Oscillations in sensorimotor cortex in movement disorders: an electrocorticography study

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Movement disorders of basal ganglia origin may arise from abnormalities in synchronized oscillatory activity in a network that includes the basal ganglia, thalamus and motor cortices. In humans, much has been learned from the study of basal ganglia local field potentials recorded from temporarily externalized deep brain stimulator electrodes. These studies have led to the theory that Parkinson’s disease has characteristic alterations in the beta frequency band (13–30 Hz) in the basal ganglia–thalamocortical network. However, different disorders have rarely been compared using recordings in the same structure under the same behavioural conditions, limiting straightforward assessment of current hypotheses. To address this, we utilized subdural electrocorticography to study cortical oscillations in the three most common movement disorders: Parkinson’s disease, primary dystonia and essential tremor. We recorded local field potentials from the arm area of primary motor and sensory cortices in 31 subjects using strip electrodes placed temporarily during routine surgery for deep brain stimulator placement. We show that: (i) primary motor cortex broadband gamma power is increased in Parkinson’s disease compared with the other conditions, both at rest and during a movement task; (ii) primary motor cortex high beta (20–30 Hz) power is increased in Parkinson’s disease during the ‘stop’ phase of a movement task; (iii) the alpha–beta peaks in the motor and sensory cortical power spectra occur at higher frequencies in Parkinson’s disease than in the other two disorders; and (iv) patients with dystonia have impaired movement-related beta band desynchronization in primary motor and sensory cortices. The findings support the emerging hypothesis that disease states reflect abnormalities in synchronized oscillatory activity. This is the first study of sensorimotor cortex local field potentials in the three most common movement disorders.

Keywords: Parkinson’s disease; dystonia; essential tremor; electrocorticography; primary motor cortex
Abbreviations: M1 = primary motor cortex; S1 = primary sensory cortex; UPDRS = Unified Parkinson’s Disease Rating Scale

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Introduction

Synchronized oscillatory activity plays a role in the large-scale organization of neural networks, and may be important in the pathophysiology of movement disorders (Hammond et al., 2007). In humans without movement disorders, alpha (8–12 Hz) and low beta (13–20 Hz) are the predominant frequency components of the sensorimotor cortex local field potential (Crone et al., 1998b). Alpha and beta band oscillations are reduced in amplitude (‘desynchronized’) during voluntary movement (Jasper and Penfild, 1949; Pfurtscheller and Aranibar, 1979).

A promising hypothesis of Parkinson’s disease posits that excessive oscillatory synchrony in the basal ganglia–thalamic cortical motor network at or near 20 Hz is a distinguishing characteristic and may be the basis for bradykinesia (Hammond et al., 2007; Eusebio et al., 2009; Engel and Fries, 2010). This model predicts that the power spectra of local field potentials recorded in the basal ganglia–thalamic cortical network should distinguish Parkinson’s disease from non-parkinsonian conditions, but this prediction has rarely been tested in humans (Silberstein et al., 2003; Weinberger et al., 2011). Alterations in beta synchrony during movement have been implicated in another movement disorder, task-specific focal hand dystonia (Toro et al., 2000; Kristeva et al., 2005), but it is not clear if this is a general feature of dystonia that is present in other subtypes.

To address these questions, we studied basal ganglia–thalamic cortical oscillations in movement disorders using a novel approach: intra-operative subdural electrocorticography performed in the awake state during placement of deep brain stimulator electrodes. We compared two disease states known to have prominent basal ganglia involvement, Parkinson’s disease and primary dystonia, with a third, essential tremor, thought not to involve the basal ganglia (Louis, 2010). We tested the hypothesis that movement disorders can be distinguished by: (i) the magnitude and predominant frequency components of the cortical alpha–beta band spectral peak; (ii) the magnitude of broadband gamma power; and (iii) movement-related changes in beta and broadband gamma power.

