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

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ABSTRACT

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., 2009; 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-Azcarate 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.

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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
Clinical detail of patients.

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

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

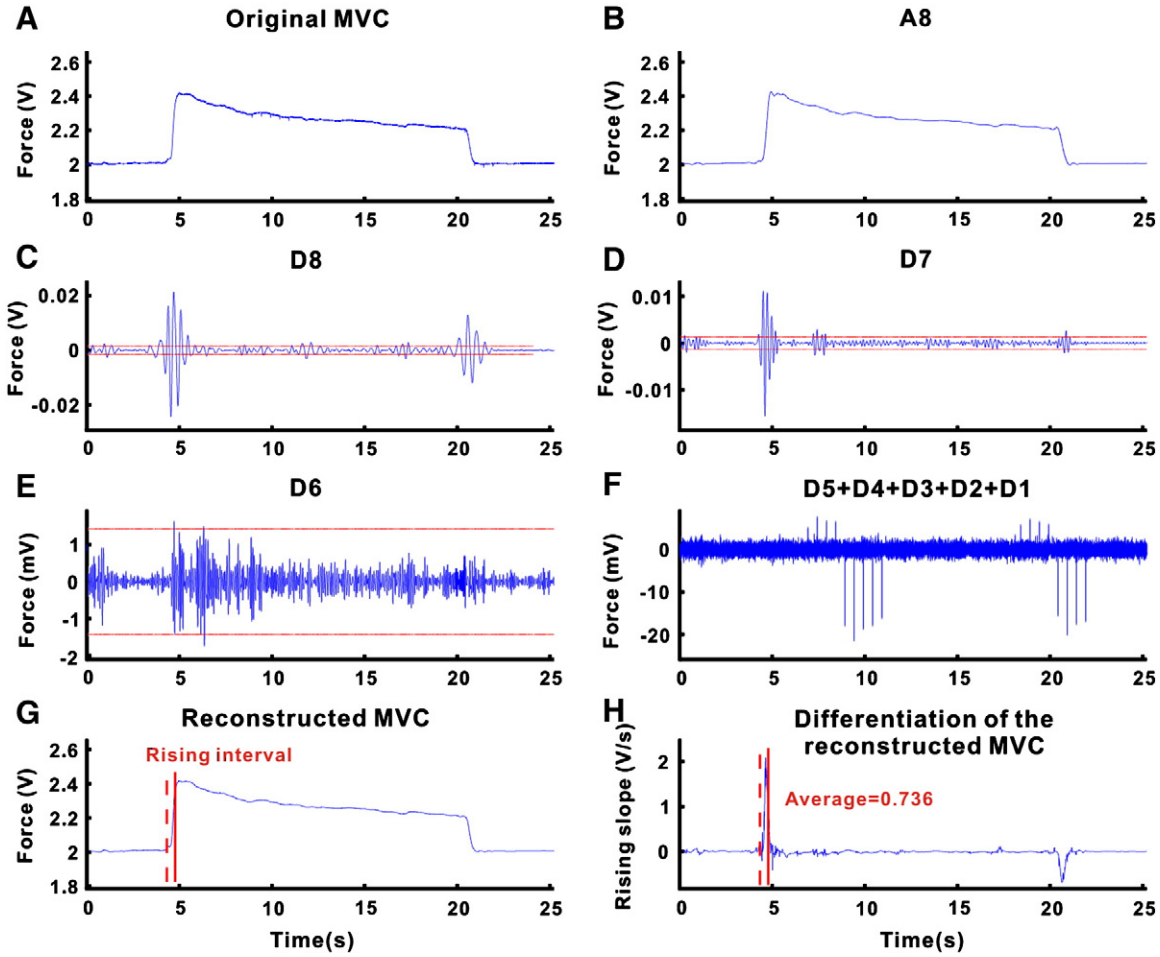

Fig. 1. The wavelet denoising of the maximal voluntary contraction (MVC). (A) Raw dynamometer signal. This was decomposed into an approximate component, A8 (B) and 8 detail components, D8-D1 (C-F). The A8 component contained the basic structure of the MVC and was retained. The D8, D7 and D6 components (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 off-set 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

