The sensory and motor representation of synchronized oscillations in the globus pallidus in patients with primary dystonia

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In 15 patients with primary dystonia (six cervical and nine generalized dystonias) who were treated with bilateral chronic pallidal stimulation, we investigated the sensorimotor modulation of the oscillatory local field potentials (LFPs) recorded from the pallidal electrodes. We correlated these with the surface electromyograms in the affected muscles. The effects of involuntary, passive and voluntary movement and muscle-tendon vibration on frequency ranges of 0–3 Hz, theta (3–8 Hz), alpha (8–12 Hz), low (12–20 Hz) and high beta (20–30 Hz), and low (30–60 Hz) and high gamma (60–90 Hz) power were recorded and compared between cervical and generalized dystonia groups. Significant decreases in LFP synchronization at 8–20 Hz occurred during the sensory modulation produced by voluntary or passive movement or vibration. Voluntary movement also caused increased gamma band activity (30–90 Hz). Dystonic involuntary muscle spasms were specifically associated with increased theta, alpha and low beta (3–18 Hz). Furthermore, the increase in the frequency range of 3–20 Hz correlated with the strength of the muscle spasms and preceded them by ~320 ms. Differences in modulation of pallidal oscillation between cervical and generalized dystonias were also revealed. This study yields new insights into the pathophysiological mechanisms of primary dystonias and their treatment using pallidal deep brain stimulation.

Keywords: dystonia; deep brain stimulation; electromyograms; globus pallidus; oscillations

Abbreviations: BFMDRS = The Burke, Fahn and Marsden dystonia rating score; DBS = deep brain stimulation; ECoG = electrocorticogram; EMG = electromyogram; GPe = globus pallidus externus; GPi = globus pallidus internus; FFT = fast Fourier transform; LFPs = local field potentials; PSD = power spectrum density; TWSTRS = The Toronto Spasmodic Torticollis rating scale


Introduction

Dystonia is characterized by abnormal muscle contractions, often causing abnormal postures with or without repetitive twisting movements. Bilateral deep brain stimulation (DBS) of the globus pallidus internus (GPI) has become a favoured treatment for medically intractable and severely disabling primary and selected secondary dystonia (Coubes et al., 2000, 2004; Andaluz et al., 2001; Krauss, 2002; Krauss et al., 2003, 2004; Lozano and Aboish, 2004; Halbig et al., 2005; Trottenberg et al., 2005; Vidailhet et al., 2005, 2007; Kupsch et al., 2006; Hung et al., 2007). Clinically patients with quick and significant improvements seem to be those with phasic or ‘mobile’ involuntary movements, whereas patients with severe tonic posturing may experience less improvement (Krauss et al., 2002, 2004; Volkmann and Benecke, 2002; Vidailhet et al., 2005). Although the pathophysiological mechanisms of primary dystonia are not fully understood (Berardelli et al., 1998; Vitek, 2002; Hutchison et al., 2003; Krauss et al., 2004), and the therapeutic outcomes of pallidal DBS vary greatly both in terms of overall effectiveness and the time course of response to treatment, increasing evidence suggests that there is excessive oscillatory activity between
3 and 10 Hz in the local field potential (LFP) of the pallidum in patients with primary dystonia (Liu et al., 2002; Silberstein et al., 2003). Furthermore, the magnitude of the pallidal oscillatory activity is correlated with involuntary dystonic muscle activity (Chen et al., 2006). Recently, we have demonstrated that significant coherence existed between the oscillatory LFPs of the GPi and only the mobile component of dystonia represented by the repetitive or rhythmic bursts in the surface electromyograms (EMGs), but not the fixed component represented by the sustained hypertonic bursting activity (Liu et al., 2006).