Previously, the most common techniques used to study synchronized oscillations in human movement disorders have been scalp EEG, and recording of basal ganglia local field potentials from temporarily externalized deep brain stimulator electrodes. Scalp EEG is limited by poor source localization and by low signal amplitude, which is problematic for the study of higher frequencies (Pfurtscheller and Cooper, 1975) and confers susceptibility to movement artefacts. Basal ganglia local field potential studies are restricted to the clinically indicated brain target, which typically precedes recording from the same brain structure across multiple disease states. The electrocorticography technique, in contrast, has high signal amplitude, excellent spatial localization and in the context of movement disorders surgery does not require additional brain penetrations or surgical exposure. Further, broadband gamma spectral power in cortical local field potentials is thought to reflect underlying pyramidal cell spiking activity (Manning et al., 2009; Miller et al., 2009), suggesting that electrocorticography may provide a novel technique for the assessment of the underlying state of neuronal activation in human movement disorders.

Although widely used in studies of ‘normal’ sensorimotor cortex physiology in humans with epilepsy (Toro et al., 1994; Crone et al., 1998a; Pfurtscheller et al., 2003; Miller et al., 2007), electrocorticography has not previously been applied to the study of the most common movement disorders.

Materials and methods

Subject recruitment and clinical evaluation

Study subjects were recruited from a population of patients with movement disorders scheduled to undergo deep brain stimulator implantation at one of two campuses: the University of California at San Francisco or the San Francisco Veterans Affairs Medical Centre. Subjects had a diagnosis of idiopathic Parkinson’s disease, primary cervical or craniocervical dystonia, or essential tremor, confirmed by a movement disorders neurologist (J.L.O. or N.B.G.). Most of the patients with dystonia included in this study were simultaneously participating in a clinical trial to evaluate the effectiveness of subthalamic nucleus deep brain stimulation in dystonia (Ostrem et al., 2011). Informed consent was obtained prior to surgery under a protocol approved by the Institutional Review Board, according to the Declaration of Helsinki. During the consent process, it was explained to each prospective subject that the temporary intra-operative placement of the cortical recording strip was performed solely for research purposes.

Potential study subjects were characterized using the following standardized rating scales: for patients with Parkinson’s disease, the Unified Parkinson’s Disease Rating Scale part III (UPDRS-III) following withdrawal of anti-parkinsonian medications for 12 h; for patients with dystonia, the Burke Fahn Marsden Dystonia Rating Scale movement score and the Toronto Western Spasmodic Torticollis Rating Scale severity score; and for patients with essential tremor, the Fahn–Tolosa–Marin Tremor Rating Scale, motor part (Questions 1–14).

Subject inclusion criteria were: age 21–75 years, normal brain MRI examination, sufficient disease severity in the setting of optimal medical management to justify treatment by deep brain stimulator and ability to cooperate during awake neurosurgery. Further criteria for specific subgroups were: Parkinson’s disease group: UPDRS-III OFF medication score ≥30, rigidity and akinesia as the most prominent OFF medication symptoms, presence of motor fluctuations and lack of prominent tremor or off-period dystonia. Primary dystonia group: dystonia affecting predominantly cervical or craniocervical muscles with minimal arm involvement, and no treatment with injected botulinum toxin for 3 months prior to surgery. Essential tremor group: absence of significant resting tremor.

