Shaping reversibility? Long-term deep brain stimulation in dystonia: the relationship between effects on electrophysiology and clinical symptoms

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Long-term results show that benefits from chronic deep brain stimulation in dystonia are maintained for many years. Despite this, the neurophysiological long-term consequences of treatment and their relationship to clinical effects are not well understood. Previous studies have shown that transcranial magnetic stimulation measures of abnormal long-term potentiation-like plasticity (paired associative stimulation) and GABAergic inhibition (short-interval intracortical inhibition), which are seen in dystonia, normalize after several months of deep brain stimulation. In the present study, we examine the same measures in a homogenous group of 10 DYT1 gene-positive patients after long-term deep brain stimulation treatment for at least 4.5 years. Recordings were made 'on' deep brain stimulation and after stopping deep brain stimulation for 2 days. The results show that: (i) on average, prior to discontinuing deep brain stimulation, the paired associative stimulation response was almost absent and short-interval intracortical inhibition was reduced compared with normal. This pattern differs from that in both healthy volunteers and from the typical pattern of enhanced plasticity and reduced inhibition seen in deep brain stimulation-naïve dystonia. It is similar to that seen in untreated Parkinson’s disease and may relate to thus far unexplained clinical phenomena like parkinsonian symptoms that have sometimes been observed in patients treated with deep brain stimulation. (ii) Overall, there was no change in average physiological or clinical status when deep brain stimulation was turned off for 2 days.
suggesting that deep brain stimulation had produced long-term neural reorganization in the motor system. (iii) However, there was considerable variation between patients. Those who had higher levels of plasticity when deep brain stimulation was ‘on’, had the best retention of clinical benefit when deep brain stimulation was stopped and vice versa. This may indicate that better plasticity is required for longer term retention of normal movement when deep brain stimulation is off. (iv) Patients with the highest plasticity ‘on’ deep brain stimulation were those who had been receiving stimulation with the least current drain. This suggests that it might be possible to ‘shape’ deep brain stimulation of an individual patient to maximize beneficial neurophysiological patterns that have an impact on clinical status. The results are relevant for understanding long-term consequences and management of deep brain stimulation in dystonia.

Keywords: deep brain stimulation; DYT1 dystonia; neurophysiology mechanism; clinic

Abbreviations: DBS = deep brain stimulation; PAS = paired associative plasticity; SICI = short-interval intracortical inhibition

Introduction

Chronic high-frequency deep brain stimulation (DBS) to the internal globus pallidus can be a very powerful treatment for dystonia. The first reports of DBS success in dystonia were published a decade ago (Coubes et al., 1999, 2000; Kumar et al., 1999b) and recent long-term results demonstrate that benefits are maintained after more than 10 years (Cif et al., 2010). Nevertheless, outstanding questions remain over the mechanism of action of DBS in dystonia as well as the long-term consequences of many years of continuous use of DBS. In contrast to the almost immediate effects of DBS on the majority of symptoms in Parkinson’s disease, it may take several weeks or months to achieve maximum clinical benefit in patients with dystonia (Yianni et al., 2003; Coubes et al., 2004; Vidalhiet et al., 2005; Tisch et al., 2006a, b; Ruge et al., 2011). The gradual clinical improvement cannot only be observed in patients with dystonia treated with DBS but also following pallidotomy (Lozano et al., 1997). This slowly progressive clinical course is paralleled by a similar normalization of several electrophysiological measures of motor inhibition in the brain and spinal cord (Tisch et al., 2006a, b; Ruge et al., 2009, 2011). The slowly progressive nature of changes in clinical status together with the electrophysiological effects, suggest that a process of neural reorganization might accompany the long-term effects of globus pallidus DBS. There are fewer descriptions of the effects of stopping DBS on dystonia symptoms; Coubes and coworkers (2004) observed a number of patients, implanted for at least 2 years, where DBS was discontinued because of accidental switch-off or infection of the internal pulse generator. In all such cases, symptoms recurred within 1 week and disappeared quickly on reactivation of stimulation. Vidalhiet and colleagues (2005) switched DBS off for 10 h in patients 3 months after surgery. All patients returned to the dystonic pattern similar to before surgery. A comparable result was observed in a subgroup of these patients after 48 h discontinuation of DBS (Grabli et al., 2009). Interestingly, the pattern of preservation or loss of achieved clinical benefit may change over time. Hebb et al. (2007) described a patient with cranial dystonia in whom the beneficial effect of DBS treatment was reversible on stopping DBS in the first 2 years of treatment, but became irreversible after 5 years, i.e. the benefits of DBS therapy were maintained even if the stimulation was discontinued. The underlying mechanism for loss or preservation of achieved benefit remains unknown so far.

