Deep brain stimulation of the subthalamic nucleus: A two-edged sword

Chiung Chu Chen[1,2], Christof Brücke[3], Florian Kempf[3], Andreas Kupsch[3], Chin Song Lu[2], Shih Tseng Lee[4], Stephen Tisch[1,5], Patricia Limousin[1,5], Marwan Hariz[1,5] and Peter Brown[1]

Chronic high frequency stimulation of the subthalamic nucleus (STN) of the basal ganglia is a highly effective treatment for Parkinson's Disease (PD). Such deep brain stimulation is thought to suppress spontaneous, including pathological, activity in the basal ganglia [1–5]. Equally, however, it must also remove any residual physiological functioning in these key motor structures, and yet there is paradoxically little evidence to suggest that the motor action of the limbs is in any way further impaired by stimulation or even focal ablation of the STN in PD patients [6–8]. This has led to the influential hypothesis that the human basal ganglia are not necessary for simple limb movements, but are particularly involved in more subtle and complex functions, such as the promotion of motor flexibility, that are not readily revealed by standard tests of motor behavior [6]. Here we show that the basal ganglia are involved in processing simple limb movements in the human, by separating the effects of deep brain stimulation on pathological and physiological activities based on baseline task performance.

Our hypothesis was straightforward. Patients that, at the time of study, have performance in a simple motor task that is compromised by PD will improve with deep brain stimulation, in tandem with the suppression of pathological activity by stimulation [1–5]. In contrast, in those patients with relatively intact task-related processing, as evidenced by a baseline performance within normal limits, deep brain stimulation would be expected to suppress physiological processing and thereby impair performance. We tested rapid repetitive depression of a keyboard key with the forefinger as our simple voluntary movement. Thirteen patients with PD (see Table S1 in the Supplemental data available online) and chronically implanted STN electrodes were studied after overnight withdrawal of anti-parkinsonian medication, although the long action of many of the drugs used to treat PD meant that patients were still likely to have been partially treated when assessed. Each hand was tested separately with and without deep brain stimulation at 130 Hz and the percentage change in tapping speed during deep brain stimulation calculated (see Supplemental Experimental Procedures). There was a striking correlation between baseline performance in the task and percentage change with deep brain stimulation, whereby those sides showing the best performance without deep brain stimulation actually slowed during stimulation, whereas those with poorer performance got quicker in the task (Figure 1A).

Next, we divided sides into two groups according to whether or not tapping performance off deep brain stimulation was within the normal limits established on 12 sides in six healthy age-matched subjects (see Supplemental Experimental Procedures). Tapping rates were confirmed to improve on those sides where performance was compromised by parkinsonism at the time of study, but deteriorated on those sides in which tapping rates were within normal limits, whether absolute (Figure 1B) or percentage change (Figure 1C) tapping rates were considered.

Finally, we confirmed the reproducibility of our findings by repeating the experiment on seven patients (13 sides) with PD (see Supplemental Table S1). Again there was a negative correlation ($r = -0.558$, $p = 0.048$) between the percentage change in tapping rate of each hand with deep brain stimulation and tapping rate prior to onset of deep brain stimulation. More importantly, tapping rates deteriorated on those six sides in which performance was within normal limits without deep brain stimulation, whether absolute (tapping rate 154.7 ± 3.3 off deep brain stimulation, 144.5 ± 5.5 during deep brain stimulation, $p = 0.02$, unpaired two-tailed t-test) or percentage change (mean %

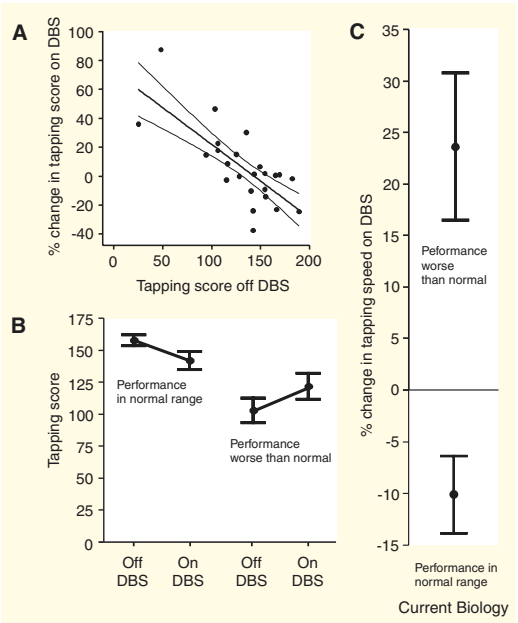

Figure 1. Dependency of deep brain stimulation effects on baseline performance.

