SHORT REPORT

Improvement of memory guided saccades in parkinsonian patients by high frequency thalamic nucleus stimulation

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Abstract

Recent studies in the monkey suggest that the subthalamic nucleus (STN) is involved in control of eye movement, yet its functional significance in humans is unknown. Saccadic eye movements were measured in eight parkinsonian patients treated with bilateral electrical stimulation of the STN. STN stimulation improved the accuracy of memory guided saccades but not of reflexive visually guided saccades and had no effect on the antisaccade task. This study shows that, by contrast with levodopa, STN stimulation improves memory guided saccade deficits, and illustrates for the first time in humans the role of the STN in the control of purposive saccades.

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Keywords: subthalamic nucleus; saccades; Parkinson’s disease

The role of the subthalamic nucleus (STN) in the control of limb movements is well established. Recent experimental studies suggest that it is also involved in eye movement control.1 In monkeys, the STN is directly connected with the frontal eye field and provides excitatory inputs to the substantia nigra pars reticulata (SNpr). Moreover, the monkey STN contains neurons that discharge during attentive fixation, and neurons with saccade related activity, discharging during memory guided saccades, and visually guided saccades.1 To investigate the role of the STN in eye movement control in humans, we took the advantage of the presence of electrodes in the STN of patients with Parkinson’s disease treated by continuous high frequency stimulation.2–7 We studied the influence of bilateral STN stimulation on reflexive visually guided saccades, antisaccades, and memory guided saccades in eight patients with severe levodopa responsive Parkinson’s disease.

Subjects and methods

Eight patients with idiopathic Parkinson’s disease and with bilateral electrodes implanted in the STN were studied (table 1). The delay between surgery and eye movement recordings was 7 (SD 5) months. At that time, all patients had significantly improved clinically (Hoehn and Yahr “off” condition=1.7 (SD 0.1) and “on” drug condition=0.8 (SD 0.1) and their drug treatment had been reduced to 545 (SD 105) mg/day (levodopa equivalent dose). Each patient was studied in two sessions in pseudorandom order. In one session (“STN on”), bilateral continuous stimulation was applied to the STN. The electrical parameters were those used chronically to treat the patients: frequency=137 (SD 27.6) Hz, pulse width=58.8 (SD 8.6) µs and voltage=2.4 (SD 0.7) V. In a session performed another day (“STN off”), stimulation was stopped 2 hours before eye movement recordings. In both conditions, levodopa treatment was given 2 hours before eye movement recordings; the patients did not receive anticholinergic drugs. Four patients began by the “STN on” condition and the four others by the “STN off” condition. The patient’s motor score (Unified Parkinson’s disease rating scale part III) was 10 (SD 7) in the “STN on” condition and 20 (SD 7) in the “STN off” condition.

A control group of 10 subjects (age 53.4 (SD 10) years) without any history of neurological disorders was studied with the same paradigms as the patient group. All subjects gave written informed consent before participation in the

Table 1 Clinical characteristics of parkinsonian patients

<table>
<thead>
<tr>
<th>Patients</th>
<th>Age (y)</th>
<th>Disease duration (y)</th>
<th>Before surgery</th>
<th>After surgery</th>
<th>Before surgery</th>
<th>After surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hoehn and Yahr (off/on)</td>
<td>Treatment (mg/day)</td>
<td>Hoehn and Yahr (off/on)</td>
<td>Treatment (mg/day)</td>
</tr>
<tr>
<td>1</td>
<td>40</td>
<td>15</td>
<td>5/4</td>
<td>1250</td>
<td>1.5/1</td>
<td>1100</td>
</tr>
<tr>
<td>2</td>
<td>45</td>
<td>11</td>
<td>5/4</td>
<td>1550</td>
<td>1.0/0</td>
<td>525</td>
</tr>
<tr>
<td>3</td>
<td>50</td>
<td>10</td>
<td>3/1.5</td>
<td>1550</td>
<td>1.0/0</td>
<td>200</td>
</tr>
<tr>
<td>4</td>
<td>54</td>
<td>17</td>
<td>4/2</td>
<td>600</td>
<td>2/1</td>
<td>250</td>
</tr>
<tr>
<td>5</td>
<td>65</td>
<td>11</td>
<td>5/2.5</td>
<td>1450</td>
<td>2/1</td>
<td>450</td>
</tr>
<tr>
<td>6</td>
<td>46</td>
<td>15</td>
<td>5/3</td>
<td>1500</td>
<td>1.5/1</td>
<td>500</td>
</tr>
<tr>
<td>7</td>
<td>59</td>
<td>14</td>
<td>5/1</td>
<td>1575</td>
<td>2.5/1</td>
<td>875</td>
</tr>
<tr>
<td>8</td>
<td>61</td>
<td>8</td>
<td>4/2</td>
<td>1750</td>
<td>2/1</td>
<td>475</td>
</tr>
<tr>
<td>Mean</td>
<td>52.5</td>
<td>12.6</td>
<td>4.5/2.5</td>
<td>1400</td>
<td>1.7/0.8</td>
<td>545</td>
</tr>
<tr>
<td>SEM</td>
<td>3.1</td>
<td>1.1</td>
<td>0.3/0.4</td>
<td>125</td>
<td>0.2/0.2</td>
<td>105</td>
</tr>
</tbody>
</table>

Treatment is expressed in dosage of levodopa equivalent.
Hoehn and Yahr scores were assessed in the “off” and “on” drug conditions.
study, which was approved by the local ethics committee.

Eye movements were recorded using horizontal binocular direct current electromyography with a sampling frequency of 200 Hz. Visual cues were presented at a distance of 95 cm with red light emitting diodes embedded in a curved ramp (Gaymard et al).