In the present study, we test the effects of long-term DBS on the interaction of electrophysiological and clinical status in 10 patients with DYT1 dystonia who had undergone at least 4.5 continuous years of DBS therapy. An overlapping sample of this patient population took part in studies addressing different scientific questions. Here, we examine the long-term effects on two electrophysiological measures that have often been found to be abnormal in dystonia. These are short-interval intracortical inhibition (SICI), a measure of the excitability of GABAergic circuits in the motor cortex, and paired associative plasticity (PAS), a test of long-term potentiation-like synaptic plasticity in cortical circuits (Stefan et al., 2000). Several authors have reported that SICI is less excitable than normal in patients with dystonia (Ridding et al., 1995; Sommer et al., 2002; Stinear and Byblow, 2004; Beck et al., 2009; Huang et al., 2010), and it has been hypothesized that reduced inhibition could contribute to the overflow of muscle activity during voluntary movement that is so characteristic of dystonia. In contrast, measures of long-term potentiation-like plasticity such as the PAS response (Weise et al., 2006; Quartarone et al., 2008; Schwingenschuh et al., 2010) have been reported to be more responsive in dystonia than in healthy individuals. Increased plasticity could lead to the formation of inappropriate connections between inputs and outputs in the motor system that are difficult to correct and that lead to the accumulation of excessive involuntary movement. We have hypothesized that when dystonic symptoms become evident, abnormal movement patterns become ‘hard wired’ into sensorimotor circuits because of increased plasticity. The result might be that it is difficult to reverse the abnormal organization and relieve the dystonia by DBS or other therapeutic rehabilitation interventions. Indeed, we proposed that this may account for the relatively slow improvement of symptoms after first starting DBS (Ruge et al., 2009, 2011).

We hypothesize that the same mechanism is also relevant for effects of long-term DBS. After turning off DBS in some patients there can be a dramatic and sudden return of dystonia, whereas in others, symptoms may not reappear for hours or even days. We know from previous work that the increased plasticity is abolished in early DBS treatment and gradually re-increases towards normal levels. We suggest that if patients have better restoration of sensorimotor plasticity after long-term DBS treatment, they are more...
likely to maintain the achieved clinical benefit because they may ‘store’ better the non-dystonic movement patterns that they have experienced during DBS. When DBS is turned off, their symptoms will return slowly. In patients with less plasticity, gained clinical benefit is less efficiently stored and symptoms will reappear quicker when DBS is turned off.

Here we have studied the SICI and PAS paradigms in 10 DYT1 gene-positive patients who had received continuous clinically effective DBS for ~5 years; and how discontinuation of DBS for 48 h influences these parameters. We compared these results with the effects on clinical symptoms.

Materials and methods

Patients

Ten patients with confirmed DYT 1 gene-positive dystonia (7 females, mean age 28.7 years, SD 17.3 years) participated in the study. Descriptive data and parameters of DBS are summarized in Table 1. The study was approved by the ethics committee of Gui de Chauliac University Hospital, Montpellier (Comité de Protection des Personnes, Interregion Sud-Méditerranée IV). Normative data are widely available. For better comparison, 10 matched healthy controls were also recorded. All patients or their guardians gave written informed consent. All experiments conformed with the Declaration of Helsinki. Originally 11 patients had planned to take part in the study, but electrophysiological assessment of one patient was impossible because of high motor thresholds.

All but one patient (who was included after 4.5 years of stimulation) had been receiving continuous therapeutic globus pallidus DBS for >5 years (range 4.5–11.5 years) at the time of the study. Monopolar stimulation was applied through one, two or three adjacent contacts with the following parameters: frequency 130 Hz, pulse width 450 µs, amplitude between 0.5 and 2.1 V (Table 1). The amplitude/number of contacts was adjusted to achieve maximum clinical benefit.

