterized clinically by tremor, rigidity, bradykinesia, and postural instability.[1] The BG, whose dysfunction may contribute to PD pathology, have 2 output pathways implicated in the control of voluntary movement: thalamocortical parallel pathways[2] and brainstem motor networks.[3] Part of the oculomotor fibers of the thalamocortical pathways project back to the frontal eye field and supplementary eye field, although not much is known about the neurophysiologic and pathophysiologic aspects. In contrast, the role of the brainstem outflow tracts in saccadic eye movement has been shown not only anatomically but also physiologically and pharmacologically.[3,4] Through the BG-superior colliculus (SC) pathway and the corticotectal pathways, the SC is thought to be involved in controlling saccadic eye movements. Therefore, saccades reflect the output of the BG and can be a good indicator of BG function.[5]

PD impairs not only somatomotor functions but also oculomotor functions. Saccades are defined as "rapid eye movements that are used to quickly bring the fovea, the portion of the retina that picks up the most detailed visual information, to bear on

Key words
- Antisaccades
- Deep brain stimulation
- Parkinson disease
- Pedunculopontine nucleus
- Saccades
- Subthalamic nucleus

Abbreviations and Acronyms
ANOVA: Analysis of variance
AS: Antisaccade
BG: Basal ganglia
DBS: Deep brain stimulation
GPi: Globus pallidus internus
PD: Parkinson disease
PPN: Pedunculopontine nucleus
SC: Superior colliculus
SNr: Substantia nigra pars reticularis
STN: Subthalamic nucleus
VGS: Visually guided saccade

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specific portions of the visual field."[6] As the ability to acquire high acuity visual information is critical to successful interaction with the environment, and as the fovea subtends only about 3° of the visual field,[7] saccades are produced frequently throughout each day.[8] Therefore, any problem in saccade processing, as occurs in PD, has a profoundly detrimental effect on the functional independence of patients, including in complex motor functions that are aided by visual feedback, such as gait and postural control (for prevention of falls).

The pedunculopontine nucleus (PPN) has been explored in primate models as a possible target for intervention to improve some of the axial motor symptoms in patients with advanced PD.[9-12] Simultaneous bilateral stimulation of the subthalamic nucleus (STN) and PPN using deep brain stimulation (DBS) has also been proposed as a treatment option for patients with severe PD who are not only refractory to medical therapy but also have prominent axial symptoms, that is, gait disturbance and postural instability.[13] In a study of patients with advanced PD, PPN DBS performed with standard STN DBS was shown to be useful in improving gait and optimizing the dopamine-mediated on state, particularly in patients whose response to STN-only DBS has deteriorated over time.[14]

STN and PPN DBS studies to date have not attempted to consider the effects of this therapy on eye movements. The aim of the present study was to assess the effects of this novel modality of DBS, that is, both STN and PPN DBS, on saccades—a measure that has been demonstrated to be a valid adjunct for quantifying the outcomes of DBS in patients with PD as well as being a source for functional improvement in everyday life, especially balance and coordination.[5,15] Furthermore, the results should help provide novel insights into the pathophysiology of PD and the neural networks involved. Based on the aforementioned current literature, we hypothesized that PPN DBS would cause an improvement in saccadic parameters for volitional antisaccadic tasks.

MATERIALS AND METHODS

Subjects

This study was approved by the Ethics Committee of Imperial College Healthcare NHS Trust. Written informed consent was obtained from all study participants. The experiments were conducted in accordance with the ethical standards of the Declaration of Helsinki. Four groups of subjects were included in the study. The first group comprised 5 patients with advanced PD undergoing bilateral STN and PPN DBS, who had 4 electrodes implanted each. These patients (all men, age 62.4 ± 5.32 years [mean ± SD]) were all Hoehn and Yahr scale stage 3 (mild to moderate bilateral disease; some postural instability; physically independent) and above in the off-DBS condition. Mean levodopa equivalent dose of patients was 530.5 ± 300.2 mg. All continued to take their usual antiparkinsonian medication dosage during the study (optimal medical therapy). Twelve patients with early PD (Hoehn and Yahr scale stage 2 and below, i.e., bilateral disease, without impairment of balance) who did not have DBS (age 68 ± 8.36 years), 12 age-matched healthy subjects (age 62.75 ± 5.57 years) and 12 healthy young subjects (age 25.83 ± 3.76 years) served as control subjects. All control groups contained equal numbers of male and female participants. With regard to the region of PPN targeted, we aim for the PPN compacta and then overshoot it by 2 mm (so that the brain lead definitely traverses the PPN). The location of the leads was confirmed by postoperative imaging (Figure 1). Furthermore, testing on the subjects was performed 3 months after implantation of the electrodes.

Experimental Setup

For this study, an experimental setup similar to that reported by Yugeta et al.[5] and Kato et al.[15] was used. The subjects were seated in a customized rotating chair, and their heads were immobilized with the built-in occipital clamp. The subject's head was immobilized with an occipital rest and temporoparietal clamps. A direct current binocular electro-oculogram was recorded with 3 silver–silver chloride gel electrodes (bilateral outer canthi for horizontal eye movement and 1 on the glabella to ground the circuit) with low-pass filtering at 20 Hz and digitizing at a sampling rate of 500 Hz. The electro-oculogram was calibrated before each experiment in steps up to 30° left and right of the midline with a laser projected target.

Experimental Procedures

Two oculomotor tasks—visually guided saccades (VGSs) and antisaccades (AS)—were performed during bilateral STN DBS, bilateral PPN DBS and simultaneous bilateral STN and PPN DBS. At least 1 hour after turning DBS off, the same tasks were performed in 5 patients in the off-DBS state. To exclude order effects, the on and off experiments were randomized in the 5 patients. Thus, the study was a double-blinded randomized controlled trial because both the experimenter and the subjects did not know their stimulation status. All experiments were performed 90–120 minutes after administration of patients' usual antiparkinsonian medication.

For the VGS task, a fixation laser point was turned on at 0°, and the subjects were instructed to fixate on this point. This was then turned off after 3 seconds, and simultaneously a new target laser point (cue) was turned on at 5°, 10°, 15°, 20°, or 30° to the left or right randomly, and the subjects were instructed to make a saccade as quickly as possible to the new position.