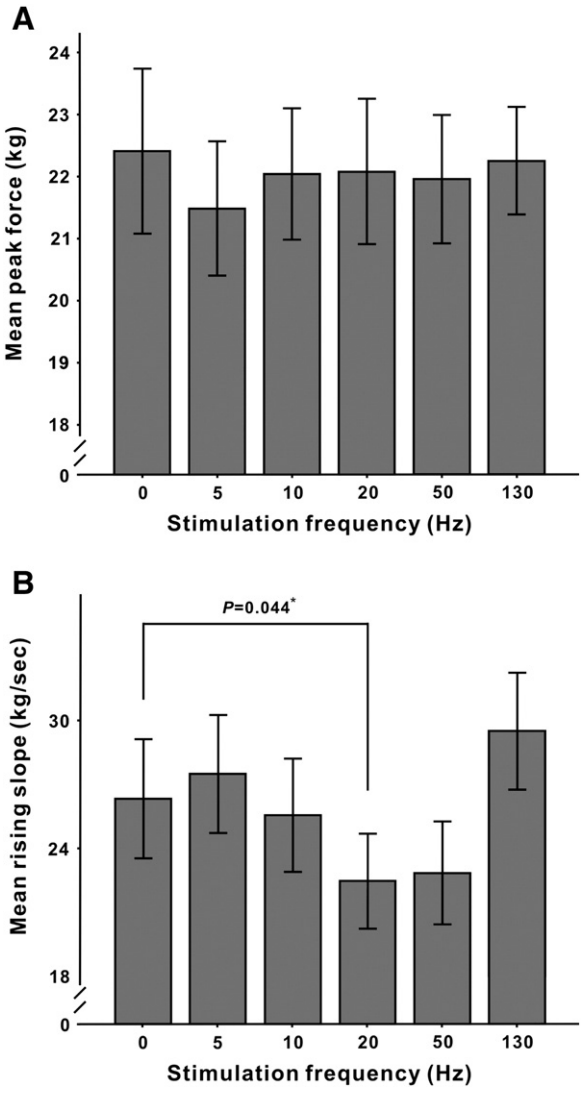

Fig. 3. Effects of stimulation frequency on different force parameters. (A) Mean (±SEM) peak forces and (B) mean (±SEM) rising slope off ("0 Hz") and on stimulation at 5, 10, 20, 50 and 130 Hz. No significant differences were noted between different frequencies for peak forces. Mean rising slope was significantly lower during stimulation at 20 Hz than without stimulation, but no other frequency of stimulation had a significant effect compared to no stimulation.

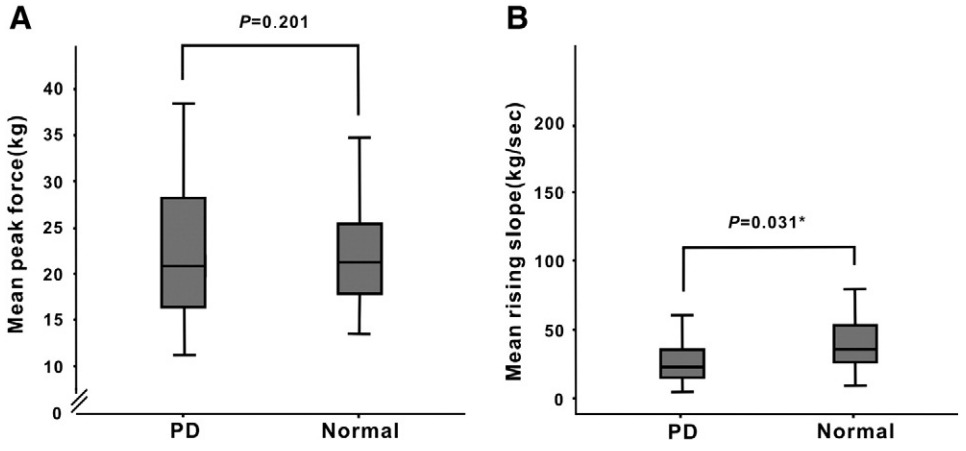

Fig. 2. Boxplots representing the different force parameters in healthy volunteers and patients with PD, (A) peak force, and (B) mean rising slope.

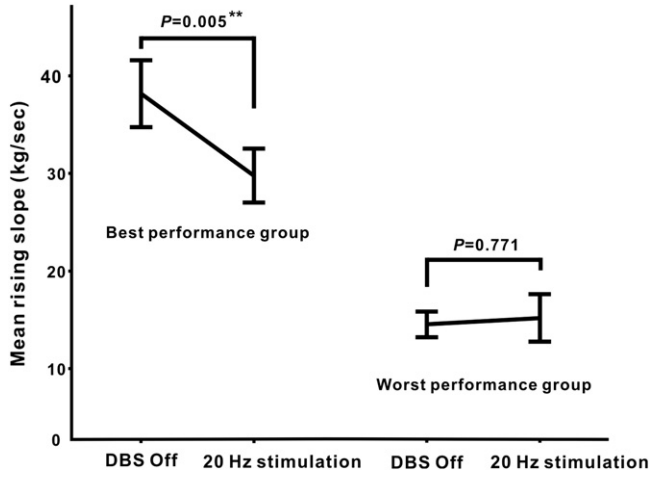

Fig. 4. Dependency of stimulation effects at 20 Hz on baseline performance. Mean (±SEM) rising slope off ("0" Hz) and on stimulation at 20 Hz in hands with best performance (N = 16 sides) and worst performance (N = 16 sides) during no stimulation. In those sides with best performance, the deterioration 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.

