Stimulation of the subthalamic region at 20 Hz slows the development of grip force in Parkinson's disease

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A B S T R A C T
Excessive synchronization of basal ganglia neuronal activity at ~20 Hz is characteristic of patients with untreated Parkinson's disease (PD). Correlative evidence suggests that this activity may contribute to bradykinesia. Attempts to demonstrate causality through stimulation imposed synchronization at 20 Hz in the region of the subthalamic nucleus (STN) have had limited success. Finger-tapping is slowed by about 8% and only in those PD patients that have a relatively normal baseline performance in this task. Here we investigate whether greater performance decrements might be seen in a reaction time grip task. We studied 32 sides in 16 patients with PD after overnight withdrawal of medication. Patients were asked to grip as hard and as fast as possible without STN stimulation and during bilateral stimulation at 5 Hz, 10 Hz, 20 Hz, 50 Hz and 130 Hz. Stimulation at 20 Hz slowed the development of force by 14.7 ± 8.3% (P = 0.044) across all patients. Slowing increased by 22 ± 7% (P = 0.005) in those patients with the best performance in the task without stimulation. The effect was frequency specific. These data provide direct interventional evidence of a mechanistic link between excessive neuronal synchronization in the beta range and motor impairment in PD.

Introduction
Excessive synchronization of neuronal activity at a frequency of about 20 Hz is a common finding in the basal ganglia of patients with untreated Parkinson's disease (Alonso-Frech et al., 2006; Bronte-Stewart et al., 2005; Brown et al., 2001; Cassidy et al., 2002; Foffani et al., 2005; Kühn et al., 2006; Priori et al., 2004; Weinberger et al., 2006; Williams et al., 2002). Correlative evidence suggests that this spontaneous activity may contribute to slowness of movement in this condition (Brown and Williams, 2005; Chen et al., 2010; Kühn et al., 2006, 2009; Lopez-Azarate et al., 2010; Ray et al., 2008; Weinberger et al., 2006; Zaidel et al., 2010). Furthermore, recent studies seeking evidence of causality have demonstrated that the external imposition of synchronization through direct stimulation of the subthalamic nucleus (STN) region at 20 Hz can impair motor performance (Chen et al., 2007; Eusebio et al., 2008; Fogelson et al., 2005). However, the effect of direct stimulation at 20 Hz was weak, albeit significant, and only manifest in those patients with the best baseline performance (Chen et al., 2007; Eusebio et al., 2008). This is an important issue, as either neuronal synchronization at about 20 Hz is quantitatively of limited relevance, or paradigms have been imperfect. In particular, it is unclear whether the finger-tapping investigated up till now is the best test of basal ganglia dysfunction. Accordingly, here we study the effect of 20 Hz STN stimulation in a grip force task in Parkinson's disease (PD) patients with chronically implanted bilateral STN deep brain stimulation (DBS) electrodes. We show that the slope of the rising phase of the contraction was reduced by about 15% across all patients during 20 Hz stimulation, and this effect was greater still among those with the best baseline performance. The present findings suggest that causal influences of exaggerated beta activity upon motor impairment in PD can be quantitatively important.
Methods

Patients and surgery

The study was approved by the local ethics committee of the Chang Gung Memorial Hospital. Sixteen patients (32 sides) with PD (mean age 63.1 ± 1.8 years, range 50 to 74 years, mean disease duration 11.8 ± 1.5 years, 4 females) and fifteen age-matched healthy subjects (mean age 61.2 ± 1.8 years, range 50 to 71 years, 6 females) participated with informed consent. The PD patients underwent simultaneous implantation of DBS electrode in the STN. Patient details are summarized in Table 1. Two of the patients (cases 2 and 8) have been previously reported with respect to their performance in a finger-tapping task (Chen et al., 2007; Eusebio et al., 2008). Indications for surgery were advanced parkinsonism with motor fluctuations and/or dyskinesia. The DBS electrode used was model 3389 (Medtronic Neurological Division, Minneapolis, USA) with four platinum–iridium cylindrical surfaces (1.27 mm diameter and 1.5 mm length) and center-to-center separations of 2 mm. Contacts 0 and 3 were the most caudal and rostral contacts, respectively. STN electrode trajectories were aimed at the center of the STN. The STN was identified on high-resolution T2-weighted axial, coronal, and sagittal magnetic resonance (MR) images. These images were superimposed on stereotactic CT to define the area corresponding in location to the STN (Schaltenbrand and Wahren, 1977). The intended coordinates for the target point were 12 mm lateral from the midline, 3 mm behind the midcommissural point, and 4–5 mm below the anterior commissural–posterior commissural line. Correct placement of DBS electrodes in the region of the STN was supported by: (1) effective intraoperative macrostimulation, (2) postoperative T2-weighted MR images compatible with the placement of at least one electrode contact in the STN region, and (3) significant improvement in the Unified Parkinson’s Disease Rating Scale (UPDRS) motor score during chronic DBS off-medication compared to UPDRS off-medication with stimulator switched off (Table 1).