For the AS task, a fixation point and a cue point were turned on and off in the same way as in the VGS task, but this time only at 30° to the left or right randomly. The subjects were instructed to make an identical saccade but in the opposite direction of the stimulus cue. In other words, the actual target point for the saccade was a mirror image of the cue stimulus and had to be a full 30° to the opposite side.

The VGS task was performed first followed by the AS task. It would be impossible to randomize the tasks because providing a cue that the subjects needed to perform the AS task would prime them and defeat the whole purpose of the experiment. Without randomization, there was a learning effect (i.e., subjects improved as the task went on); however, this learning effect was present for all the subjects equally and therefore was controlled for and cancelled out in data analysis.

A schematic representation of the tasks is provided in Figure 2.

Data Analysis and Statistical Assessment

To omit artifactual saccades, inclusion and exclusion criteria were set. All data were extracted into Analysis software (MathWorks,

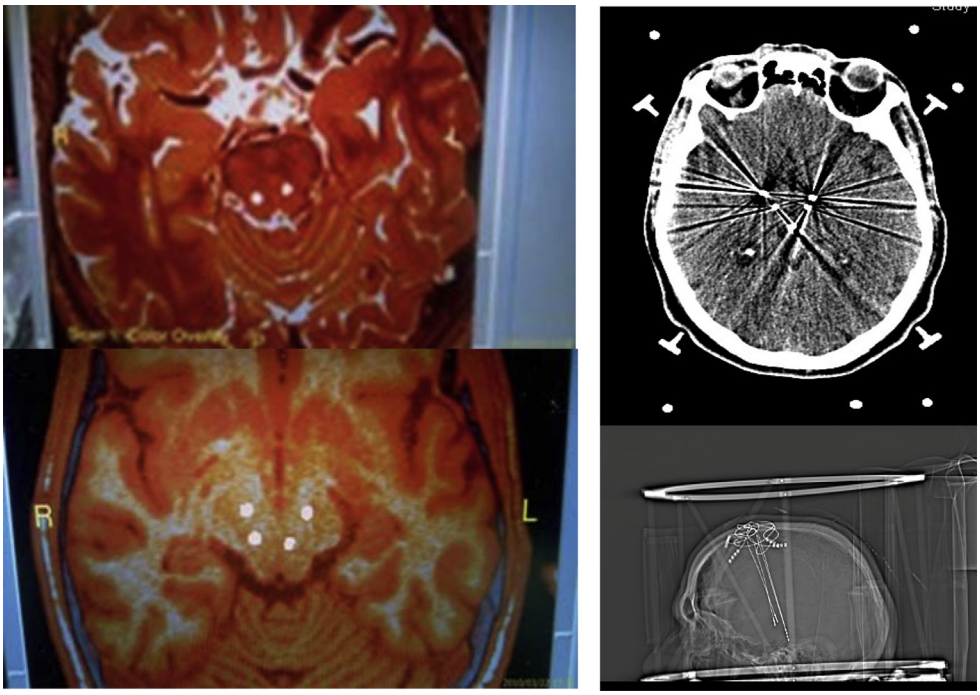

Figure 1. (**A**) Two axial magnetic resonance imaging scans obtained after subthalamic nucleus (STN) and pedunculopontine nucleus (PPN) electrodes implanted at 2 different craniocaudal planes. Top image shows the PPN electrodes; lower image shows both STN and PPN electrodes with the STN electrodes anterior and the PPN electrodes posterior. (**B**) Postoperative computed tomography images of the head showing 4 electrodes—2 in the STN and 2 in the PPN.

Natick, Massachusetts, USA), which was used for calibrating and measuring saccades. An eye movement (candidate for a saccade) was counted if its velocity and acceleration exceeded threshold values (28°/second and 90°/second, respectively). Also, after the onset of a saccade, the velocity had to exceed 88°/second, and this suprathreshold velocity had to be maintained for at least 10 ms. Saccades with a latency of <60 ms were classified as anticipatory and were excluded from further analyses.[16] Calibration for both tasks was carried out before and after the tasks to ensure accuracy. For all saccadic parameters, mean and SD were calculated.

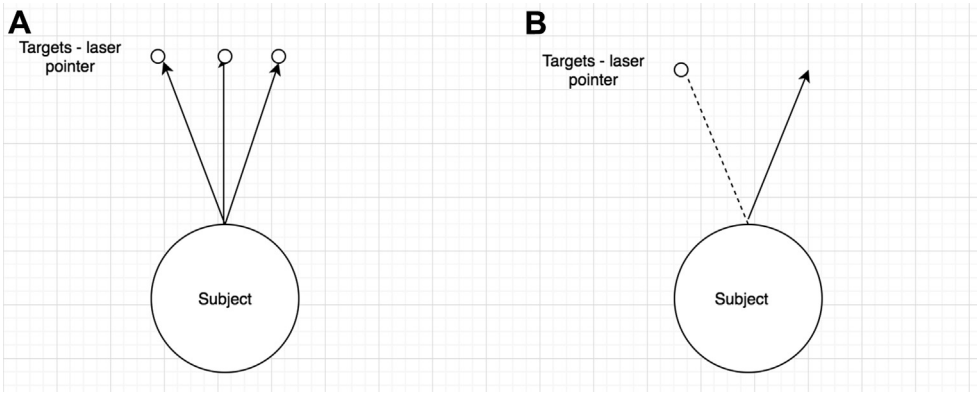

Figure 2. (**A**) Visually guided saccade task. The targets were presented randomly at different angles and directions, and the accuracy and velocity of the saccades were measured. (**B**) Antisaccade task. The target was presented, and the subjects were instructed to deliberately look in the opposite direction.

Four parameters were measured: mean latency, mean accuracy, and mean peak velocity were calculated for both the VGS and the AS tasks, and number of prosaccades was calculated exclusively for the AS task. Saccade accuracy was calculated as the ratio of the amplitude of the first saccade in degrees to the actual target presented in degrees. The number of prosaccades was calculated by counting the number of saccades the subjects made toward the visual target in error rather than the opposite direction as required of the task. The peak velocity of each saccade was calculated using digital differentiation. Saccadic parameters for prosaccades and ASs were always kept separate. However, the effects of DBS were analyzed separately as mentioned earlier. To assess the effect of STN and PPN DBS, both in combination and separately, one-way analysis of variance (ANOVA) was performed comparing all the subject groups followed by post hoc Tukey-Kramer testing to see which specific groups differed from each other.