The precise role of oscillations in the globus pallidus is still unclear. In parallel to the alleviation of rhythmic or phasic involuntary movements (Trottenberg et al., 2005; Kupsch et al., 2006; Hung et al., 2007; Vidailhet et al., 2007) and the reversal of hypertonic co-contraction (Liu et al., 2004; Tisch et al., 2006) by high-frequency pallidal DBS, increasingly evidence suggests that sensory deficits exist in dystonias at the cortical (Hallett, 1995; Bar-Jimenez et al., 1998, 2000; Ng and Jones, 2007) and subcortical levels (Lenz et al., 1998, 1999; Zirh et al., 1998; Tang et al., 2007). Critically, however, it is still uncertain whether the functional link revealed by significant coherence (Liu et al., 2002, 2006; Foncke et al., 2007) and magnitude correlation (Chen et al., 2006) between pallidal LFPs and EMGs of affected muscles reflects the sensory afferent from muscle to pallidum, the motor efferent drive from pallidum to muscle or a combination of these two activities leading to bi-directional flow between pallidum and muscle. Studies have used signal processing tools to reveal the directional coupling between two simultaneously recorded signals of either spontaneous electrocorticogram (ECoG)-LFP (Sharott et al., 2005) in rats or LFP-EMGs in stable parkinsonian tremor (Wang et al., 2007) using Granger causality-based techniques. We felt that the above approach may have obtained inconclusive results due to its mathematical limitations, which may be amplified by the complex patterns (in terms of signal waveform and composition) in hypertonic muscle EMGs (Wang et al., 2003; Wang et al., 2006). Consequently, a physiological approach to investigate the sensorimotor nature of the pallidal oscillation was taken in our previous study on eight patients with primary dystonia affecting various body parts (Liu et al., 2006). We investigated how the oscillatory pallidal LFPs were modulated in their magnitude over a frequency range of 0–30 Hz by different sensory and motor conditions in the affected body parts. Those sensory and motor conditions were defined as those relative to the resting condition, so that changes in the magnitude of pallidal LFPs over repetitive voluntary movements of the affected muscles would relate to both motor efferent of the pallidum and the sensory reafferent to the pallidum, whereas the magnitude change of the pallidal LFPs over the repetitive passive movements primarily related to the sensory feedback. Our results showed that the power of the GPi LFPs significantly increased at low-frequency range of 1–3 Hz and decreased over frequency range of 8–16 Hz following both active and passive movements without significant interaction between motor condition and frequency range.

The objective of the present study is to further investigate the sensorimotor nature of the pallidal oscillations by revealing the modulation of the pallidal LFPs over physiologically defined sensory and motor conditions of the affected body parts, including rest, voluntary and involuntary movements, passive movements and muscle-tendon vibration. We hypothesized that the pallidal oscillation may be differently modulated by these sensory and motor conditions, so that the sensorimotor nature and the specific generative roles of sensory afferent or motor efferent components of the pallidal oscillation in the dystonic symptoms may be revealed. The primary challenge of the study is to effectively represent and sample the dystonia symptoms, as these are highly variable in nature both amongst patients and over time in individual patients and also, in terms of the involved body parts and the nature of the involuntary movements (namely phasic or prolonged spasms). Thus the following key issues were incorporated into the study design: (i) The involvement of axial and distal body parts in primary dystonia, for which the patients with cervical dystonia without clear limb involvement were compared with the patients with generalized dystonias. The grouping was based on the patients’ clinical presentation rather than the onset site of their dystonia symptoms; (ii) for the sensory condition, in order to avoid possible contamination by voluntary movements during passive movement of the dystonic muscles (likely caused by hypertonic pain or subconscious movement), sensory feedback was induced later in the study using muscle-tendon vibration; (iii) the motor conditions were defined by EMG activity, and the appropriate segments from continuously recorded signals were selected as: (a) rest (no or little hypertonic bursts); (b) involuntary (phasic bursts of muscle spasms) and (c) voluntary movements (regular alternating bursts between antagonist muscles); (iv) the frequency profile of the sensory and motor modulation LFP signals and correlation in the LFP magnitude were analysed over different sub-frequency bands and (v) the temporal relationship between the pallidal LFPs and muscle spasms were investigated using the EMG-triggered averaging on time-frequency analysis of pallidal LFPs.

Methods

Patients

Fifteen patients with primary dystonia (six cervical and nine generalized dystonias) were recruited to take part in this study. These patients presented severe and disabling dystonias with a later onset age in cervical dystonia patients (22–65, median 42.5 years old) than in generalized dystonia patients (2–37, median 14.5 years old). None of the 15 patients was DYT1 positive. They underwent bilateral implantation of DBS electrode into the GPi at Radcliffe Infirmary, Oxford. Approval of the local research ethics committee of Oxfordshire, UK, and informed consent for this study were obtained. The patients were assessed clinically and video recorded for the purpose of obtaining the Toronto
Table 1 Summary of patients’ demographics