### Table 1

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (years)/sex</th>
<th>Disease duration (years)</th>
<th>Main symptoms</th>
<th>UPDRS III preoperatively, off/drugs</th>
<th>UPDRS III at the time of task, off drugs, on/off stimulation</th>
<th>Postoperation medication (mg/day)</th>
<th>Stimulation parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50/M</td>
<td>9</td>
<td>Tremor, diphasic dyskinesia, off dystonia</td>
<td>12/18 NA²</td>
<td>Levodopa 750 Entacapone 1000</td>
<td>L STN: 3-, 1.0v, 60 μs, 130 Hz; R STN: 5-, 2.0v, 60 μs, 130 Hz</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>62/M</td>
<td>16</td>
<td>Bradykinesia, rigidity, on dyskinesia</td>
<td>14/21 34/55</td>
<td>Levodopa 700 Entacapone 800 Pergolide 1 Amantadine 400</td>
<td>L STN: 3-, 3.3v, 90 μs, 130 Hz; R STN: 7-, 2.4v, 90 μs, 130 Hz</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>69/M</td>
<td>15</td>
<td>Tremor, rigidity, on dyskinesia</td>
<td>16/58 38/47</td>
<td>Levodopa 800 Amantadine 200 Trihexyphenidyl 1</td>
<td>L STN: 2-, 2v, 60 μs, 100 Hz; R STN: 6-, 1.8v, 60 μs, 100 Hz</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>50/M</td>
<td>11</td>
<td>Bradykinesia, tremor, on dyskinesia, off-drug phenomenon</td>
<td>24/49 21/33</td>
<td>Levodopa 100 Entacapone 600 Biperiden 4 Amantadine 200 Levodopa 1200</td>
<td>L STN: 3-, 1v, 60 μs, 130 Hz; R STN: 7-, 1.5v, 60 μs, 130 Hz</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>60/F</td>
<td>20</td>
<td>Bradykinesia, rigidity, off periods</td>
<td>42/61 NA</td>
<td>Levodopa 400 Pramipexole 1</td>
<td>L STN: 0-, 3v, 60 μs, 185 Hz; R STN: 4-, 3.3v, 60 μs, 185 Hz</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>66/F</td>
<td>17</td>
<td>Tremor, rigidity, Bradykinesia, diphasic dyskinesia</td>
<td>9/20 NA</td>
<td>Levodopa 400 Amantadine 200 Entacapone 800</td>
<td>L STN: 1-, 1.2v, 60 μs, 130 Hz; R STN: 5-, 2.5v, 60 μs, 130 Hz</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>54/M</td>
<td>13</td>
<td>Tremor, Bradykinesia, on dyskinesia, off dystonia</td>
<td>21/43 32/38</td>
<td>Levodopa 1000 Entacapone 800 Biperiden 4 Amantadine 400</td>
<td>L STN: 3-, 1.2v, 60 μs, 130 Hz; R STN: 5-, 1.2v, 60 μs, 130 Hz</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>69/M</td>
<td>17</td>
<td>Bradykinesia, rigidity, off dyskinesia, off periods</td>
<td>39/71 33/69</td>
<td>Levodopa 1900 Pergolide 1 Levodopa 450</td>
<td>L STN: 2-, 3.5v, 60 μs, 170 Hz; R STN: 6-, 3.5v, 60 μs, 170 Hz</td>
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</tr>
<tr>
<td>9</td>
<td>63/F</td>
<td>15</td>
<td>Bradykinesia, tremor, off periods, freezing gait</td>
<td>17/32 23/35</td>
<td>Levodopa 400 Amantadine 100</td>
<td>L STN: 1-, 1.5v, 60 μs, 130 Hz; R STN: 6-, 1.4v, 60 μs, 130 Hz</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>63/M</td>
<td>18</td>
<td>Gait freezing, on/off phenomenon</td>
<td>25/39 26/41</td>
<td>Levodopa 400 Amantadine 100</td>
<td>L STN: 3-, 2.2v, 60 μs, 130 Hz; R STN: 6-, 2.1v, 60 μs, 130 Hz</td>
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</tr>
<tr>
<td>11</td>
<td>70/M</td>
<td>4</td>
<td>Tremor, off periods</td>
<td>50/69 14/17</td>
<td>Levodopa 200 Amantadine 100 Biperiden 4</td>
<td>L STN: 1-, 3v, 60 μs, 130 Hz; R STN: 5-, 3.2v, 60 μs, 140 Hz</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>70/M</td>
<td>5</td>
<td>Tremor, off periods, off dystonia</td>
<td>42/56 34/70</td>
<td>Levodopa 200 Amantadine 150</td>
<td>L STN: 3-, 3v, 60 μs, 130 Hz; R STN: 4-, 3.5v, 60 μs, 140 Hz</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>69/M</td>
<td>2</td>
<td>Tremor, rigidity, off periods</td>
<td>47/52 31/34</td>
<td>Levodopa 200 Amantadine 100 Biperiden 0.5</td>
<td>L STN: 3-, 3v, 60 μs, 130 Hz; R STN: 4-, 2.7v, 60 μs, 130 Hz</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>74/F</td>
<td>5</td>
<td>Tremor, Bradykinesia, off periods</td>
<td>27/32 31/48</td>
<td>Levodopa 300 Amantadine 100 Pergolide 0.75</td>
<td>L STN: 3-, 3.2v, 60 μs, 145 Hz; R STN: 5-, 2.6v, 60 μs, 145 Hz</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>57/M</td>
<td>4</td>
<td>Tremor, off periods</td>
<td>8/18 19/30</td>
<td>Levodopa 300 Amantadine 100 Trihexyphenidyl 1</td>
<td>L STN: 2-, 2v, 60 μs, 145 Hz; R STN: 4-, 3v, 60 μs, 135 Hz</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>64/M</td>
<td>17</td>
<td>Off periods, off dystonia, on dyskinesia</td>
<td>20/29 39/46</td>
<td>Levodopa 300 Entacapone 200 Amantadine 100</td>
<td>L STN: 0-1-3+, 3v, 60 μs, 135 Hz; R STN: 4-5-7+, 3v, 60 μs, 135 Hz</td>
<td></td>
</tr>
</tbody>
</table>