RESULTS

VGS Task

All the subjects, from the healthy young control subjects to the patients with PD, performed better in the VGS task compared with the AS task (reduction in latency and increase in accuracy and velocity). The general trend of the results was that the latencies seemed to increase with increasing age, with the longest latency recorded in the patients with advanced PD in off-DBS state. An improvement (i.e., a reduction in mean latency and increase in accuracy and velocity) was seen for prosaccades with STN DBS. Simultaneous bilateral STN and PPN DBS caused an even greater on-top effect of reduction of saccadic latencies and increase in velocities and accuracy, but there was no such effect after PPN DBS alone. **Figure 3A** illustrates the findings for the different groups, whereas **Figure 3B** illustrate the results for the individual subjects. ANOVA results of only the groups (i.e., a common pool of saccades per group) have been included for ease of understanding because the individual patient results were in agreement with the grouped data.

The general trend of increasing latencies from the young healthy control subjects to the age-matched control subjects and patients with PD and a decrease with DBS for the VGS task was found to be statistically significant ($F_6 = 4.19$, $P < 0.001$). To check for specific differences between the individual groups, a post hoc Tukey-Kramer test showed that STN DBS on its own caused a significant decrease of 41% ($P < 0.05$) in the mean latency of patients compared with their off-DBS state. Furthermore, a greater decrease of 50% at $P < 0.01$ was caused by simultaneous bilateral STN and PPN DBS compared with the off-DBS state. Although causing a greater improvement in the mean latency, simultaneous bilateral STN and PPN DBS was not significantly different from STN-DBS. Also, PPN DBS on its own produced a negligible decrease in the mean latency.

Regarding saccadic accuracy (i.e., the ratio of the first saccade to the actual desired target angle), there was a general trend of decreasing mean accuracy from the younger to older control subjects (1.03 ± 0.31 vs. 0.94 ± 0.30), with the patients with advanced PD in off-DBS state making the least accurate saccades (0.53 ± 0.28). The near-perfect accuracies seen in the healthy control subjects can be attributed to a floor-ceiling effect—slight overshooting and undershooting of saccades average out to give values close to 1.[17] STN DBS improved saccadic accuracy on its own (0.83 ± 0.28) or combined with PPN DBS (0.89 ± 0.15), whereas PPN DBS alone had no effect (0.54 ± 0.34). ANOVA for these 3 results was statistically significant ($F_6 = 3.74$, $P < 0.001$).

STN DBS on its own produced an increase from 0.42 to 0.86 (i.e., 109.70%; $P < 0.05$) in mean accuracy compared with off-DBS state. An increase of 117.07% from 0.42 to 0.89 ($P < 0.05$) in mean accuracy was seen with simultaneous bilateral STN and PPN DBS compared with off-DBS state; however, the difference between the additive effect of simultaneous bilateral STN and PPN DBS over STN DBS on its own was not significant (**Figure 3A**).

A general trend toward decreasing velocities with age, with patients with advanced PD with DBS off being the slowest, was noted. Saccadic velocities depend on the amplitude of the saccades, and because patients with PD have hypometric saccades (i.e., smaller amplitudes), the saccadic velocities for the VGS task were compared for the same amplitude target (i.e., 20°) for all the groups to allow for a fair comparison. The results showed that simultaneous bilateral STN and PPN DBS seemed to improve velocities in patients with advanced PD (from 235.21 ± 50.54°/second to 290.36 ± 41.64°/second) as did STN DBS alone (from 235.21 ± 50.54°/second to 285.45 ± 53.51°/second) compared with the off-DBS state (**Figure 4A**). ANOVA showed that this general trend of the greatest increase in velocity caused by combined STN and PPN DBS was statistically significant ($F_6 = 3.61$, $P = 0.05$). However, post hoc Tukey-Kramer testing showed that when looked at individually, this 23.45% increase in velocity by combined STN and PPN DBS and 21.36% increase by STN DBS alone compared with the off-DBS OFF state were not enough to be statistically significant; all results are given in **Table 1**.

Antisaccade Task

The AS task followed a similar pattern to the parameters in the VGS task, with latencies tending to increase with age and with patients with advanced PD with DBS off having the longest latencies (mean latency 914.72 ± 285.01 ms compared with 441.70 ± 135.07 ms for the young control subjects—ANOVA, group effect, $F_6 = 3.52$, $P < 0.005$) (**Figure 4B**). DBS did improve the latencies from the off-DBS condition, however, with simultaneous bilateral STN and PPN DBS causing a decrease in mean time of 50.44% ($P < 0.05$) and STN DBS only causing a decrease of 46.89% ($P < 0.05$). PPN DBS alone in this case decreased the latency by 16.72% from the off-DBS state, but this was not significant. A graphic representation of the AS task data is provided for the data divided into groups (**Figure 3C**) and for data of each individual patient (**Figure 3D**). Again, only the statistically significant data for the pooled data across all subjects in each group were included for ease of interpretation and owing to the agreement of the individual data with the grouped set.

There was similarly a general trend of decreasing accuracy from the younger to older controls (0.83 ± 0.55 vs. 0.75 ± 0.57), with patients with advanced PD with DBS off performing least accurately (0.54 ± 0.50). However, STN DBS stimulation, both alone and combined with PPN DBS, seemed to improve their accuracy, whereas PPN DBS alone seemed to have a negligible effect. This trend was not statistically significant.