Surgery and placement of subdural electrodes

Surgery and recording was performed at least 12 h after stopping all dopaminergic medications (Parkinson’s disease group), and oral
benzodiazepines and baclofen (dystonia group). All subjects underwent typical procedures for planning and stereotactic surgical placement of deep brain stimulator electrodes into the subthalamic nucleus (patients with primary dystonia and Parkinson’s disease) (Starr et al., 2002) or ventrolateral thalamus (patients with essential tremor) (Papavassiliou et al., 2004). On the MRI study used for planning of surgical target and trajectory, we identified a point on the primary motor cortex (M1), 3 cm from the midline, based on anatomical identification of the central sulcus (Fig. 1A and B). The intention was to target the arm-related area of M1, slightly medial to the ‘hand knob’ (Yousry et al., 1997), in the same parasagittal plane as the typical surgical entry site for placement of subthalamic nucleus or thalamic deep brain stimulator electrodes. A radio-opaque marker was stereotactically placed on the scalp over this location. When bilateral deep brain stimulator implantations were planned, cortical recording was performed on one side only, typically the side with the clearest anatomical demarcation of the central sulcus. After drilling of frontal burr holes, and opening of the dura mater, we placed a six-contact subdural electrocorticography strip (3 mm contacts, 1 cm spacing) (Ad-Tech) on the brain surface and directed it posteriorly in a parasagittal plane to provide contacts covering M1 and primary sensory cortex (S1) in all cases, with coverage of premotor cortex in most cases. The locations of the burr holes were determined solely by the selection of the safest entry point for the intended deep brain stimulator trajectory, and no additional skull or scalp exposure was needed for electrocorticography strip placement. After placement of the electrocorticography strip (and guide tube for microelectrode recording/deep brain stimulator lead placement), the burr hole was sealed with a fibrin sealant.

**Confirmation of electrode location**

Electrocorticography contact locations were confirmed anatomically using intra-operative CT (O-arm, Medtronic Inc.) or lateral fluoroscopy. Intra-operative CT images were computationally fused to the preoperative planning MRI using standard surgical planning software (Framelink 5.1, Medtronic), and windowed so as to visualize each electrocorticography contact with respect to underlying MRI anatomy (Fig. 1C and D). For cases where lateral fluoroscopy only was used, a lateral X-ray documented the location of the electrocorticography contact in the anterior–posterior direction with respect to the radio-opaque scalp marker (Fig. 1E).

For physiological confirmation of electrode location, we recorded somatosensory-evoked potentials generated by median nerve stimulation. The stimulation parameters were: pulse frequency = 2 Hz, pulse width = 200 μs, pulse train length = 160, amplitude 25–40 mA (typically 50% higher than the threshold for visible thumb twitch). Signals recorded from the electrocorticography strip during the somatosensory-evoked potentials were sampled at 5000 Hz, band-pass filtered (1–500 Hz) and amplified ×7000. Signal averaged somatosensory-evoked potentials for each adjacent contact pair were then visually inspected to determine the M1 location by reversal of the N20 waveform. For each bipolar pair, the more posterior contact was used as the ‘active’ electrode while the more anterior was the ‘reference’. The posterior contact of the most posterior bipolar contact pair that showed a negative-going waveform was considered to be the contact best localized to M1. For subsequent analyses, four contact pairs, the ‘premotor’, ‘M1’, ‘central sulcus’ and ‘S1’ pairs, were defined in relation to M1 as shown in Fig. 3A. There was high concordance between anatomical and physiological determinations of contact position with respect to central sulcus (Fig. 1).

**Local field potential recording**

Cortical local field potentials were recorded using the Guideline 4000 system (FHC Inc.) \((n = 23)\) or the Alpha Omega Microguide Pro (Alpha Omega, Inc.) \((n = 8)\). These are customized 14-channel data collection systems approved by the United States Food and Drug Administration for human use. Five-channel local field potential recordings were obtained from each of the five most posterior contacts (1–5), differentially referenced to the most anterior contact (6). A needle electrode in the scalp served as the ground. Signals were bandpass filtered 1–500 Hz, amplified ×7000 and sampled at 1000 Hz (Guideline 4000 system) or 1500 Hz (Alpha Omega system). A 60–Hz notch filter was employed to reduce line artefact. The frequency response of the intrinsic 1 Hz high pass filter in each system was tested empirically by inputting a 200-μV sinusoid from a function generator (Stanford Research Systems model DS360), at 2 Hz intervals from 4 to 120 Hz, and measuring the amplitude of the output waveform. The frequency responses differed slightly, with no attenuation >4 Hz for the Alpha Omega system, and a slight attenuation up to 20 Hz in the GS4000 due to the slow roll-off characteristics of an intrinsic 1 Hz high pass filter. In subsequent data analyses in the frequency domain, the square of the ratio of input to output amplitude was used to correct each power spectral density data point at each frequency <20 Hz. Data collected with the Alpha Omega system were downsampled to 1000 Hz in post-processing to match the sampling frequency of the Guideline 4000 system. All subjects had been sedated with propofol for the initial surgical exposure, but data collection was performed at least 30 min after stopping propofol. This is sufficient time for all neuronal effects of this agent to be eliminated (Fechner et al., 2004; Raz et al., 2008).