<table>
<thead>
<tr>
<th>Patients</th>
<th>Gender</th>
<th>Age at onset (years)</th>
<th>Duration of disease (years)</th>
<th>Site of initial symptoms</th>
<th>Clinical rating scores*</th>
<th>Electrode contacts</th>
<th>Stimulation parameters (V/Hz/μs)</th>
</tr>
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<tr>
<td></td>
<td></td>
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<td>Pre-op/Post-op (months)</td>
<td>Left/Right</td>
<td></td>
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<tr>
<td>Cervical dystonia</td>
<td>#1</td>
<td>M</td>
<td>52</td>
<td>7</td>
<td>Neck</td>
<td>5/87</td>
<td>39/87 (12)</td>
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<tr>
<td>#2</td>
<td>F</td>
<td>36</td>
<td>10</td>
<td>Neck</td>
<td>69.5/87</td>
<td>28/87 (12)</td>
<td>1–2+/5–6+</td>
</tr>
<tr>
<td>#3</td>
<td>M</td>
<td>65</td>
<td>14</td>
<td>Face</td>
<td>56.5/87</td>
<td>27.5/87 (12)</td>
<td>1–3+/5–7+</td>
</tr>
<tr>
<td>#4</td>
<td>M</td>
<td>38</td>
<td>15</td>
<td>Neck</td>
<td>50.5/87</td>
<td>46.5/87 (2)</td>
<td>0–3+/5–6+</td>
</tr>
<tr>
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<td>22</td>
<td>14</td>
<td>Neck</td>
<td>43/87</td>
<td>14/87 (12)</td>
<td>1–3+/5–7+</td>
</tr>
<tr>
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<td>47</td>
<td>10</td>
<td>Neck</td>
<td>38/87</td>
<td>25/87 (12)</td>
<td>1–5–</td>
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<td>Generalized dystonia</td>
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<td>M</td>
<td>33</td>
<td>13</td>
<td>Neck</td>
<td>32.5/150</td>
<td>28.5/150 (11)</td>
</tr>
<tr>
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<td>12</td>
<td>Neck</td>
<td>79/150</td>
<td>28.5/150 (12)</td>
<td>0–3+/4–7+</td>
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<td>#9</td>
<td>F</td>
<td>13</td>
<td>45</td>
<td>Hand</td>
<td>52/150</td>
<td>17.5/120 (11)</td>
<td>2–3+/5–6+</td>
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<tr>
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<td>F</td>
<td>16</td>
<td>38</td>
<td>Leg</td>
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<td>20/150 (12)</td>
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<tr>
<td>#11</td>
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<td>10</td>
<td>9</td>
<td>Leg</td>
<td>74/150</td>
<td>22/150 (9)</td>
<td>1–3+/5–7+</td>
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<td>2</td>
<td>34</td>
<td>Neck</td>
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<td>30/150 (11)</td>
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<td>#13</td>
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<td>Arm</td>
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<td>1–2+/5–6+</td>
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<tr>
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<td>F</td>
<td>8</td>
<td>25</td>
<td>Hand</td>
<td>63.5/150</td>
<td>32/120 (12)</td>
<td>1–3+/5–7+</td>
</tr>
<tr>
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<td>21</td>
<td>11</td>
<td>Neck/Arm</td>
<td>44/150</td>
<td>24/150 (7)</td>
<td>1–5–</td>
</tr>
</tbody>
</table>

*Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) for cervical dystonia; Burke, Fahn and Marsden dystonia rating score (BFMDRS) for generalised dystonia.

Spasmodic Torticollis rating scale (TWSTRS) (Comella et al., 1997) on patients with cervical dystonia, and the Burke, Fahn and Marsden dystonia rating score (BFMDRS) (Burke et al., 1985) on those with generalized dystonia. Assessments were carried out pre-operatively and during follow-up for 12 months. Patient demographics are summarized in the Table 1.

Electrode implantation and chronic stimulation

The surgical procedures of GPi targeting and implantation of DBS electrodes have been previously reported (Parkin et al., 2001; Liu et al., 2006), and summarized here: The GPi was localized on the fused CT/MRI images using Radionics Image Fusion™ and Stereoplant™ (Radionics, MS, USA) pre-operatively and electrode implantation was then performed under general anaesthetics. The electrode of Medtronic’s 3387 (Medtronic Neurological Division, Minneapolis, USA) was passed to the centre of the posterior half of the medial pallidum whilst monitoring the impedance to avoid the trajectory going through the ventricle with a Radios™ electrode of 1.8 mm in diameter and 2.0 mm in length exposed tip. Within the medial pallidum, the impedance is 500–600 Ω rising to 800–1000 Ω at the ventral margin. Having identified this, the Radios™ electrode was removed and replaced by the DBS electrode. To ensure that the electrode was not placed too close to the internal capsule posteriomedially the two ventral contacts were stimulated at up to 5.0 V to check that there were no unwanted motor responses. Then the DBS electrode was plated to the skull. Post-operative sequential CT axial scans (2 mm slice thickness) were fused onto the pre-operative MRI images or post-operative MRI images were obtained to confirm the electrode placement by relating the electrode contacts to the anatomic landmarks of the optical tract, the GPi/GPe and the GPe/putamen borders. All the patients included in this study clearly had at least one pair of electrode contacts in the GPi.