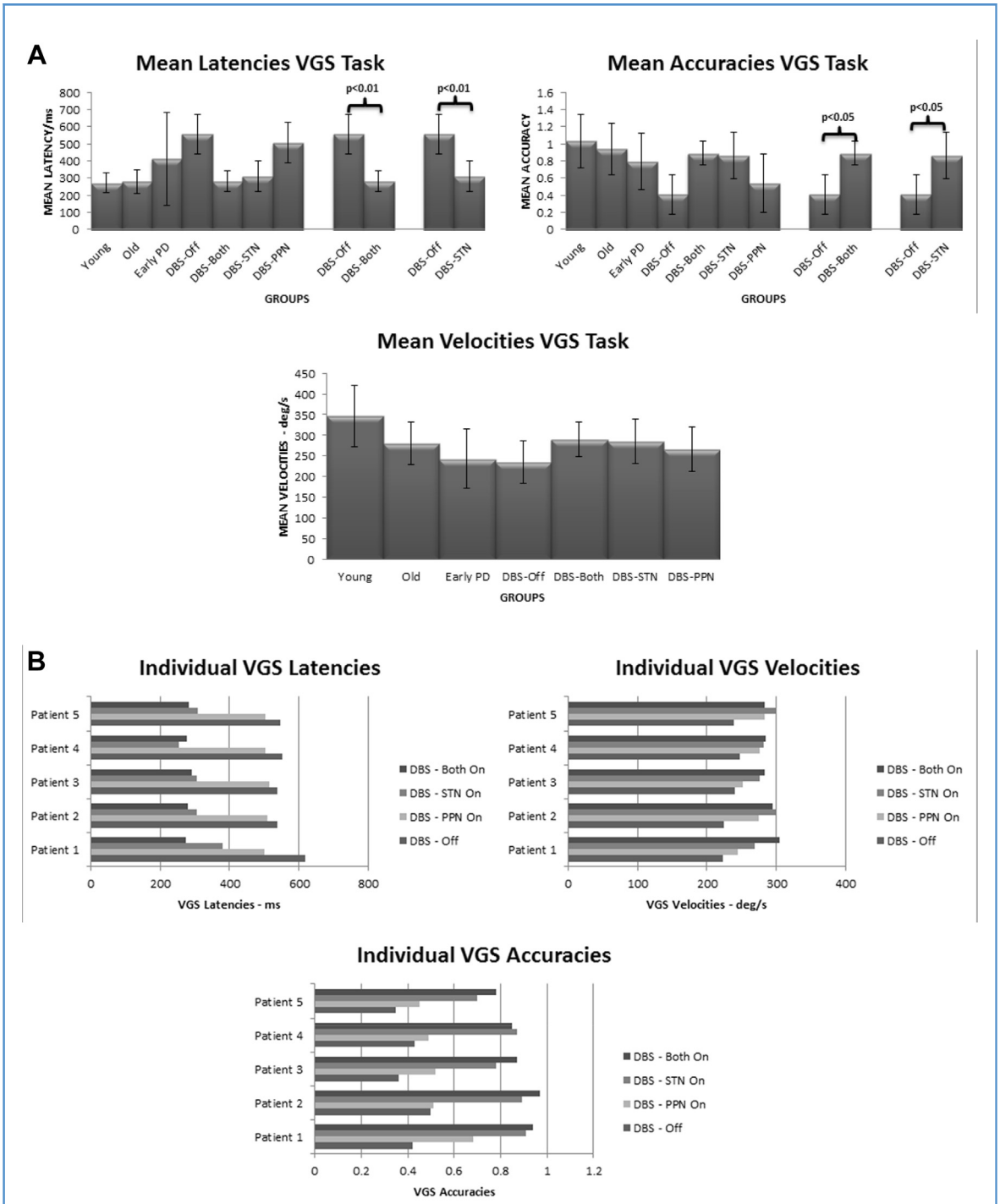

Figure 3. (**A**) Parameters for visually guided saccade task. Mean latencies and accuracies are represented, and statistically significant results are indicated by brackets. Vertical lines represent SD. (**B**) Individual patients showed a similar trend of improvement of parameters for the reflexive visually guided saccade saccades with deep brain stimulation. The greatest improvement was seen with combined deep brain stimulation of subthalamic nucleus and pedunculopontine nucleus ($P < 0.01$). (**C**) Graphic representation of antisaccade task in terms of mean latencies, prosaccades, and velocities. Statistically significant results are indicated by brackets. Vertical lines represent the SD. (**D**) Individual representation of patients with respect to volitional antisaccade task. VGS, visually guided saccade; DBS, deep brain stimulation; STN, subthalamic nucleus; PPN, pedunculopontine nucleus; AS, antisaccade. (Continues)