(A) Negative correlation (thick line, $r = -0.742$, $p < 0.001$) between % change in tapping rate of each hand with deep brain stimulation and tapping rate prior to onset of deep brain stimulation. Positive % change = improvement with deep brain stimulation. Thin lines = 95% confidence limits. n = 24 tapping sides in 13 patients (right hand rejected in case 4 as contralateral to previous pallidotomy and tapping made impossible by tremor in the left hand in case 9). (B) Mean (± s.e.m.) tapping rate off and on deep brain stimulation in hands with baseline tapping performance within (n = 13) or less than (n = 11) normal range (difference on and off deep brain stimulation $p = 0.018$ and $p = 0.003$, respectively, two-tailed paired t-tests). (C) Mean (± s.e.m.) % change in tapping rate with deep brain stimulation in hands with baseline tapping performance within or less than normal range ($p < 0.001$ for difference between groups, unpaired two-tailed t-test and $p = 0.019$ and $p = 0.008$ for each group differing from zero, two-tailed one-sample t-tests).

deterioration 6.7 ± 2.1, p = 0.025, two-tailed one-sample t-test) tapping rates were considered.

Thus, sides with performance compromised at the time of study improve with deep brain stimulation. It is the subthalamic nuclei contralateral to these sides that are likely to have the most pronounced pathological activity at the time of testing and, in line with this, there is a linear relationship between pathological synchronisation as evidenced by oscillatory activity in the STN local field potential and motor impairment [9]. Subjects with existing difficulties therefore have more to gain from the suppression of local activity. On the other hand, sides with relatively normal performance in a given task are likely to have less contralateral pathological synchronisation at the time of study, so that the effects of suppression of physiological activity dominate motor performance during deep brain stimulation. Simple tapping was slowed in these subjects. Although the degree of slowing was relatively small and likely to be overlooked in retrospective assessments of the effects of basal ganglia lesions [10], it was reproducible in our paired comparisons using reversible functional blockade. Indeed, the slowing in tapping rate observed here may represent the lower limit of basal ganglia function in the task, as this is the impairment despite any compensation by other motor systems.

We infer that the basal ganglia are involved in processing of simple limb movements in humans, something that could not be assumed from the positive 'release' phenomena of improvement in motor performance in parkinsonian patients following focal lesioning/ deep brain stimulation or development of hemiballismus in previously healthy subjects after subthalamic infarction [10]. The finding is in keeping with the increasing evidence from focal recordings that activity in the STN of patients with PD changes prior to and during simple movements of the upper limb [11], although these studies by themselves only suggest and do not prove involvement of the basal ganglia in these tasks. Only a behavioral approach, showing a decrement in motor performance, as here, can prove that the basal ganglia are necessary for the normal execution of simple limb movements. Hitherto, evidence of impairment of performance during STN deep brain stimulation has been limited to selected cognitive tasks [12,13], a complex bimanual task [14] and to occasional reports of diminished intelligibility of speech [15].

The negative correlation between change in task performance with deep brain stimulation and performance prior to onset of deep brain stimulation also has important therapeutic implications. First, it suggests that the efficacy of deep brain stimulation in patients with mild PD may be limited and counsels against the use of this intervention very early in the course of the disease, whether or not to slow future deterioration [16]. Second, it suggests that the effectiveness of deep brain stimulation in PD may be improved by use in an on-demand mode, possibly with stimulation being triggered by the level of pathological local field potential activity in the STN [11]. Continuous stimulation, as utilized presently, may even impair performance in tasks relatively spared by parkinsonism or temporarily improved by concurrent medication.

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Supplemental data

Supplemental data including experimental procedures and a table are available at http://www.current-biology.com/cgi/content/full/16/22/R952/DC1

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[1]Sobell Department of Motor Neuroscience and Movement Disorders, Institute of Neurology, London, UK. [2]Department of Neurology, Chang Gung Memorial Hospital and University, Taipei, Taiwan. [3]Department of Neurology, Charité, University Medicine, Berlin, Campus Virchow, Berlin, Germany. [4]Department of Neurosurgery, Chang Gung Memorial Hospital and University, Taipei, Taiwan. [5]Unit of Functional Neurosurgery, Institute of Neurology, London, UK.
E-mail: p.brown@ion.ucl.ac.uk