Surgical procedures

Details of the surgical procedures are published elsewhere (Coubes et al., 2002). All patients underwent MRI-guided and MRI-verified bilateral implantation of a single electrode into the posterior–ventral globus pallidus internus. None had had previous brain surgery or other neurological diseases. Quadripolar electrodes (model 3389) and either Soletra or Kinetra (Medtronic Neurological Division) model 7428 pulse generators were implanted.

Study design

Electrophysiological recordings and clinical assessments were taken on DBS and 2 days after switching off DBS. The time interval between these two recordings/assessments was 5 days. No changes in the DBS settings or medication were made for 3 months preceding the study. Clinical evaluation was performed by two independent expert raters using the movement section of the Burke–Fahn–Marsden dystonia rating scale (Burke et al., 1985).

Transcranial magnetic stimulation

Patients were seated comfortably in an armchair. Forearms rested in front of them. Patients were instructed to relax arm and hand muscles. Trials contaminated by background activity were excluded. Two Magstim 200 stimulators were coupled via a Bistim module. Stimulators were connected to a figure-of-eight shaped coil (external wing diameter of 9 cm) (Magstim). The handle of the coil was pointing posteriorly and laterally ~45° to the sagittal midline of the subject’s head. This evoked an anteriorly directed current in the brain. Magnetic pulses were delivered at the optimal scalp site (‘hot spot’) for producing motor evoked potentials in the target muscle. To eliminate a risk of close range exposure to damaging magnetic flux (Kumar et al., 1999a), physical shielding was fastened over the implanted pulse generators.

Experimental procedures

Recording techniques

Surface EMG in a belly–tendon montage was recorded from the first dorsal interosseus muscle (intracortical excitability) and abductor pollicis brevis muscle (PAS). The raw signal was amplified and filtered (Digitimer Ltd.) from 3 Hz (low cut) to 2 kHz (high cut). Signals were sampled using a CED Power 1401 interface (Cambridge Electronic design) at 5 kHz.

Table 1 Descriptive patient data

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Age at onset (years)</th>
<th>Age at surgery (years)</th>
<th>Duration of stimulation (years)</th>
<th>Number of active contacts left GPI</th>
<th>Number of active contacts right GPI</th>
<th>Voltage left GPI</th>
<th>Voltage right GPI</th>
<th>BFM score before surgery</th>
<th>BFM score ON DBS</th>
<th>BFM score OFF DBS</th>
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<td>1</td>
<td>60</td>
<td>8.5</td>
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</table>

BFM = Burke–Fahn–Marsden dystonia rating scale; GPI = globus pallidus internus.
Short-interval intracortical inhibition

SICI is thought to reflect the excitability of GABAergic interactions in the cortex (Di Lazzaro et al., 2000). A paired pulse protocol by Kujiial et al. (1993) was used that consisted of a subthreshold conditioning pulse (the intensity was set at 80% of active motor threshold) preceding a suprathreshold test stimulus (the intensity was adjusted to produce a motor evoked potential of ~1 mV in the target muscle). Interstimulus intervals of 2 and 3 ms were tested. Active motor threshold was defined as the lowest intensity that evokes a motor evoked potential of >200 μV during a minimal background contraction of 5–10% of maximal voluntary contraction in at least 5 out of 10 consecutive trials. Resting motor threshold was defined as the lowest intensity able to evoke a motor evoked potential of >50 μV at rest in at least 5 out of 10 consecutive trials. For each experimental recording, randomly intermixed conditions (two double-pulse conditions plus the single test pulse) were presented 12 times each. The interval between consecutive trials was ~5 s.

Paired associative stimulation

The PAS protocol used in this study pairs a peripheral nerve stimulus with a transcranial magnetic stimulation stimulus. If a median nerve stimulus at the wrist is repeatedly paired with a transcranial magnetic stimulation pulse to the sensorimotor cortex 25 ms later, then motor evoked potentials are facilitated for the next ~30 min. The PAS protocol serves as a model for brain plasticity. As it is an indirect measure of plasticity, the term long-term potentiation-like plasticity is used.