contrasts indicated that the mean rising slope during 20 Hz stimulation was lower than that without stimulation ($F_{[1,31]} = 4.416$, $P = 0.044$). The average drop in rising slope during 20 Hz stimulation compared to no stimulation was 14.7 ± 8.3% (Fig. 3B). However, this global estimate of the effects of 20 Hz stimulation could have been overshadowed by the beneficial effects of DBS-induced suppression of spontaneous pathological activity or limited by ceiling effects due to baseline impairment (Chen et al., 2006, 2007; Eusebio et al., 2008; Ray et al., 2009). Accordingly, we divided the mean rising slope estimates into those 16 sides with the highest baseline rising slopes off stimulation ("0 Hz") and those 16 sides with the lowest baseline rising slopes off stimulation. The average drop in mean rising slope during 20 Hz stimulation compared to no stimulation ("0 Hz") was 22 ± 7% in the better performing group ($P = 0.005$, two-tailed paired t-test, Fig. 4). There was no effect in the worse performing group (4.5 ± 16.1% improvement with 20 Hz stimulation, $P = 0.771$, Fig. 4).

Discussion

We recently reported that STN DBS at 20 Hz slows movement by about 8% during a finger-tapping task in PD patients that have a relatively normal baseline performance in this task (Chen et al., 2007; Eusebio et al., 2008). Here we extend these findings in a different cohort of patients (with the exception of two overlapping subjects) asked to perform a different task; maximal grip performed as fast as possible. Stimulation at 20 Hz slowed the development of force by about 15% across all patients. This increased to 22% in those patients with the best performance in the task without stimulation. Thus imposed synchronization at 20 Hz consistently impaired performance in the grip task and the degree of impairment was considerably greater than in a simple finger-tapping task. The effect was frequency selective.

This result adds to the growing evidence that pathological synchronization at 20 Hz in the STN area is causally linked to motor impairment in patients with PD. But why are the deleterious effects of 20 Hz stimulation of the STN greater during a maximal hand grip performed as fast as possible as compared to those reported in studies of finger-tapping? And why did stimulation compromise the rate of force development but not peak force? It seems likely that the basal ganglia are particularly involved in the scaling of force generation (Desmurget et al., 2004; Nowak et al., 2005, 2006; Spraker et al., 2007; Turner et al., 2003). In line with this, slowing of the development of force during MVC tasks is a consistent feature of PD (Corcos et al., 1996; Jordan et al., 1992; Park and Stelmach, 2007; Pedersen et al., 1997; Wierzbicka et al., 1991). In contrast, any reduction in maximal force voluntarily achieved in PD patients is of a smaller degree and less consistent between studies. A decrease in strength compared to healthy age-matched control subjects has been reported in some studies (Koller and Kase, 1986; Nallegowda et al., 2004; Stelmach et al., 1989) but not others (Jordan et al., 1992; Stelmach and Worringham, 1988), although variability may relate, in part, to age differences (Larsson and Karlsson, 1978), cuing (Gonzalez et al., 2010), movement velocity (Kakinuma et al., 1998), muscle groups tested (Kakinuma et al., 1998; Nogaki et al., 2001) and whether contractions are isometric or isokinetic (Koller and Kase, 1986; Nogaki et al., 1995).

The important role of the basal ganglia in the scaling of force generation is also likely to explain the greater effect size in the current task relative to finger-tapping. The STN seems particularly important in controlling the dynamic parameters of grip, particularly the rate of force generation (Kinoshita et al., 2000; Prodoehl et al., 2008; Spraker et al., 2007; Vaillancourt et al., 2004). In contrast, simple repetitive movements, such as finger-tapping, appear more responsive to levodopa than STN DBS (Limousin et al., 1997; Sturman et al., 2010). Likewise, focal lesions in the basal ganglia improve hand squeezing but not finger-tapping in PD (Limousin et al., 1999).

This differential susceptibility may be heightened by the involvement of more proximal musculature in the maximal grip task relative to finger-tapping (Kuhtz-Buschbeck et al., 2008). Primary motor cortex (M1) appears more important in the control of distal, intrinsic hand muscles than proximal arm muscles (Colebatch et al., 1991; Deiber et al., 1991; Jeannerod, 1986; Lemon, 1993; Lemon et al., 1996; Muir and Lemon, 1983). The latter are preferentially controlled by premotor cortex and the supplementary motor area (Freund and Hummelsheim, 1984; Macpherson et al., 1982), which shows greater activation than M1 during effective STN stimulation (Limousin et al., 1997). Consistent with this, STN DBS and pallidotomy have a larger effect on proximal than distal muscles (Limousin et al., 1999; Timmermann et al., 2008; Wenzelburger et al., 2003).

Conclusions

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.

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