The electrodes were externalized for 1 week and then connected to a subcutaneous programmable pulse generator (Kinetra or Synergy, Dual Channel Itrel, Medtronic Inc., Minneapolis, MN, USA) implanted in the subclavicular tissue. The clinical justification for externalizing the DBS electrodes is mainly due to the fact that under general anaesthesia the intra-operative investigation for any early prediction of success during electrode implantation is very limited. We have found that very small changes particularly subjective loss of pain and decrease in jerky movements during post-implantation days correlate with good long-term outcome. The period of externalization ensures that the large majority implanted will benefit long term. No significant peri-operative complications occurred. Initial stimulator parameters were set in the common region of: 2.0–7.0 V, 130–180 Hz and 150–240 μs as tolerated by the individual patient (Kumar, 2002; Krauss et al., 2004).

Neurophysiological recordings

The detailed description of the neurophysiological recordings has been previously reported (Liu et al., 2006), and summarized here: The LFPs were recorded from the GPs during the period of 4–6 days post-operatively via the externalized electrodes. Three channels of LFPs were simultaneously recorded from the adjacent pairs of four contacts of DBS (contact 0–1, 1–2 and 2–3) with a common electrode placed on the surface of the mastoid. The location of the electrode contacts were identified on the post-operative fused CT-MRI images, and the locality of the GPi LFPs was reflected by the graded changes in both amplitude and frequency of the oscillatory activity recorded via different pairs of contact. The artefacts resulting from movement of extension cable of the DBS lead was carefully identified, avoided if possible and marked on the recordings to be excluded during analysis. In all 15 patients, recordings from 30 electrodes were analysed, among which recordings were excluded from further analysis due to sub-optimal placement in three electrodes (in three different patients) and due to excessive noise in signals in one electrode. Surface EMGs were recorded using disposable adhesive Ag/AgCl electrodes (H27P, Kendall-LTP, MA, USA) placed with a tri-polar...
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configuration (active-common-reference electrodes) over the affected muscles of both body sides in each case. Muscles included the wrist extensor (carpi ulnaris), flexor (digitorum superficialis), biceps and triceps in generalized dystonia, and trapezius and sternocleidomasoid muscles in cervical dystonia. Signals were amplified using isolated CED 1902 amplifiers ($\times 10,000$ for LFPs and $\times 1000$ for EMGs; Cambridge Electronic Design, Cambridge, UK), filtered at 0–1000 Hz and digitised using CED 1401 mark II at rates of 2500 Hz, displayed on line and saved onto a hard disk using a custom written program in Spike2 (Cambridge Electronic Design, Cambridge, UK).

Sensorimotor conditions

Patients were seated and relaxed in a quiet environment after the DBS had been turned off at least an hour before the investigation although it was unclear if the effect of stimulation on dystonia was completely reversed 1 h after discontinuation of stimulation. Firstly, the spontaneous LFPs were recorded when the patients were at rest, and then during repetitive alternating wrist movements performed either by the patient (active movements, 15 patients, 27 GPs) or by the experimenter (passive movements, 12 patients, 21 GPs). The movement was self-paced at approximately one movement every 2 s without specific audio or visual guidance. In 8 out of 15 patients, (14 GPs) including both the cervical and generalized dystonias, muscle-tendon vibrations were applied onto the tendon of the forearm extensor muscles above the wrist using a common physiotherapy massage vibrator. Each condition was maintained over a period of 30–35 s with 1 min rest between two consecutive sessions to allow a segment of 25 s stable recording to be selected for further analysis. The rest and motor conditions were defined by EMG signals (Fig. 1, data from the Patient #8 in Table 1), as the rest (no or little hypertonic bursts in EMGs, Fig. 1A), active movements (regular, with a duration of tens of milliseconds, alternating between antagonist muscles, Fig. 1B), and involuntary contractions (phasic spasms over seconds, Fig. 1E). During passive movements and muscle-tendon vibration, the EMGs were silent with baseline shifts synchronized with the passive movements (Fig. 1C and D).

Signal processing and analysis

The GPi LFPs in segments of 25 s were selected based on the simultaneously recorded EMGs to represent conditions of resting, active and passive movements, vibration and involuntary dystonic movements in each patient for further analysis. The data segment was linearly de-trended and transformed into frequency domain using FFT with 2 s windows and 0.5 s overlapping to obtain the power spectra density (PSD) of data segments over conditions, and to present in the frequency range of 0–90 Hz. Given the substantial inter-recording variation, active, passive, vibration or hypertonic condition was normalized with respect to the rest condition, expressed as the percentage increase/decrease in PSD for each recording. The normalized PSD was averaged across recordings in 2 Hz-bands over the range of 0–90 Hz for each condition.

In order to reveal the temporal relationship between modulation in pallidal LFPs and involuntary movement, on one selected patient of generalized dystonia (Patient #11 in Table 1), with clear phasic muscle spasms on which the onsets of 18 episodes of the spasms could be clearly identified on the EMG signal, EMG-triggered time-frequency analysis was carried out on the pallidal LFPs and averaged over 18 epochs. Detailed description on short-time Fourier transform based time-frequency analysis has been previously reported (Wang et al., 2005).