**Behavioural paradigms**

Cortical local field potentials were recorded during two tasks, ‘rest’ and ‘movement’, with a total of three behavioural states: ‘rest’, ‘move’ and ‘stop’. For the rest condition, the subject was instructed to relax, with eyes open for 30 s, focusing on the investigator’s hand held ~1 m away. Resting state recordings used for this study were performed at the beginning of the first microelectrode penetration into the target nucleus, within 0.5 mm of entry into the nucleus. Rest recordings were repeated after insertion of the deep brain stimulator electrode, to check for potential effects of lead insertion on resting state cortical spectral power. In the movement task, the subject performed a simple alternating stop/move task that has been previously characterized in studies of sensorimotor cortex local field potentials in patients with epilepsy (Miller et al., 2007). The subject was instructed to perform slow voluntary movement of a specified body part for at least 3 s.
**Figure 1** Method of localization of subdural recording electrodes (from Subject PD-7). (A and B) Intended location of middle of 6-contact recording strip (white arrows) over presumed M1, 3 cm from the midline, on axial (A) and parasagittal (B) images from the preoperative planning MRI. (C and D) Actual location of the recording strip, shown on intra-operative CT, computationally fused to preoperative MRI and reformatted in a parasagittal plane through the recording strip. Images are windowed to optimize visualization of bone and metal contacts (C) or to show the contacts blended onto the preoperative MRI (D). Contacts C1 and C5 are labelled in C (contact C6 is out-of-plane and not visible). White arrows indicate presumed M1 as in A and B. (E) Alternative means of confirming anatomic location of recording strip, using intra-operative two-dimensional lateral X-ray. A radio-opaque marker (black arrow) is sutured to the scalp along a trajectory (dotted black line) that passes through anatomic M1 and terminates at the intended deep brain stimulator electrode tip location. Intersection of the trajectory with the subdural recording strip shows the anteroposterior localization of the contacts with respect to the preoperative MRI. (F) Somatosensory-evoked potentials used to physiologically localize the contacts with respect to the central sulcus. Stimulation of the median nerve is performed at time zero (black arrow). Bipolar somatosensory-evoked potential recordings are stacked from anterior (top trace) to posterior (bottom trace). The downward direction is negative. For each bipolar pair, the posterior contact of the pair is ‘active’ while the anterior contact is ‘reference’. The most posterior contact pair with a negative N20 waveform in this example is the 3–4 pair, localizing contact 3 to M1, immediately anterior to central sulcus.
Detection of movement onset and movement velocity

The method of detecting movement onset and movement velocity for all limb movements is described in Supplementary Fig. 1A and B. Briefly, the time of onset of limb movement was detected from EMG using an automated MATLAB routine, based on the time at which the EMG or accelerometry signal crossed a threshold defined as 7 SD above the mean signal during a 'baseline' period. The baseline period was defined during each rest epoch as a 1-s period beginning 2 s before the investigator-initiated button push that marked the investigator’s visual observation of the beginning of movement at the start of each ‘move’ epoch. For jaw movements, EMG/accelerometry were not available, therefore, in the few analyses where movement onset for jaw were required (Fig. 5), we utilized the investigator-initiated button push signalling visually detected onset of movement. To characterize limb movement velocity, since all movements performed were stereotyped and cyclical in nature (Supplementary Movie 1), we assessed ‘angular velocity’ (number of movement cycles/s) using either accelerometer or EMG as described in Supplementary Fig. 1A–C. For jaw movements, or for some limb movements for which the number of movement cycles was not readily counted from accelerometry or EMG, we counted the number of movement cycles on the intra-operative videotape of the task and utilized the investigator-initiated button pushes to define the duration of each move epoch.