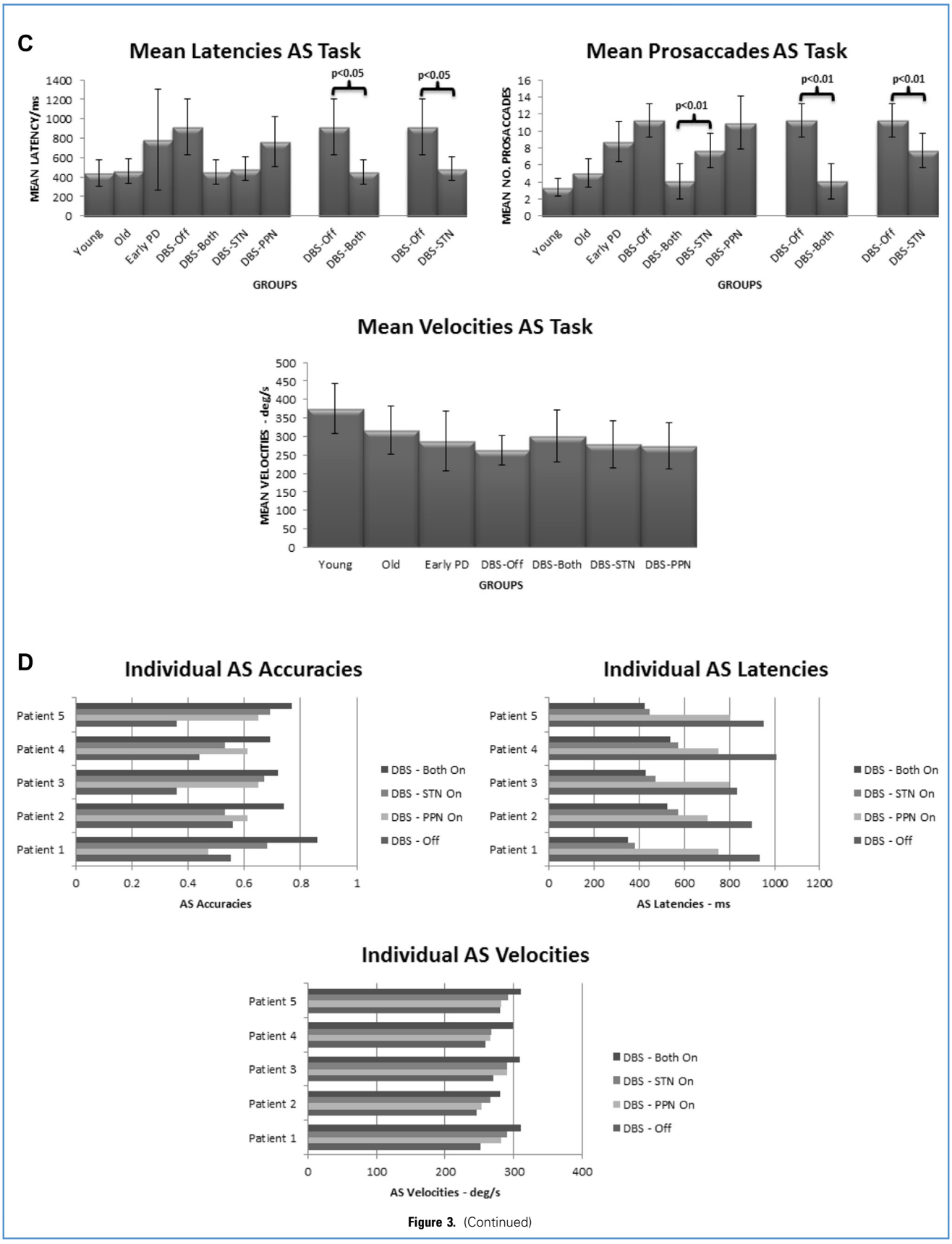

Figure 3. (Continued)

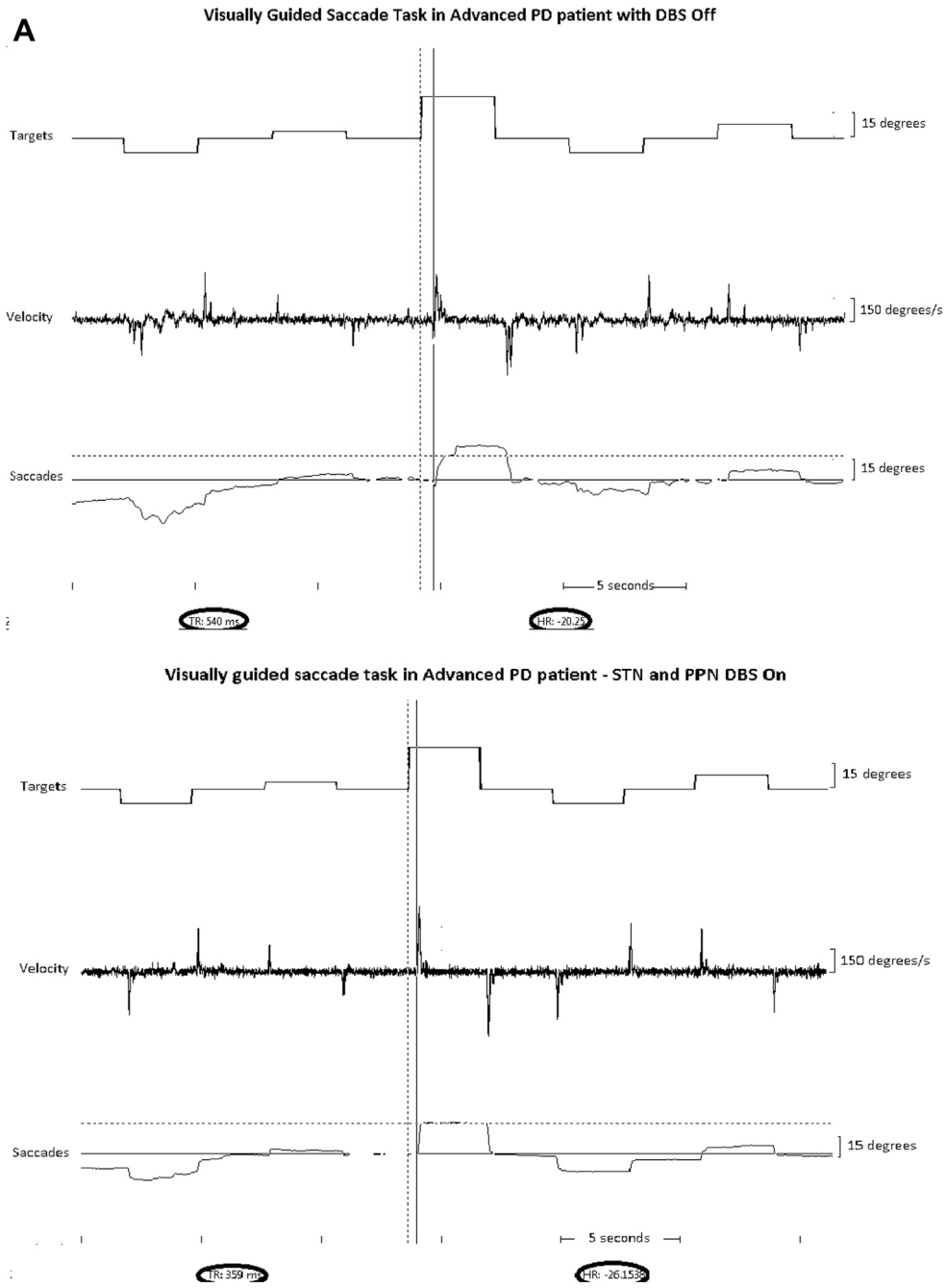

Figure 4. (**A**) Saccadic trace showing a patient with advanced Parkinson disease with no deep brain stimulation performing the reflexive visually guided saccade task. Lower trace showing the same patient performing the same task with combined subthalamic nucleus and pedunculopontine nucleus deep brain stimulation switched on. There is marked improvement in the accuracy—26.15° compared with 20.25° (numbers circled in black on the right), both aiming for 30° target. Similarly, the latency improved from 540 ms to 359 ms (numbers circled in black on the left) with the deep brain stimulation on. (**B**) Upper saccadic trace showing a patient with advanced Parkinson disease with deep brain stimulation switched off. Lower trace showing the same patient with subthalamic nucleus and pedunculopontine nucleus deep brain stimulation switched on. The trace in the middle of the diagrams shows the velocity measured in°/second. The prosaccades (errors) are underlined, and the bottom right-hand reading circled in black is the velocity (°/second), and the left hand reading circled in black is the latency (ms). As shown, the number of prosaccades decreased with deep brain stimulation subthalamic nucleus and pedunculopontine nucleus deep brain stimulation on in the lower trace. Also, the velocity increased from 150°/second to 198. 21°/second with deep brain stimulation in the lower trace. PD, Parkinson disease; DBS, deep brain stimulation; STN, subthalamic nucleus; PPN, pedunculopontine nucleus. (Continues)