Statistical analysis of the averaged data

The power spectra of 0–90 Hz were compared on sub-frequency bands defined in the recent literature, i.e. 0–3 Hz, 3–8 Hz (theta), 8–20 Hz (alpha, 8–12 Hz and low beta, 12–20 Hz), 20–30 Hz (high beta), 30–60 Hz (low gamma) and 60–90 Hz (high gamma). The significance of changes in each sensorimotor condition over the rest was then tested using paired t-test. The mean power value within each frequency band was statistically tested against conditions using two-factor analysis of variance (ANOVA).

Focusing on the GPi activity in dystonic condition over the segment where involuntary movements were identified in EMG singles, correlation analyses were performed between the frequency bands of 8–20 Hz and 30–60 Hz, and between 8 and 20 Hz and 60–90 Hz on the mean normalized power value of each frequency band over all 15 patients (bilateral recordings from nine patients and unilateral recordings from six patients, $n = 24$). Separated analyses for the cervical and generalized dystonia groups were inconclusive as the number of samples was too small.

Results

Modulation of pallidal LFP oscillation over sensorimotor conditions

In comparison with rest condition (100%), significant decreases in the oscillation power were induced in the frequency ranges of 8–20 Hz (alpha and low beta bands) over the conditions of voluntary movements (86 ± 3%, mean ± SE), passive movements (82 ± 4%) and vibration (93 ± 5%), and with only significant increases in the higher frequency range of 20–90 Hz (high beta, low and high gamma bands, 115 ± 6%, 115 ± 4%, 116 ± 5%, respectively) during voluntary movements but not passive movements and vibration. In contrast, significant increases in power were induced in the frequency range of 3–20 Hz (theta, alpha and low beta bands; 119 ± 8% and 108 ± 3%, respectively) in the hypertonic condition. Multi-variance analyses on the mean power values of the normalized spectra were then carried out over influential factors including frequency bands, sensorimotor conditions and groups of cervical and generalized dystonias. Significant differences were found across frequency bands ($P < 0.0001$), between conditions ($P < 0.001$) and between dystonia groups ($P < 0.01$). Significant interaction was only found between the frequency band and sensorimotor condition, but not between the dystonia group and two other factors. Further statistical tests on the data presented in Fig. 2 were carried out to look at the detailed comparisons between factors and are presented in Fig. 3, which confirmed that the most intriguing difference in modulation of pallidal
oscillation was between dystonic and other conditions in the frequency range of 3–18 Hz (theta, alpha and low beta bands). Furthermore, significant inverse correlations were found in the mean power values of the GPi activity related to hypertonic spasms between 8 and 20 Hz (alpha and low beta bands) and gamma bands of 30–60 Hz (low gamma, \( r = -0.44, n = 24, P < 0.05, \) Fig. 4A) and 60–90 Hz (high gamma band, \( r = -0.47, n = 24, P < 0.05, \) Fig. 4B).

Fig. 1 Physiological definition of sensorimotor conditions using surface EMG signals. (A) Rest, little in EMG activity; (B) Alternating voluntary movements, regular muscle bursts of \( \sim 2 \text{s} \) in duration; (C) Passive movements, little EMG activity; (D) Muscle-tendon vibration, little EMG activity and (E) Involuntary muscle spasms, prolonged episodes of muscle bursts of 10–20 s in duration. Data are presented as rectified surface EMG signal (top), raw LFP signal (middle) and power spectrum of LFPs in the frequency range of 0–20 Hz (bottom) for each condition.
Comparison between cervical and generalized dystonias

In addition to what is expected that the patients with cervical and generalized dystonia had hypertonic symptoms predominantly affecting different body parts, not only the vertical segments of the body, but mainly the axial muscles in the cervical dystonia and limbs in the generalized dystonia.

In the present study, it was firstly demonstrated using the multi-variance analysis on the neurophysiological signals that the dystonia type was not the most significantly influential factor on the modulation of pallidal oscillation in comparison with sensorimotor conditions (Fig. 5). In summary, in both voluntary and dystonic conditions, modulation of pallidal LFPs in patients with generalized dystonia was wider in frequency range and, in particular involved the 0–3 Hz band and gamma (30–90 Hz bands) more than the modulation in patients with cervical dystonia (Fig. 5A and D, \( P < 0.05 \), two-way ANOVA); and voluntary movement induced significantly larger desynchronization (21%) in the frequency range of 8–20 Hz in cervical dystonia than the 9% decrease in generalized dystonia.
(Fig. 5B, \( P < 0.01 \), \( t \)-test); whereas passive movement induced similar desynchronization in the frequency range of 3–20 Hz in both types of dystonia.