Signal processing

Data analysis was performed using custom designed software in MATLAB (The Mathworks). Raw recordings from the six-contact subdural strip were computationally re-referenced to obtain adjacent bipolar pairs (e.g. contacts 1–2, 2–3, etc). For local field potentials recorded during the resting condition, we calculated power spectral density for a 30-s data segment using the Welch periodogram method, with a 512 point fast Fourier transform (for 1.95 Hz frequency resolution) and 50% overlap, using a Hann window to reduce edge effects (MATLAB function ‘pwelch’). For the movement task (stop phase), the Welch method (as above) was used on 2-s data segments, starting 0.5 s after onset of the stop phase. For analyses of movement-related broadband gamma power (Fig. 5), we used 1-s epochs beginning at the onset of movement, compared to 1-s epochs beginning 2 s prior to the onset of movement. We averaged power spectral density across all five epochs of the same activity type (move or stop).

For the movement task, to determine spectral power changes relative to movement onset, we calculated cortical power spectral density using the short time Fourier transform [MATLAB function ‘spectrogram’, using a 512-point fast Fourier transform and 50 sample (50 ms) frame advance], with the zero time point corresponding to movement onset. For each time–frequency point, spectral power was averaged over all five epochs. Data were plotted as the ratio of power spectral density at each point to the mean baseline power spectral density between 2 and 1 s prior to movement as the reference period (Fig. 4B).

Statistical analysis of grouped data

The frequencies at which the alpha-beta spectral peak occurred in each individual subject were summarized by their medians and ranges, and analysed using the Kruskal–Wallis test for equality of medians. Power spectral density was log transformed for all statistical analyses to allow for use of parametric statistics in comparing grouped data. The Lilliefors test (MATLAB function lillietest) was used to confirm normality. Power spectral density at frequencies <4 Hz were not analysed due to the presence of low frequency artefacts generated by the heartbeat, respiration and subject movement.

To assess the effect of disease state on broadband spectral power, we averaged log power over each frequency point in multiple spectral bands: low beta (13–20 Hz), high beta (20–30 Hz) and multiple regions of broadband gamma, from 30 to 500 Hz, selecting the band edges to avoid 60 Hz and its harmonics. We then performed one-way analysis of variance (ANOVA) on log power in each frequency band, separately for each cortical contact pair (premotor, M1, central sulcus and S1).

To analyse the effect of different body part movements on movement-related power changes, we calculated the difference in mean log power (move phase versus stop phase) for the beta (13–30 Hz) and selected gamma bands, and performed a two-way repeated measures ANOVA using body part as the within subjects factor (five levels) and disease state as the between subjects factor (three levels). Significant main effects and interactions were then assessed post hoc using t-tests with the least significant difference correction for multiple comparisons.

To construct Z-scored spectrograms for each patient group (Fig. 4C), peri-movement power spectral density was compared...
statistically with a baseline period, defined as the segment from 1 to 2 s prior to movement. Each frequency was analysed separately. For each time frequency point (‘test value’), a Z-score was calculated from the difference between the mean of the test value (across all subjects in the group), and the mean power spectral density during the baseline period, divided by the standard deviation of the test value (Brucke et al., 2008). Movement-related decreases or increases in spectral power (Fig. 4D) were also calculated for each frequency as the difference in the mean log power during the move phase and mean log power during the stop phase. Statistical testing on movement-related log power difference was performed using a sliding window one-way ANOVA with disease state as the between subjects factor, on each frequency point from 4 to 50 Hz, with the significance threshold adjusted for the number of frequency points tested using the Bonferroni method.