NA: not applicable.
Protocol

All patients were assessed after overnight withdrawal of antiparkinsonian medication, although the long action of the drugs used to treat PD meant that patients may still have been partially treated when assessed. They were studied when the stimulator was switched off and during bilateral STN stimulation at 5 Hz, 10 Hz, 20 Hz, 50 Hz and 130 Hz. The stimulation types were assessed in pseudo-randomized order across patients. Stimulation contacts, amplitude and pulse duration remained the same as utilized for therapeutic high-frequency stimulation in each subject (see Table 1). There was no evidence of capsular spread during stimulation, as determined by clinical examination. Patients were blinded to the stimulation type. We did not stimulate each side at a time to avoid possible functional compensation by the non-stimulated side. We waited 30 min after changing stimulation frequency before testing. This period is sufficient to elicit about 75% of DBS effects (Temperli et al., 2003).

Task

Patients and normal controls were comfortably seated in a chair and asked to hold a isometric hand grip force transducer (Dynamometer G100, Biometrics Ltd., UK), with standard Jamar design and its handle in the second position. Subjects were seated with their shoulders adducted (so that elbows rested against the trunk), their elbows flexed at about 90° and their forearms in neutral, as recommended by the American Association of Hand Therapists (Fess, 1992). During each run the patient was instructed to grip the apparatus as hard and as fast as possible. Maximal voluntary contraction (MVC) was held for 15 s and repeated three times per hand and per stimulation frequency with 15 s rests in between trials. Each trial began and stopped with an oral instruction. Each run of three trials was also separated by ~30 s rest and each hand tested separately. The sequence of hands was also randomized.

Recordings and analysis

Force signals were digitized by a 1401 A–D converter (Cambridge Electronic Design, Cambridge, UK), and recorded onto a computer using Spike2 software (Cambridge Electronic Design). They were sampled at 1 kHz and monitored online. During analysis the force signal was first filtered by wavelet denoising. The original signal (Fig. 1A) was decomposed into an approximate component (A8) and 8 detail components (D8–D1), in the frequency ranges of 0–1.9, 1.9–3.8, 3.8–7.9, 7.9–15.8, 15.8–31.7, 31.7–62.5, 62.5–125, 125–250 and 250–500 Hz, respectively. The A8 component (Fig. 1B) was retained...