**The temporal relationship between increase in LFP synchronization and the phasic hypertonic muscle spasms in generalized dystonia**

In one selected generalized dystonia patient (Patient #11 in Table 1) with regular muscle spasm the onsets of 18 episode of hypertonic spasm over a period of 8 min could be clearly identified (Fig. 6A), which enabled us to perform EMG-triggered time-frequency analysis on the pallidal LFP, and a further cross-correlation analysis between the EMG and LFP signals. The results are very interesting: there was a significant increase in LFP synchronization in the frequency range of 3–20 Hz (Fig. 6B) which was cross-correlated with the amplitude of the hypertonic muscle spasm (\( r = 0.59, P < 0.05 \), Fig. 6C), and the pallidal activity preceded the onset of the muscle (labelled as time zero) by \( \sim 320 \) ms.

**Discussion**

The present study investigated the sensorimotor nature of pallidal oscillation in primary dystonias by comparing the modulation of pallidal LFPs across physiologically defined sensorimotor conditions and analysing the temporal relationship between the pallidal activity and muscle activity during involuntary muscle spasms. The most intriguing results of the present study may be summarized as: (i) the sensory-related modulation of the pallidal oscillation induced by voluntary movement, passive movement and vibration was represented by significant decreases in LFP synchronization in the 8–20 Hz; (ii) modulation related to voluntary movement was represented as the increase in synchronization in the gamma bands of 30–90Hz and (iii) involuntary muscle spasms in dystonia was specifically associated with significantly increased synchronization in the theta, alpha and low beta bands of 3–18 Hz. Furthermore, in one selected generalized dystonia patient, it was demonstrated that the increase in synchronization in the 3–20 Hz band significantly correlated with and preceded the muscle spasms by \( \sim 320 \) ms. It was also demonstrated that the dystonia type was not the most significantly influential factor on the modulation of pallidal oscillation.

**Sensorimotor representation of oscillatory activity in the pallidal LFPs**

One of the fundamental questions about the physiological functions of the globus pallidus is what the synchronized
neural activity represents. The answer is not easy to find because GPi receives efferents from both the ‘direct’ and ‘indirect’ pathways and sends afferents via the ‘ascending’ pathway to the cortex via the thalamus (Montgomery, 2006) and the ‘descending’ pathway to the brainstem via structures such as the pedunculopontine nucleus (Nandi et al., 2002; Mena-Segovia et al., 2004). We looked at this question from a different angle and attempted to elucidate whether the pallidal oscillation represents the activity of either the sensory or motor neuronal components in nature. Primate studies and intra-operative microelectrode recordings from independent laboratories worldwide (Hamada et al., 1990; Sterio et al., 1994; Lozano et al., 1996; Lenz et al., 1998; Vitek et al., 1998; Hutchison et al., 2003; Bar-Gad et al., 2004; Lee et al., 2007) have provided convincing evidence that neurons related to both sensory afferent and motor efferent systems co-exist in the GPi, and dysfunction of both types of neurons may directly contribute to the pathogenesis of movement disorders such as Parkinson’s disease and primary dystonia. However, it should be pointed out that one needs to be careful in interpreting the results of studies on patients for revealing the physiological function of GPi. Furthermore, in a clinical study, steps can be taken to assist disentangling the function of GPi from the dysfunction resulting from the disorder on which the study was carried out. For instance, a comparison of frequency distribution of pallidal LFPs between Parkinson’s disease and primary dystonia (Silberstein et al., 2003) revealed a specific feature of dystonia, was a significant increase in synchronization in the <10 Hz range. In the present study, we compared the modulation of the pallidal LFPs over different physiologically defined sensorimotor conditions defined by EMG recordings in the same group of patients with primary dystonias. The power values of pallidal LFPs were normalized against resting condition. By these measures, we assumed that between conditions of rest, voluntary movement, passive movement and vibration, there may be a common influence specifically related to dystonia across conditions, and such a common factor may likely be minimized by the normalization process, at least to some extent. Consequently, the similarities or differences between conditions may reflect the remaining physiological functions of the GPi whilst under the influence of dystonia. For the sensory condition of passive movements, during which we suspected that voluntary movements may have occurred as patients assisted unintentionally, we applied muscle-tendon vibration to the affected body parts to generate pure proprioceptive feedback. This was then compared with the combined sensorimotor conditions of voluntary and involuntary movements. Thus attempting to differentiate the sensory component from the motor component embraced in the compound pallidal LFPs related to both involuntary and voluntary movements. The power of such a comparison may be further enhanced by normalizing the power spectra of each condition against that of the rest, during which EMGs were silent, and by decomposing the spectra into frequency bands of 2 Hz over the range of 3–90 Hz. Our results clearly showed that decreased synchronization in the 8–20 Hz (alpha and low beta bands)
may represent the sensory afferents to the GPi following voluntary, passive movements and vibration. Clearly, both tactile and proprioceptive modalities may be involved during passive movement and vibration, but tactile stimulation was not present in voluntary movement. Therefore, one may speculate that the sensory afferent to the GPi in the present study primarily represent the proprioceptive and not the tactile modality. Meanwhile, the increase in synchronization over the gamma bands of 30–90 Hz was specifically associated with the motor efferent during voluntary movements. This finding is in line with the theory that the gamma oscillation is ‘pro-kinetic’ in nature (Brown and Williams, 2005).