**Results**

**Study subjects**

Characteristics of the study subjects, including preoperative medications, are provided in Table 1. There were 11 subjects in the Parkinson’s disease group, and 10 each in the dystonia and essential tremor groups. Ten in each group contributed data to the resting state study, and nine in each group contribute to the movement task study. The exclusion of resting state data from one subject with Parkinson’s disease, and of movement task data from two subjects with Parkinson’s disease and one subject each in the dystonia and essential tremor groups was necessary because of a malfunction of the data recording equipment during the relevant data collections. Mean ages for the patients groups were 56.7 years for Parkinson’s disease, 58.5 years for dystonia and 64.0 years for essential tremor (no difference by one-way ANOVA). Seven patients with Parkinson’s disease had a zero UPDRS score for contralateral arm tremor (Question 20b or 20c from the UPDRS-III), and all had a ratio of contralateral arm tremor score (UPDRS-III items 20–21) to contralateral arm rigidity Bradykinesia score (UPDRS-III items 22–25) of $<0.25$. Thus, tremor was much less prominent than rigidity/akinesia in the patients with Parkinson’s disease. No patient with Parkinson’s disease experienced off-period dystonia during intra-operative recording. Primary patients with dystonia had mainly craniocervical involvement, with minimal symptoms in the contralateral arm, as shown by contralateral arm Burke Fahn Marsden Dystonia Rating Scale movement score of 0 (eight patients) or 1 (two patients) (Table 1). All patients had significant cervical involvement, with a mean $\pm$ SD Toronto Western Spasmodic Torticollis Rating Scale severity score of $18.3 \pm 3.4$ (range 13–24). No patient had resting dystonic tremor in any limb. The tremor in the essential tremor group was predominantly postural, with a mean rest tremor score for contralateral arm (Question 5a or 6a from the Fahn–Tolosa–Marin Tremor Rating Scale motor scale) of $0.9 \pm 0.9$.

**Cortical local field potential characteristics in the resting state**

Example recordings of the M1 local field potential for each disease state are shown in Fig. 2A, with corresponding log power plots in Fig. 2B and C. In all subjects in all disease states, there was a peak in the power spectrum in the alpha-beta range, as has been reported for M1 local field potential recordings in subjects without movement disorders (Crone et al., 1998b; Miller et al., 2007). The frequency at which the alpha-beta peak occurred (arrow in Fig. 2C) varied between subjects in all groups (Fig. 2D). In spite of this variability, the median frequencies for peak power differed between groups, with a high beta median in Parkinson’s disease and low beta medians for essential tremor and dystonia, for both M1 and S1 (Table 2).

A schematic diagram of the anatomic relationship between bipolar contact pairs and underlying gyral anatomy is shown in Fig. 3A. The definitions of the four spectral bands analysed statistically in this figure are provided in Fig. 3B. Grouped data for resting state log power across all subjects in each disease group are shown in Fig. 3C, for contact pairs covering S1, M1 and pre-motor cortices. Broadband gamma spectral power was increased in Parkinson’s disease compared to both other disorders, in both the 30–55 Hz and 76–100 Hz bands. This relative increase was restricted to the two sets of contact pairs that crossed M1, i.e. the ‘M1’ and ‘central sulcus’ pairs (one-way ANOVA for mean log power 76–100 Hz, $P$-values provided in Fig. 3C). In the high beta band, log power in Parkinson’s disease was greater than in essential tremor ($P = 0.003$ for M1 and $P = 0.006$ for central sulcus) but was not significantly greater compared to the dystonia group.