Fig. 1. The wavelet denoising of the maximal voluntary contraction (MVC). (A) Raw dynamometer signal. This was decomposed into an approximate component, A8 (B) and 8 detail components, D8–D1 (C–F). The A8 component contained the basic structure of the MVC and was retained. The D8, D7 and D6 components (C–E) were subtracted according to soft adaptive thresholds (dashed lines) based on Stein’s Unbiased Risk Estimate. The D5–D1 components (F) were disregarded as artefacts. The reconstructed signal (G) was obtained by adding the retained and the reduced components. The mean rising slope (H) was defined as the average of the differentiation of the reconstructed signal between the onset (the dashed line) and the offset (the solid line) of the rising phase. Note that the dynamometer has a baseline offset of 2 V (A, B and G) and that the y-axes in (C) and (D) are in V, whereas those in (E) and (F) are in mV.
and components D8, D7 and D6 reduced by incorporating soft adaptive thresholds that were respectively derived from each component using the principle of Stein’s Unbiased Risk Estimate (SURE) (Stein, 1981) (Figs. 1C–1E). The remaining components (D5,...,D1) were disregarded as they represented artifacts (Fig. 1F). The force signal was then reconstructed from the retained and the reduced components. Two parameters, peak force and mean rising slope were used to quantify each contraction. The baseline offset in the force signal was subtracted (Fig. 1). The onset of each contraction (dashed line in Fig. 1G) was defined as the time when the force signal first exceeded a tenth of the mean force present during the established contraction. The peak force was that identified within a 2-s window from contraction onset. The mean rising slope was the average of the differentiation of the force signal between contraction onset and offset, with the latter defined as the point at which force reached 85% of peak force (solid line in Fig. 1H). Data processing was implemented in Matlab 2007 (The MathWorks Inc., Natick, MA, USA).

Statistical analysis

The trial with maximal peak force in each run (e.g. out of the three trials for each hand and each stimulation frequency) was selected for further analysis, which was performed in the Statistical Program for Social Sciences (SPSS) statistical software (version 17.0, SPSS Inc., Chicago, IL, USA). An independent samples t-test was used to compare the peak force and mean rising slope in the control group with those in the patients without stimulation. Two separate repeated measures analysis of variance (ANOVAs) with within-subjects simple contrasts (planned comparison of different stimulation frequencies to no stimulation) were used to test the influence of frequency on peak force and rising slope. Mauchly's test confirmed the sphericity of the data analyzed. Values are expressed as means ± standard error of the mean (SEM).

Results

The peak force in healthy age-matched volunteers (22.4±1.3 kg) was not significantly different from that in patients with PD (22.4±1.1 kg, P = 0.201). However, the mean rising slope in the control group (46.1±6.2 kg/s) was significantly higher than that in patients with PD (26.3±2.7 kg/s, P = 0.031) (Fig. 2), consistent with the presence of bradykinesia. Repeated measures ANOVA with factor FREQUENCY (six levels: 0, 5, 10, 20, 50 and 130 Hz) demonstrated a significant effect on the rising slope (F[5,31] = 3.307, P = 0.007) but not on the peak force (F[5,31] = 0.338, P = 0.889) (Fig. 3). Within-subjects

Fig. 2. Boxplots representing the different force parameters in healthy volunteers and patients with PD, (A) peak force, and (B) mean rising slope.

Fig. 3. Effects of stimulation frequency on different force parameters. (A) Mean (± SEM) peak forces and (B) mean (± SEM) rising slope off (“0 Hz”) and on stimulation at 5, 10, 20, 50 and 130 Hz. No significant differences were noted between different frequencies for peak forces. Mean rising slope was significantly lower during stimulation at 20 Hz than without stimulation, but no other frequency of stimulation had a significant effect compared to no stimulation.
The average drop in mean rising slope during 20 Hz stimulation compared to no stimulation ("0 Hz") was 22 ± 7% ($P = 0.005$). There was no significant difference between 20 Hz stimulation and no stimulation in sides with the worst performance.

In conclusion, the present findings provide direct interventional evidence of a mechanistic link between excessive neuronal synchronization in the beta range and motor impairment in PD. The effect was apparent even without stratification of patients according to their baseline task performance. The consistency and scale of the effect shown here probably relates to the choice of task, as this tests an aspect of performance, rate of force generation, which seems particularly relevant when considering the STN. It remains to be seen to what extent the present results can be extrapolated to other voluntary movements in PD.

Acknowledgments

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