**Synchronized GPi activity and their physiological modulation related to primary dystonias**

The strongest evidence to support the view that GPi plays a generative role in movement disorders such as Parkinson’s disease and primary dystonia has to be that parkinsonian and dystonic symptoms can be effectively alleviated by pallidal lesions and DBS. Subsequent long-term clinical studies have established that the bilateral GPi are the primary DBS targets for treatment of dystonias (Coubes et al., 2000, 2004; Andaluz et al., 2001; Krauss, 2002; Krauss et al., 2003, 2004; Lozano and Abosch, 2004; Halbig et al., 2005; Trottenberg et al., 2005; Vidailhet et al., 2005, 2007; Kupsch et al., 2006; Hung et al., 2007). Based on this clinical consensus, investigations have been carried out to establish the role that GP plays towards the generation of either the ‘hyperkinetic’ or the ‘hypo-kinetic’ symptoms in the affected muscles, by revealing the pallidal oscillatory activity and its functional coupling with the activity of the affected muscle in patients with primary dystonias (Liu et al., 2002, 2006; Chen et al., 2006). In comparison with the previous studies, the most striking contrast in LFP modulation revealed by the present study was the excessive synchronization over the 3–18 Hz range, peaking at the theta band of 3–8 Hz that occurred in the GPi in association with involuntary movements of rhythmic muscle bursts and prolonged muscle spasms. In fact that the extent of the increase in synchronization over the alpha and low beta bands during hypertonic muscle spasms should be more accurately presented by the peak-to-peak measurement of overall modulation within the alpha and low beta bands between the hypertonic and other conditions rather than the hypertonic condition alone (Fig. 2). Based on our results, the increase in synchronization over the similar frequency range induced by the hypertonic spasms overlapped with the decrease in alpha and low beta synchronization induced by sensory feedback associated with the involuntary movements. Take all the neurophysiological evidence together, it is reasonable to speculate that the excessive synchronization in the frequency range of 3–18 Hz may be responsible for generating various dystonic symptoms including the rhythmic muscle activity such as tremor or myoclonus (Liu et al., 2002; Wang et al., 2004, 2006; Foncke et al., 2007), the prolonged muscle spasms, and the hypertonic co-contraction (Liu et al., 2004; Tisch et al., 2006) as the reciprocal inhibition mechanism between the antagonist muscles may be abolished by this excessively synchronized down-flow drive. In addition, based on the frequency overlapping of sensory and hypertonic modulation of the synchronization in the alpha and low beta bands, one may propose that the sensorily induced desynchronization had the opposite effect on modulating the excessive hypertonic synchronization in alpha and low beta bands. This may provide a possible explanation for the ‘sensory trick’ phenomenon in primary dystonias, and in cervical dystonia in particular (Schramm et al., 2004; Tang et al., 2007).

Although it is an accepted fact that pallidal DBS or lesion alleviates dystonia and reverses co-contraction, it has been a long search for direct neurophysiological evidence that the excessive synchronization of pallidal oscillation is generatively responsible for the abnormal hypertonic muscular activity. In the present study, we demonstrated on a selected patient with generalized dystonia who manifested phasic episodes of muscle spasms, of which the onset of each spasm could be clearly identified, not only that the pallidal oscillation in the frequency range of 3–20 Hz significantly correlated with muscle spasms in the EMGs in magnitude, but also that the increased synchronization of pallidal LFPs in that frequency range preceded the muscle spasms by ~320 ms. Although the increase in synchronization preceding the muscle spasms by 320 ms was only documented in one patient and its significance made from this observation should be taken more carefully, this clearly demonstrated temporal coupling between the pallidal oscillation and muscle activity strongly reinforces our claim mentioned earlier that the excessive synchronization in the range of 3–20 Hz involved in hypertonic symptoms of primary dystonia, and the involvement of the abnormal pallidal synchronization in primary dystonia is further evident to be generative. The 320 ms conduction time would also suggest that the connection between the GPi and the muscle is multi-steps. Furthermore, it was observed that the magnitude of excessive synchronization in the 3–20 Hz over the period of hypertonic spasms reversely correlated with the oscillation power in the gamma bands (low gamma, 30–60 Hz, Fig. 4A; high gamma, 60–90Hz, Fig 4B), suggesting that the overall activity of the GPi distributed among different frequency bands may represent a balanced system between sensory afferent and motor efferent or between activities of ‘hyper-kinetic’ and ‘hypo-kinetic’ in nature (Brown and Williams, 2005).