Electrical stimulation was applied to the median nerve at the wrist at 300% of perceptual threshold using a constant current generator (Digitimer). The stimulus duration was 0.2 ms. It was given 25 ms before a transcranial magnetic stimulation pulse over the abductor pollicis brevis muscle ‘hot spot’ at an intensity predetermined to yield a ~1 mV resting motor evoked potential (Stefan et al., 2000). Two hundred paired stimuli were delivered at a rate of 0.25 Hz. During PAS, patients were instructed to focus on the abductor pollicis brevis muscle, as done by others (Tisch et al. 2007). The motor evoked potential amplitude was recorded before, immediately after, 15 min and 30 min after PAS. As described by others (Tisch et al., 2007; Schmidt et al., 2009) input–output curves were recorded by inducing motor evoked potentials using 20–70% maximum stimulator output (increments of 10%, five stimuli per condition) pre- and post-PAS. The intertrial interval was ~5 s.

Statistical analysis

Data were analysed off-line using custom-written software. Peak to peak motor evoked potential amplitudes were measured and averaged. SICI was expressed as percentage of the single unconditioned test pulse. Long-term potentiation-like plasticity was expressed as the per cent change compared with the pre-PAS motor evoked potential amplitude size. For comparison of ‘on’ versus ‘off’ DBS condition with only one factor a paired t-test was used. Repeated-measures ANOVAs were performed where appropriate and post hoc tests were corrected for multiple comparisons if appropriate. Details are described further in the ‘Results’ section. For correlation of electro-physiological measures and clinical status, the Spearman correlation coefficient was calculated. For correlation of current drain and electrophysiology measures, Pearson correlation was used. For statistical evaluation of the change in clinical scores between the ‘on’ DBS and the 2 days ‘off’ DBS state, the non-parametric Wilcoxon matched-pairs test was used. For all analyses, a P-value < 0.05 was considered significant.

Results

Clinical effects

Since there was a significant correlation between the two raters (R = 0.82, P < 0.0001), the results were averaged. When DBS was switched off, the mean clinical (n = 10) score did not change significantly (t = 12, z = 1.57, P = 0.11; Wilcoxon matched pair). However, evolution of clinical symptoms varied profoundly between patients, ranging from none to significant worsening when DBS was switched off. None of the patients or controls experienced adverse events due to the transcranial magnetic stimulation. DBS settings, impedance, activations and current drain were checked after the study and confirmed to be unchanged (Table 1).

Motor thresholds do not change after deep brain stimulation arrest

Resting motor threshold

A two-factorial repeated-measures ANOVA revealed no significant effect of time (on DBS versus off DBS) [F(1,18) = 1.3, P > 0.1] or hemisphere (right/left), [F(1,18) = 0.1, P > 0.5] and no significant interaction of both [F(1,12) = 3.9, P > 0.05]. Left hemisphere: on DBS 39.4 ± 2.0; off DBS 41.7 ± 2.3. Right hemisphere: on DBS 41.8 ± 1.7; off DBS 41.2 ± 2.0 (Fig. 1).

Short latency intracortical inhibition is reduced and does not change after deep brain stimulation arrest

Data recorded with an interstimulus interval of 2 and 3 ms were pooled as there was no significant difference (t = 0.69, P > 0.1). SICI did not change significantly (t = 1.05, P > 0.1) after DBS was switched off for 2 consecutive days (on: 70.1 ± 9.2; 2 days off: 62.3 ± 7.5). Note that the unconditioned test pulse size (in millivolts) was not significantly different after DBS arrest (on: 0.87 ± 0.16; off: 1.11 ± 0.25) (Fig. 2).

SICI was less efficient in patients than in the matched control group (37.37 ± 6.91%; t = 2.83, P = 0.01). Comparison was also made with a group of DBS-naive patients with dystonia (n = 8; six females; mean age 45.3 years, SD 11.9 years; Burke–Fahn–Marsden = 26.8, SD 15.2; DYT1-positive = 1) from another sample (Ruge et al., 2011; 92.1 ± 16.61; t = 1.32, P = 0.19).

Changes in clinical benefit in the DBS ‘2 days off’ condition were not correlated with changes in SICI. Spearman correlation of change in SICI (‘on’ DBS condition minus ‘2 days off’ DBS condition) versus change in clinical scores (on–off): R = 0.09, P = 0.80. There was no correlation between absolute SICI and clinical measures on either occasion (Fig. 5).
Paired associative stimulation-induced plasticity is reduced and does not change following deep brain stimulation arrest

The maximum PAS response did not change between ‘on’ DBS and ‘2 days off’ DBS (on DBS 116.1 ± 8.7%; 2 days off DBS 118.3 ± 19.5%; t = −0.10, P = 0.91). There was also no change when we measured the average PAS response (on DBS 98.0 ± 4.9%; 2 days off DBS 103.3 ± 11.1%; t = −0.42, P > 0.5). Both were done for better comparability with different studies. The PAS response was less efficient than in age-matched healthy controls (160.29 ± 18.78; t = −2.13, P < 0.05) (Fig. 2).