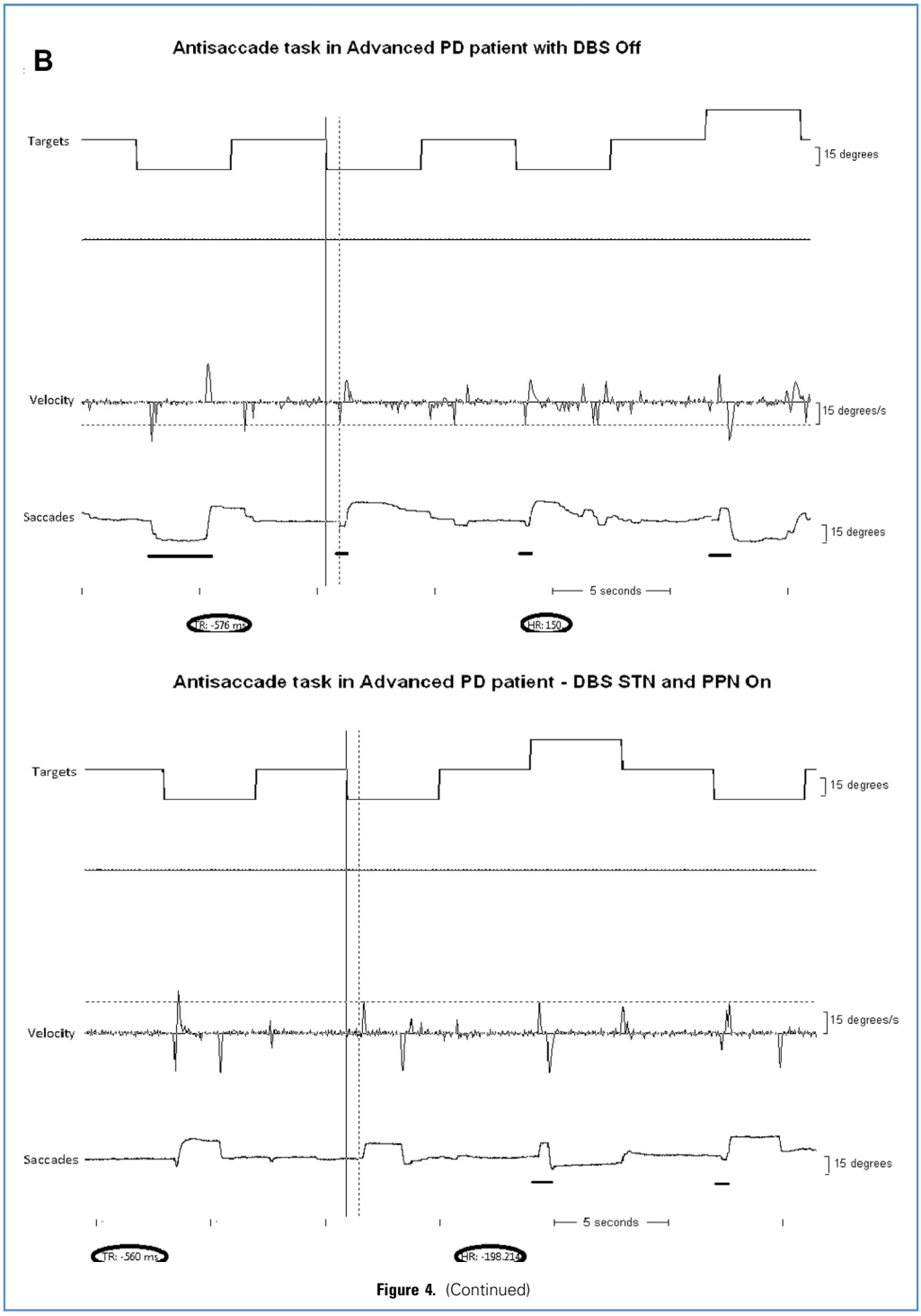

Figure 4. (Continued)

In keeping with published literature, we used the total number of prosaccades as a measure of improvement or worsening in the AS task.[5,15] The general trend of worsening of the parameters with age and PD continued, with healthy young control subjects having a mean number of 3.34 ± 1.03 prosaccades out of 20 saccadic trials and patients with advanced PD having a mean of 11.24 ± 1.98 out of 20 saccadic trials. STN DBS, both alone and combined with PPN DBS, seemed to decrease the number of prosaccades. This

Table 1. Mean Visually Guided Saccade Velocities

Group	Mean Velocities	SD
Young control subjects	347.129	73.927
Age-matched control subjects	279.937	50.961
Early PD patients	243.200	71.183
DBS—both off	235.210	50.544
DBS—both on	290.360	41.639
DBS—STN on	285.445	53.509
DBS—PPN on	266.465	53.516

PD, Parkinson disease; DBS, deep brain stimulation; STN, subthalamic nucleus; PPN, pedunculopontine nucleus.

Table 3. Mean Velocities for Antisaccade Task

Group	Mean Velocities	SD
Young control subjects	375.37	68.39
Age-matched control subjects	316.26	64.59
Early PD patients	287.57	80.09
DBS—both off	262.65	38.71
DBS—both on	301.28	69.81
DBS—STN on	279.50	64.31
DBS—PPN on	273.95	62.56

PD, Parkinson disease; DBS, deep brain stimulation; STN, subthalamic nucleus; PPN, pedunculopontine nucleus.

aforementioned trend of results for the data was statistically significant ($F_6 = 19.42$, $P < 0.001$).

The 63.79% improvement (i.e., reduction in number of prosaccades) caused by simultaneous bilateral STN and PPN DBS in patients with advanced PD compared with DBS off was significant on post hoc testing ($P < 0.01$). The 31.76% improvement caused by STN DBS alone was also found to be significant on the Tukey-Kramer post hoc test ($P < 0.01$). Furthermore, the Tukey-Kramer test showed that the effect of simultaneous bilateral STN and PPN DBS was significantly different from the effect of STN DBS alone ($P < 0.01$); this is the most important finding of the study and is further highlighted in the Discussion. The slight decrease in the number of prosaccades caused by PPN alone was not significant compared with the baseline off-DBS state. Table 2 presents results for the number of AS prosaccades.