**The pallidial activity between cervical and generalized dystonias**

In this study, we also compared the pallidal activity between patients with cervical and generalized dystonias, as in the former the axial muscles are predominantly involved, with much lesser or non-involvement of limb muscles, whilst in the latter both the axial and limb muscles are affected. Our results
showed that the differences in the magnitude of LFP modulation between two types of primary dystonias were much less dramatic than that between sensorimotor conditions. As one may expect, modulation of the pallidal oscillation by voluntary (Fig. 5A) and involuntary (Fig. 5D) movements appeared in a wider frequency range in generalized dystonia than in cervical dystonia, reflecting the increased number of body parts affected and larger variation in the representation of the hypertonic movements in generalized dystonia. To look at the results more carefully, one may notice that in cervical dystonia the desynchronization induced by passive movement (Fig. 5B) fitted better, in the frequency range of 3–20 Hz, with the increase in synchronization associated with hypertonic muscle spasms (Fig. 5D). This may be the physiological evidence for the clinical observation that the ‘sensory trick’ is more common in cervical than generalized dystonia.

The relevance of synchronized GPI activity to DBS treatment for primary dystonias

How do the results of the present study help us to understand the mechanisms of pallidal DBS? Firstly, our study confirms that there is excessive synchronization in GPI in the frequency range of 3–20 Hz which is directly responsible for the either the highly rhythmic ‘mobile’ symptoms or sending this excessive synchronized activity via the indirect descending pathways to the brainstem and spinal cord, which causes the prolonged hypertonic muscle spasms of the ‘fixed non-mobile’ symptoms largely by abolishing the reciprocal inhibition mechanism between the antagonist muscles, and the hypertonic co-contraction (Liu et al., 2004; Tisch et al., 2006). High-frequency bilateral pallidal DBS may alleviate the hypertonic activity by desynchronizing these excessive synchronized pallidal efferents via both the ascending and descending pathways; secondly in the present study, it was also demonstrated that the dystonia type was not the most significantly influential factor on the modulation of pallidal oscillation in comparison with sensorimotor conditions. One may speculate that the differences in the magnitude and frequency range of LFP modulation in the pallidum may make it possible that, perhaps, there is a preference for certain pallidal oscillations go through the ascending pathway via the thalamus to the cortex causing more generalized dystonia in the limbs which are primarily unilaterally controlled, whereas the other goes through the descending pathways via the brainstem causing dystonia in the neck and trunk which are primarily bilaterally controlled (Nandi et al., 2002). The bilateral control of the axial muscles may be responsible for the delayed clinical manifestation of dystonic symptoms. In parallel to our neurophysiological findings of difference in pallidal oscillations between generalized and cervical dystonias, our recent clinical studies (Bittar et al., 2005a, b) revealed that, at 2 years follow-up, both the spasmodic torticollis (a 59% improvement in their total TWSTRS rating score) and generalized group (a 46% improvement in their overall BFMDRS evaluation) exhibited similar clinical improvement with similar time course, i.e. 95% of the final improvement was attained by 6.4 months in the generalized dystonia group and by 6.6 months in those with spasmodic torticollis; and thirdly, it has been recognized that the electric energy required for achieving the clinical efficacy in DBS for primary dystonia is usually higher than that in Parkinson’s disease or essential tremor (Krauss et al., 2004). This may be related to the fact that excessive synchronization responsible for hypertonic muscle contractions was revealed to concentrate in the low-frequency range of 3–20 Hz (theta, alpha and low beta bands), whereas the anti-kinetic synchronization in Parkinson’s disease mainly concentrates in the frequency range of beta band (13–30 Hz). Perhaps, desynchronizing the low-frequency synchronization demands higher energy or intensity reflected in the longer pulse width required in dystonia.

In conclusion, the present study revealed that the modulation of the pallidal oscillation represents both sensory and motor activity in different frequency bands. The involuntary muscle spasms in dystonia were specifically associated with significant increases in pallidal synchronization in the theta, alpha and low beta bands of 3–18 Hz; decreased synchronization in the 8–20 Hz (alpha and low beta bands) may represent the sensory afferents to the GPI; and the increase in LFP synchronization in the 3–20 Hz significantly correlated with and preceded the muscle spasms.

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References


Wang S, Aziz TZ, Stein JF, Liu X. Time-frequency analysis of transient neuromuscular events: dynamic changes in activity of the subthalamic...