Comparison with a DBS-naïve group of patients with dystonia (207.2 ± 31.9) (data taken from another sample, see above) showed a decreased PAS response (t = 3.03, P = 0.007).

Unlike the usual increase seen in healthy controls and in untreated dystonia, input–output curves did not change (repeated measures ANOVA intensities 20–70%) after PAS whether the patients were ‘on’ DBS [PAS effect F(1,9) = 0.02, P > 0.8; effect of stimulus intensity F(5,45) = 24.1, P < 0.0001] or ‘off’ DBS [PAS effect F(1,9) = 0.004, P > 0.5; effect of stimulus intensity F(5,45) = 30.1, P < 0.0001]. Baseline input–output curve (before PAS application) did not change significantly [F(1,9) = 5.08, P > 0.05] (Fig. 1B).

The amount of long-term potentiation-like plasticity in the ‘on’ deep brain stimulation state is related to the change in clinical benefit after deep brain stimulation arrest

Clinical Burke–Fahn–Marsden scores in the ‘2 days off’ DBS condition were subtracted from the ‘on’ DBS score for each patient, i.e. the change in clinical severity was calculated. This value was correlated with the individual maximum PAS response in the ‘on’ DBS state. The lower the PAS response in the ‘on’ DBS state was, the more worsening of symptoms occurred when DBS was turned off (Spearman correlation R = 0.76, P < 0.01). There was no correlation between the change in amount of PAS when DBS was switched off and the change in clinical severity (Spearman correlation R = 0.26, P = 0.46) (Fig. 3).

The amount of plasticity ‘on’ deep brain stimulation is related to the amount of current drain

In the literature, the amount of stimulation is often expressed in terms of stimulus voltage. However, the level of stimulation in an individual patient depends on numerous factors. The current drain (taken from the N-Vision-device) (for an overview see Kuncel and Grill, 2004), provides a measure of the amount of stimulation that takes into account the amplitude, pulse width, frequency and impedance. The amount of current drain in both the right hemisphere (82.1 ± 14.4 μA) and the left hemisphere (91.8 ± 9.76 μA) were inversely correlated with the amount of plasticity ‘on’ DBS (correlation with right: R = −0.78, P < 0.01; correlation with left: R = −0.71, P < 0.01). A smaller current drain was associated with a larger response to PAS (Fig. 4).

Clinical change after stopping DBS (clinical status ‘on’ DBS minus ‘off’ DBS) was correlated with the amount of current drain. A lower current drain was associated with better preservation of clinical benefit (right globus pallidus: R = −0.65, P < 0.05; left globus pallidus: R = −0.67; P < 0.05).

Other factors

Age, age at onset, severity of symptoms, disease duration until surgery and electrode position were all not correlated with clinical or electrophysiological outcome. The detailed results for the effect of electrode position are summarized in Table 2 and Fig. 6.
The electrode position within the globus pallidus is expressed as the percentage of the posterior–anterior axis and the internal–external axis of the globus pallidus.

**Discussion**

**Electrophysiological measures after long-term deep brain stimulation treatment: a different pattern?**

DYT1 gene-positive patients on long-term DBS treatment can maintain good control of dystonic symptoms (Cif et al., 2010). As did the patients in this study. The results suggest that after ~5 years or more of DBS, electrophysiological data differ not only from those of healthy individuals but also from those of DBS-naive patients. We found that SICI, usually regarded as a measure of the excitability of GABAergic motor cortex inhibition, was less effective than in healthy controls but tendentially more effective than in DBS-naive patients. In contrast, the PAS response, which is a measure of long-term potentiation-like synaptic plasticity in the motor cortex, was on average reduced or absent compared with healthy volunteers and DBS-naive patients.