**REFLEXIVE VISUALLY GUIDED SACCADES**

Reflexive visually guided saccades were studied with a gap paradigm. Subjects were instructed to initially fixate a central fixation point that was illuminated to allow a corrective saccade to appear randomly right or left 200 ms (temporal gap) after the extinction of the central fixation point. Saccade latency and saccade gain (saccade amplitude over target amplitude) were measured by averaging values from at least 12 trials in each direction.

**Antisaccades**

The ability to inhibit reflexive visually guided saccades and to trigger voluntary non-visually guided saccades was tested by the antisaccade task. The same stimulus condition as in the visually guided saccade task was used, but subjects were instructed to look, as quickly as possible, in the direction opposite to the peripheral target (perform an antisaccade) without instructions about saccade amplitude. The result was expressed as percentage of errors by averaging values from at least 18 trials in each direction. Only correct antisaccades were used for the calculation of saccade latency.

**Memory guided saccades**

Purposive saccades and spatial short term memory were tested by a memory guided saccade task. The central fixation point was maintained during the entire delay, and to trigger a saccade towards the remembered location of the flash as soon as the central fixation point was switched off. Two seconds later, a target with the same location as the flash was illuminated to allow a corrective saccade to be triggered, if necessary. Saccade latency and gain (accuracy) of the initial saccade and of the final eye position (the eye position reached just before the reillumination of the target) were measured by averaging values from at least 25 trials in both directions (Gaymard et al). We maintained the attention of the patients by repeating the instruction between the blocks.

The three paradigms were conducted within the same session for all the subjects. The two sessions of the patients (“STN on” and “STN off”) were executed in the same conditions with the same number of trials (n=55).

**STATISTICS**

All variables were checked for significant lateralisations by means of a two tailed Wilcoxon matched pairs signed ranks test, both in patients and controls. In the patient group, this test was used to compare saccade parameters in “STN on” and “STN off” conditions. An analysis of variance (ANOVA) and a t test were used for comparisons with the control group. Significance was accepted at a p<0.05 level.

**Results**

As there were no significant differences between rightward and leftward values, all parameters were pooled. Results are presented in table 2. In the gap task, no significant differences in saccade latency or saccade accuracy were found in either group, although saccade latency was longest in the “STN off” condition. Likewise, in the antisaccade task, the percentage of errors was similar in all groups. However, latency of correctly executed antisaccades was significantly increased both in the “STN on” (r=2.12; df=16; p<0.05) and “STN off” conditions (r=3.37; df=16; p<0.004) compared with controls (F(2, 23)=4.95; p<0.016). In the memory guided saccade task, saccade latency was significantly increased in the “STN off” condition compared to controls (r=2.16; df=16; p<0.04). In all tasks, saccade latency was shorter in the “STN on” condition than in the “STN off” condition, but without reaching significance. Saccade accuracy was similar in the “STN on” condition and controls. However, in the “STN off” condition, first saccade gain was significantly decreased compared with that of the “STN on” condition (Z=−2.52; n=8; p<0.01) and controls (F(2, 23)=−3.56; p<0.04, figure) and also significantly decreased compared with the final eye position gain (Z=−2.38; n=8; p<0.01). In the “STN off” condition, accuracy of final eye position showed only a partial improvement, remaining slightly but significantly decreased compared with that of the “STN on” condition (Z=−1.96; n=8; p<0.049).

**Table 2  Saccade parameters**

<table>
<thead>
<tr>
<th></th>
<th>Visually guided saccades</th>
<th>Antisaccades</th>
<th>Memory guided saccades</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Latency (ms)</td>
<td>Gain Mean (SD)</td>
<td>Latency (ms)</td>
</tr>
<tr>
<td>Patients:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STN on</td>
<td>201 (45)</td>
<td>0.95 (0.03)</td>
<td>*</td>
</tr>
<tr>
<td>STN off</td>
<td>220 (71)</td>
<td>0.94 (0.04)</td>
<td>**</td>
</tr>
<tr>
<td>Controls</td>
<td>180 (44)</td>
<td>0.94 (0.02)</td>
<td></td>
</tr>
</tbody>
</table>

Comparison with the control group: *p<0.05; **(p<0.01). Comparison between “STN on” and “STN off” conditions in PD patients: †p<0.05; ††p<0.001. Comparison between the first gain and the final gain ‡‡(p<0.01).
Effect of subthalamic nucleus stimulation on saccades in human

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Neurological truant

The eminent surgeon Lord Moynihan picturesquely described those qualified in medicine but who abandoned the profession to take up pure science, literature, politics, etc., or who studied medicine only for a time as “truants from medicine”. Professor Ivan Donaldson, a New Zealand neurologist, has combined truancy with neurological practice. With his family Ivan Donaldson has established a nationally famous vineyard. The very high quality wine has led to the vineyard being portrayed on a stamp and in so doing Ivan Donaldson is probably the only neurological vigneron who has been philatelically honoured.

Two or three glasses of wine daily have been found to reduce deaths from coronary and cardiovascular disease by 35%, and two glasses of wine a day diminish deaths from cancer by 22%. Although mortality from all causes is reduced by 30% by moderate amounts of wine, it increases again when drinking more than seven glasses daily with a glass judged to contain 120 ml.1 Wine may also reduce the incidence of dementia.2 Assuming moderation by imbibers, Professor Ivan Donaldson may be responsible more than any other neurologist for protecting the brain from at least two ominous threats of advancing age.

This stamp shows part of Dr Donaldson’s 80 acre vineyard situated in Waipara some 35 miles north of the city of Christchurch in the South Island of New Zealand. In the foreground left is a bunch of grapes and on the right is one of Professor Donaldson’s sons (Stanley Gibbons 2060, Scott 1432).

L F HAAS