Table 2. Mean Number of Prosaccades and Analysis of Variance Statistics for Antisaccade Task

Group	Mean Number of Prosaccades	SD
Young control subjects	3.34	1.03
Age-matched control subjects	5.05	1.67
Early PD patients	8.70	2.35
DBS—both off	11.24	1.98
DBS—both on	4.07	2.03
DBS—STN on	7.67	2.00
DBS—PPN on	10.98	3.08

Source of Variation	Sum of Squares	Degrees of Freedom	Variance	*F* Value	*P* Value
ANOVA Statistics					
Between groups	450.08	6	75.01	19.42	<0.001
Within groups	189.20	49	3.86		
Total	639.28	55			

PD, Parkinson disease; DBS, deep brain stimulation; STN, subthalamic nucleus; PPN, pedunculopontine nucleus; ANOVA, analysis of variance.

Saccadic mean velocity in AS results also matched the previous trend of parameters decreasing with age and being slowest in patients with advanced PD in the off-DBS state. There was an increase of 14.71% caused by simultaneous bilateral STN and PPN DBS as opposed to smaller increases of 6.42% caused by STN DBS alone and 4.3% seen with PPN DBS alone compared with OFF-DBS. This overall trend was found to be significant on ANOVA ($F_6 = 2.92$, $P = 0.016$); however, Tukey-Kramer post hoc analysis showed that when looked at individually, these increases in velocity were not statistically significant. Table 3 shows the detailed results for the AS velocities.

DISCUSSION

The main findings of the study, depicted in Figure 3A and B for the VGS task and Figure 3C and D for the AS task, can be summarized as follows:

1. Both VGSs and ASs are affected by age. Patients with early PD and patients with advanced PD were the most seriously affected in that order, faring worse than age-matched control subjects.
2. STN DBS causes improvement in mean latency and accuracy for the VGS task and mean latency, velocity, and number of prosaccades for the AS task.
3. Simultaneous bilateral STN and PPN DBS causes an even greater on-top effect of improvement in the prosaccades for the AS task.
4. PPN DBS alone has no significant effect on VGSs or ASs.

We found that both VGSs and ASs deteriorate with age and are significantly affected by PD. This has been found by numerous studies looking at the effects of age and PD on saccades.[18-20] Thus, our results confirm results in the literature showing that age and PD are detrimental to all parameters of both prosaccade and AS tasks. The reasons behind this have been discussed previously.[18-21]

The fact that STN DBS alone causes an improvement in various saccadic parameters has been documented before. Yugeta et al.[5] showed that STN stimulation improves both VGSs and ASs; they

found that with STN DBS there were shorter latencies and increased amplitudes for the VGS tasks. This was similar to our findings in that latencies were improved; however, we used velocity rather than amplitude as a comparable parameter, which, in keeping with the results of Yugeta et al.,[5] increased with STN-DBS significantly. Yugeta et al.[5] also found that in the volitional AS tasks the improvement in accuracy with STN DBS was insignificant, in contrast to the clear improvement documented in this study. Furthermore, Yugeta et al.[5] found the number of prosaccades (errors) in the AS task to be significantly decreased, a finding that we were able to confirm (**Figure 3C**).

There are 2 current theories regarding BG function and DBS that may be invoked for analyzing the STN DBS findings of this study. The first is the rate model theory, which proposes that when DBS is applied to the STN, it reduces its firing rate and hence the excessive inhibitory output through the globus pallidus internus (GPi)—substantia nigra pars reticularis (SNr) circuit, meaning that STN-DBS would not only facilitate initiation of saccades but also would increase the frequency of unwanted prosaccades to cue in the AS task.[22] This should mean that STN DBS would cause an improvement in the VGS task but more prosaccades and worse accuracy in the AS task. However, this conflicts with the results of the present study. STN DBS decreased the frequency of prosaccades and improved AS accuracy, suggesting that DBS at least partially restored the inhibitory control of VGSs. This restorative effect indicates that STN DBS helps to modulate the inhibitory function of the BG in PD, setting the excitability of SC at an appropriate threshold, both for initiating and for inhibiting saccades. This result seems consistent with the suggestion that the STN plays an important role in keeping the eye position fixed.[23]

Compared with the rate model, the second model of the BG circuit, known as the oscillation model, better explains our results. Studies done recently on the BG and related structures have taken into account oscillations in the BG.[24-27] In PD, beta band oscillations in BG are abnormally elevated. A disruption in the synchronization of these beta band oscillations by gamma band oscillation is required to fulfill motor commands and override the elevated threshold for saccade generation because the gamma band appears to be more conducive to movement. Therefore, STN DBS would decrease the pathologic beta band oscillations and facilitate movement in PD by enhancing the gamma band. Although this process lowers the threshold for movement for the BG, it does so by actually reducing the output of the BG to its connecting structures. According to Yugeta et al.,[5] reduction in oscillatory activities by DBS would help maintain appropriate SC excitability required for saccade initiation and inhibition by normalizing the leaky suppression exerted by BG and decrease the emergence of unwanted saccades to cue. Therefore, STN DBS facilitates the initiation commands for saccades, while offsetting the inhibition commands. Furthermore, it has been proposed by the same authors that the pathologic beta band oscillations may also disrupt the processing involved in saccade inhibition at the cortical and subcortical regions via disruption of the BG-thalamocortical pathway.[28] STN DBS would occlude this disruptive input and enable effective neural processing in these cortical and subcortical circuits, thus facilitating saccades.

Regarding ASs, the AS task has been consistently used for measuring the ability to inhibit unwanted and reflexive saccades; that is, it is a volitional, top-down task under cortical control.[29] In our study, the frequency of prosaccades in the AS task was higher in patients with PD than in control subjects, which is consistent with previous reports.[30-32] The occurrence of prosaccades in the AS task has been explained by the failure of the prefrontal cortex to inhibit the SC directly via descending pathways,[30,33,34] although some involvement of the BG (i.e., the caudate nucleus) has also been suggested for ASs.[35-37] Therefore, STN DBS may specifically affect the inhibitory mechanism of saccades mediated by the BG output through the GPi-SNr outflow rather than that mediated by the frontal cortex, leaving the frequency of prosaccades unaffected.