The markers we examined are generally regarded as typical of dystonic disorders (e.g. Tinazzi et al., 2009). Long-term potentiation-like synaptic plasticity has often been reported to be enhanced in patients prior to surgery (Quartarone et al., 2003), whereas GABAergic inhibition is depressed (Ridding et al., 1995; Sommer et al., 2002). Tisch et al. (2007) investigated the PAS response at 6 months after DBS surgery. At this time point with DBS ‘on’, the PAS response was reduced on average compared with the level in healthy controls. In a longitudinal study (Ruge et al., 2011), a very similar result was found on average at 3 months after surgery, whereas the long-term potentiation-like plasticity levels increased towards normal levels at 6 months. The cause of this ‘jitter’ in the time course of DBS effects on the PAS response might be related to DBS stimulation parameters or clinical differences in the two patient groups. Nevertheless, our data show that on average, in the present group of patients, long-term DBS is associated with a reduced level of plasticity that is even below the level of healthy controls, thus indicating that continuous long-term DBS might have long-term effects on this measure.

The reduced PAS response we observed after long-term DBS may be relevant to reports regarding the induction of unbeneficial effects of DBS in some patients with dystonia; despite the maintained efficient control of dystonic symptoms, non-beneficial effects are reported that cannot be explained by the more or less immediate side effects produced by current spread to adjacent areas, such as the internal capsule. These include the

<table>
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<th>Axis within globus pallidus</th>
<th>Current drain</th>
<th>Amount of plasticity</th>
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<tr>
<td>Percentage of posterior–anterior axis in right globus pallidus</td>
<td>0.50 &gt; 0.1</td>
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<td>Percentage of posterior–anterior axis in left globus pallidus</td>
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<td>−0.28 &gt; 0.1</td>
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</table>

**Figure 2** Neurophysiological pattern after long-term DBS. (A) SICI and (B) the PAS-induced plasticity in the ‘on’ state versus the ‘off’ state in comparison with a matched healthy control group. Error bars indicate standard error of the mean. In A, the y-axis indicates percentage of the unconditioned motor evoked potential (MEP) amplitude evoked by a single pulse. Therefore, a value < 100% indicates inhibition. In B, the y-axis indicates percentage of the motor evoked potential amplitude before PAS. The red line represents the level of SICI or the PAS response in a group of DBS-naive dystonia patients. This sample is taken from another study (see main text). The figure shows that patients on long-term DBS treatment do not show a normal pattern of intracortical GABAergic inhibition (reduced) and long-term potentiation-like plasticity (reduced). It also does not resemble a pattern usually seen in patients with dystonia (enhanced plasticity, reduced inhibition). Switching DBS off for 2 consecutive days leaves these measures unchanged (group mean). Asterisk indicates significance.
demonstration of delayed-onset akinesia in primary dystonia (Tisch et al., 2007), delayed-onset bradykinesia in cranio-cervical dystonia (Berman et al., 2009) and micrographia in segmental dystonia (Blahak et al., 2009). Schrader et al. (2010) recently reported on a Parkinsonian-like gait disorder in 10% of patients with dystonia on DBS. The pattern of a reduced or absent PAS response (i.e. a less-sensitive long-term potentiation-like plasticity) seen here resembles the pattern seen in bradykinetic patients with Parkinson’s disease (Morgante et al., 2006; Schwingenschuh et al., 2010) and may therefore be one factor that contributes to potential parkinsonian side effects after long-term DBS.

In the present study, we found that SICI, as a marker of GABAergic inhibitory circuits in the cortex, was reduced compared with normal, but nevertheless tended to be more effective than expected from a typical group of DBS-naive patients with dystonia. In a previous study, on a different group of patients followed up during early DBS treatment, we found that SICI approaches levels seen in healthy individuals over the first months of DBS treatment (Ruge et al., 2011) with a time course similar to the progressive normalization of other forms of inhibition at the spinal and brainstem level (Tisch et al., 2006a, b). Bearing in mind that previous data have been collected from a different patient group and that therefore formal comparison between early and long-term treatment is not possible, the result might suggest that control of these neuronal circuits becomes less effective over time. Nevertheless, in both studies, SICI was greater than...
usually seen in DBS-naive dystonia, suggesting that long-term DBS has some persistent effect on GABAergic inhibition. Finally, it should be noted that neither reduced inhibition nor increased plasticity is the primary cause of clinical symptoms since both measures have been reported to be abnormal in unaffected body parts of patients with focal or segmental dystonia (Sommer et al., 2002). This might explain why several of the patients, despite having reduced GABAergic inhibition and PAS response, had an excellent control of dystonic symptoms.