Lead insertion into the subthalamic nucleus could potentially produce a ‘stun effect’ that alters oscillatory activity in the basal ganglia–thalamocortical network. To control for this possibility, local field potential power from post-lead insertion recordings were compared with those made pre-lead insertion, which showed no difference at any frequency point (Fig. 3D).

**Movement-related beta and gamma changes at the onset of movement**

Examples of M1 local field potential recordings made during the motor task, at the transition from a stop epoch to a move epoch, are shown in Fig. 4A (elbow joint movement). The mean $\pm$ SD durations of the stop and move epochs were $4.37 \pm 1.30$ s and $5.43 \pm 2.56$ s, respectively. Time varying power spectral density for the stop–move transition, for the individual examples and for all subjects in a disease group (elbow joint movement), are shown in Fig. 4B and C. These show that the onset of movement is associated with a sustained (>2 s) decrease in beta band power relative to the baseline from the ‘stop’ phase, as well as an increase in gamma power that is more transient (often most prominent in the first 1 s after the start of movement). The magnitude of the movement related beta band power decrease is reduced in the primary dystonia group (Fig. 4C). To determine the specific frequency points at which the movement related beta power
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Table 1 Characteristics of study subjects

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<th>Case</th>
<th>Age (years)</th>
<th>Gender</th>
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Mean ± SD 59.0 ± 10.1 ± 6.1 43.3 ± 20.8 10.4 ± 4.9 10.2 11.5 17.9 ± 8.4 0.2 ± 0.4 17.7 ± 8.4 5.5 ± 2.7

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<sup>a</sup> Missing data for Questions 11, 12 and 13 for right hand.
<sup>b</sup> Motor score in patients with Parkinson’s disease = Unified Parkinson’s Disease Rating Scale part III (OFF medication); in patients with primary dystonia = Burke–Fahn–Marsden Rating Scale, movement score; in patients with essential tremor = Fahn–Tolosa–Marin Tremor Rating Scale, motor part (sum of Questions 1–14).
<sup>c</sup> Motor score for contralateral arm was the sum of Items 20–25 of the UPDRS III (Parkinson’s disease), the arm subscore of the Burke Fahn Marsden Dystonia Rating Scale movement scale (dystonia), or Items 5 or 6 of the Fahn–Tolosa–Marin Tremor Rating Scale motor part (essential tremor), using only the part of each item specific to the arm contralateral to the side of Electrocoorticography recording.
<sup>d</sup> For patients with Parkinson’s disease, the preoperative levodopa equivalent dose was calculated using the following conversion factors: ropinirole × 20; pramipexole × 100; levodopa with decarboxylase inhibitor × 1; controlled release levodopa with decarboxylase inhibitor × 0.7; levodopa with decarboxylase and catechol-O-methyltransferase inhibitor × 1.3 (Wenzelburger et al., 2002). All doses are daily totals.
<sup>e</sup> This patient developed severe nausea from levodopa and dopamine agonists, and stopped all dopaminergic medications 6 months prior to surgery.

PD = Parkinson’s disease; DYS = primary dystonia; ET = essential tremor; M = male; F = female; LED = levodopa equivalent dose; IT = intrathecal.

decrease best distinguishes between disease states, we performed a sliding one-way ANOVA on (log power move phase—log power rest phase) at each frequency point between 4 and 50 Hz (Fig. 4D). This analysis shows that the greatest difference in the magnitude of movement related desynchronization in dystonia occurs in the mid-beta range (19.5 and 21.5 Hz). We examined the timing of onset of movement related beta band (13–30 Hz) reduction in each disease group, and found that the time of onset slightly preceded the time of EMG activation, but there was no detectable difference between groups (Fig. 4E and F).