Until now, the discussion has focused on the effects of STN DBS on saccades in advanced PD. However, the novel aspect in our study was the effect of PPN DBS, alone and with STN DBS, on saccades in patients with advanced PD. Interestingly, acting alone, PPN DBS seemed to have no significant effect on any of the parameters for both the AS and VGS tasks. However, when combined with STN DBS, PPN DBS produced the highest increased improvement in the latency, velocity, and accuracy parameters for the VGS task and the latency, velocity, accuracy, and prosaccades in the AS (volitional) task on ANOVA. The over and above effect of PPN DBS when combined with STN DBS compared with STN DBS alone was statistically significant only on post hoc testing for reduction of the number of prosaccades in the AS task. The importance of this finding is that both our study and previous studies examining PPN DBS have not reported any effects on eye saccades.[38] Also, anatomically and physiologically, the role of the PPN in the above-mentioned functional loops controlling saccades has not been ascertained, in contrast to the well-documented involvement proposed for the STN. As mentioned earlier, this enhancing effect brought on by the combination of PPN with STN DBS was significantly larger than the effect of STN DBS alone for the AS task and number of prosaccades. This novel observation that PPN DBS facilitates the effects of STN DBS suggests a role for it in the GPi-SNr-SC loop. This finding opens up interesting neurophysiologic and neuroanatomic possibilities; in particular, it may help to explain the manner in which PPN stimulation may influence axial motor function in PD, as discussed subsequently.

Previous studies on PPN DBS have shown that modulation of the activity of the PPN with DBS may be beneficial in the treatment of gait dysfunction and akinesia.[39] This is because the PPN is involved in locomotion, control of posture, and behavioral states (i.e., wakefulness, rapid eye movement sleep). Another study set out to see how PPN DBS improved gait.[40] The 2 possible mechanisms tested were attentional augmentation and enhanced motor function. The results suggested that the improvements seen in certain parameters of gait were due to a benefit in motor performance, rather than augmentation of attention.[40] Our study may suggest that this effect may depend on the influence of PPN DBS on the GPi-SNr inhibitory outflow.

Another study on PPN DBS showed that stimulation of the PPN induced significant regional cerebral blood flow increment in subcortical regions, such as thalamus, cerebellum, and midbrain, and different cortical areas involving medial sensorimotor cortex extending into the caudal supplementary motor area.[41] The study

showed that PPN DBS in advanced PD resulted in blood flow and presumably neuronal activity changes in subcortical and cortical areas involved in balance and motor control including the mesencephalic locomotor region (e.g., PPN) and closely interconnected structures within the cerebello-rubrothalamocortical circuit. This suggested that stimulation of the PPN may cause functional changes in neural networks associated with motor control. The fact that these motor cortex regions as well as the midbrain (more specifically the SC) are involved in the control of saccades may suggest a role for the PPN in controlling eye movements. However, the fact that PPN DBS alone showed no improvement in any saccadic parameter suggests that the structural circuits are more complex than the structural circuits of the STN. Furthermore, the amplified improvement when STN and PPN DBS were combined suggests that there is some overlap and interaction in the neural circuits controlling saccades from both these nuclei. This study shows that PPN DBS has no direct effect on controlling saccades on its own but does have an indirect, beneficial, modulatory effect, as evidenced by the fact that it causes improvement in both visually guided and antisaccadic parameters when deployed in combination with STN DBS.

Various studies have reported that of the BG nuclei, the substantia nigra pars compacta and the STN receive the bulk of the PPN efferents.[42-44] This suggests that a possible mechanism for the improvement in various saccadic parameters by the combination of STN and PPN DBS could be via these anatomic connections with the STN. This added improvement caused by the PPN working with the STN could perhaps be facilitated by helping the STN improve saccadic function through the oscillation model mentioned earlier.

Furthermore, Androulidakis et al.[38] have shown reciprocal connectivity between the PPN and the cortex, including the frontal eye fields involved in controlling ASs. The AS task is a top-down task controlled by the frontal eye fields and the SC.[29] Our results that show the on-top effect of STN and PPN DBS compared with STN DBS on its own is statistically significant for the reduction in number of prosaccades reiterate this point and suggest, although in no way prove, a structural and functional link between the PPN and the frontal cortex, more specifically the frontal eye fields.

As mentioned before, the present study shows that PPN DBS does not ameliorate saccadic movements but has an additive effect on improvements induced by STN DBS. The mechanism that may explain this effect remains unclear, but it may be searched in the BG circuitry governing the preparation and execution of saccades. It is not easy to answer this question, as PPN neurons are lost in PD, and it is impossible to know at what extent PPN neurons are lost in individual patients with PD. It may be that the effects are facilitated by surviving PPN neurons activating STN neurons, which activate GPi neurons that are inhibitory to SNr neurons, thus inhibiting the SNr-SC pathway, the inhibition of which allows for saccades.[45] Another issue is that PPN neurons in monkeys performing visually guided tasks codify for saccade execution and fixation target.[46] However, if these neurons are lost in patients with PD, their action would not be seen during PPN DBS. A direct action of PPN neurons on oculomotor neurons would be excluded, as anatomic tracing studies have not demonstrated the existence of a direct pathway between PPN and oculomotor neurons. In contrast, fibers linking the PPN to cranial nerve V, VII, and XII nuclei have been reported, and this may account for the improvements of oromandibular movements and speech during PPN DBS reported by some authors.[47,48]

Limitations

A major limitation of this study is the relatively small sample size of subjects with DBS. Another limitation is that more parameters could have been looked at, including the direction of and measurements of vertical and rotational saccades for both tasks.

CONCLUSIONS

This study shows that STN and PPN DBS work synergistically to improve VGSs and, as a novel finding, ASs in patients with advanced PD. These results build on previous work that looked at the effect of STN DBS alone and provide insight into the possible neural motor control mechanisms and frontal pathways involved in PD. In the current clinical management of PD, PPN DBS is being explored as an important adjunct to STN DBS in patients with advanced PD with prominent axial motor and balance problems. The results from this study add further data that support the clinical usefulness of simultaneous STN and PPN DBS in improving motor function. Eye movements are an important part of the ecologic control of balance and gait,[49] and so improvement of voluntary gaze control in this study could be particularly relevant for the prevention of falls in these patients by allowing appropriate visual inspection of the environment.[50] Future work should involve testing more patients with PPN DBS for the effects on saccades and correlating findings with clinical and imaging changes. The latter may include functional magnetic resonance imaging and positron emission tomography scans to establish a more complete picture of the neurobiologic and metabolic changes involved as well as computational modeling studies, as have been previously done for STN DBS.[51,52]

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