No overall significant change in clinical or electrophysiological measures after 2 days of deep brain stimulation arrest

In the past, switching DBS off has been described to lead to a wide range of clinical responses from rebound phenomena with more severe dystonic symptoms than before DBS, to a complete preservation of the achieved clinical benefit. In the present study, the mean level of the PAS response and SICI within the patient group did not change when DBS was stopped; neither was there any change on average in the patients’ clinical state.

The physiological effects are in contrast to a previous on–off study that was undertaken only 6 months after starting DBS treatment (Tisch et al., 2007). At that time, stopping DBS led to an immediate increase of the PAS effect, almost back to levels seen prior to DBS surgery. The discrepancy between the two studies might imply, like the clinical observations previously reported by Hebb and co-workers (2007) that the effects of DBS change from being reversible to non- (or less-) reversible over the course of several years of treatment. However, caveats to this conclusion are: (i) that the present group of patients might have behaved differently at 6 months compared with the group studied by Tisch et al. (2007); and (ii) Tisch et al. (2007) did not study patients after 48 h withdrawal from DBS, as we did in the present study. It might therefore be possible that the immediate effect of turning DBS off does not persist.

Interindividual variation in clinical response to stopping deep brain stimulation

The evolution of symptoms after stopping DBS varied profoundly between individuals; with three patients not changing at all, several with mild clinical worsening and others with severe worsening of dystonic symptoms. The changes in clinical state were not correlated with changes in PAS or SICI, suggesting that these modalities are influenced in different ways by the sudden withdrawal of pallidal DBS. However, there was an association between individual levels of plasticity measured during DBS and the variation in clinical state 48 h after stopping DBS.

The amount of plasticity when on is associated with the change in clinical symptoms 2 days after stopping deep brain stimulation

The larger the response to the PAS protocol the more likely were patients able to maintain the clinical benefit they had reached on long-term DBS. Although an association is never sufficient to claim a causal relation, we would like to make the tentative suggestion that the PAS response is thought to reflect long-term potentiation-like synaptic plasticity in the cortex, and therefore it is possible that patients who have the 'highest plasticity' can store the most robust representations of normal, or less dystonic, movement patterns that had been present during the preceding years of DBS. We hypothesize that turning DBS off allows aberrant basal ganglia output back into the system, but that return of symptoms is resisted by the stored patterns of movements that are still present in the motor system. Patients with the most stable memories (and the highest PAS response after years of DBS) are the ones who experience the least decline in clinical symptoms on stopping DBS. In contrast, patients with a lower PAS response may have less robust motor memories and therefore experience a faster decline in symptoms after turning DBS off.
The response to paired associative stimulation ‘on’ deep brain stimulation depends on the current drain of the individual patient: less is more

The current drain can be calculated from the combination of stimulation parameters (pulse height, duration and frequency) used for DBS and the impedance (see Kuncel and Grill, 2004). Our results show a strong relationship between the current drain and the amount of the PAS response that is present after long-term continuous DBS. A higher current drain is associated with a smaller response to PAS and a greater loss of clinical benefit when DBS is stopped. This result is intriguing as it suggests that the amount of long-term potentiation-like plasticity (as evidenced by the response to PAS) when ‘on’ DBS could be shaped by DBS programming.

However, an association between two factors (current drain and response to PAS) does not necessarily imply a causal connection, so that this conclusion must be considered with caution until we have more evidence to link long-term stimulation parameters to electrophysiological effects. Our study showed that current drain itself is related to the stability of clinical symptoms after 48 h withdrawal of DBS, leaving open the possibility that there exists some underlying factor that is directly responsive to current drain and which has separate but related effects on the PAS response and stability of clinical symptoms.

In conclusion, our work shows that when DBS is stopped after ~5 years or more of continuous stimulation, the return of clinical symptoms after 48 h is related to the levels of the PAS response that had been observed when patients were ‘on’ DBS. The greater the response to PAS, the better the clinical benefit was maintained in the ‘off’ condition. A good response to PAS is associated with good levels of long-term potentiation-like plasticity (Ziemann et al., 2004) in cortex, and we speculate that this may help the motor system store representations of more normal movement patterns that resist degradation when DBS is turned off. A good response to PAS is also associated with low levels of DBS current drain. If this link is causal, then it may be possible to adjust stimulus parameters to maximize long-term clinical effects.

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