To compare cortical oscillations during movement across disease states, it is important to record during a motor task for which the
Figure 2  M1 local field potential recordings and their power spectra in the resting state. (A) Examples of 1-s recordings from M1 in each disease state. (B) Log power spectral density 4–100 Hz for each example in A, from a 30-s recording. (C) Log power spectral density 5–35 Hz for each example in A, with the frequency corresponding to alpha–beta peak power indicated with an arrow. (D) Box plot of frequencies at which the alpha–beta peak occurred across 10 subjects in each disease group. Horizontal line = median, box = 25th and 75th percentiles, ‘whiskers’ = range of values. Dys = Dystonia; ET = essential tremor; PD = Parkinson’s disease.

Table 2  M1 and S1 local field potential median frequencies for the alpha–beta spectral peak in each disease group

<table>
<thead>
<tr>
<th>Behavioural condition</th>
<th>Cortical location</th>
<th>Median frequency (Hz)</th>
<th>Statistical analysis (difference in medians)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PD</td>
<td>DYS</td>
<td>ET</td>
</tr>
<tr>
<td>Rest</td>
<td>M1</td>
<td>22.5</td>
<td>14.6</td>
</tr>
<tr>
<td></td>
<td>S1</td>
<td>22.5</td>
<td>10.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.025</td>
</tr>
<tr>
<td>Stop phase of task a</td>
<td>M1</td>
<td>21.5</td>
<td>13.7</td>
</tr>
<tr>
<td></td>
<td>S1</td>
<td>19.5</td>
<td>15.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.0002</td>
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<tr>
<td>Movement phase of task a</td>
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<td>23.4</td>
<td>21.5</td>
</tr>
<tr>
<td></td>
<td>S1</td>
<td>9.7b</td>
<td>17.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.005</td>
</tr>
</tbody>
</table>

- a Frequency of peak power for all arm movement tasks (hand, elbow and shoulder) were combined, resulting in 27 data points per group.
- b During movement, the alpha–beta spectral peak took a bimodal form in many subjects, with separate peaks in alpha and high beta.
- Dys = dystonia; ET = essential tremor; NA = not applicable; PD = Parkinson’s disease.
kinematics of movement did not differ. Although subjects in the Parkinson’s disease group all had arm bradykinesia, the task was deliberately made very easy, with all patients instructed to make movement slower than 1 flexion/extension cycle per second. As a result, the angular velocities of movement during the move phase of the alternating stop/move elbow task did not differ between disease groups ($P = 0.72$, one-way ANOVA) (Supplementary Fig. 1).

We next quantified the mean change in beta (13–30 Hz) and gamma (76–100 Hz) log power for each of the five body part movements (Fig. 5). For the change in M1 beta band log power, there were main effects of both body part ($P < 0.001$) and disease state ($P = 0.030$). Post hoc pairwise comparisons revealed that the effect of body part was due to reduced beta band power change during jaw and foot movement compared with hand, elbow and shoulder movement ($P < 0.001$ for all arm versus non-arm task comparisons) and that the effect of disease was due to reduced movement related power change in dystonia compared with the other groups ($P = 0.011$ versus Parkinson’s disease and $P = 0.043$ versus essential tremor). The disease × body part interaction term was not significant, indicating that the disease specific pattern revealed for dystonia (impaired movement related beta power reduction) was true for all five body part movements, not just arm movements. Results for the S1 local

Figure 3 Cortical resting state power spectral density grouped over all subjects in each disease state. (A) Schematic drawing of the relation of the cortical bipolar recording pairs to the underlying frontal and parietal gyri and sulci. (B) Method of comparing spectral power across disease states. For each individual subject, the mean log power in each of four frequency bands (low beta, high beta = blue; low gamma, high gamma = orange) was calculated, and grouped data were compared statistically. (C) Mean (±SEM) log power 4–100 Hz for the three disease states, for the four bipolar pairs covering primary sensory, primary motor and premotor cortices as illustrated in A. The yellow bars indicate frequency bands for which mean log power in Parkinson’s disease (PD) was significantly different from both dystonia (Dys) and essential tremor (ET) disease groups, and the $P$-value corresponds to a one-way ANOVA for overall difference in mean log power in the relevant bands. Only contact pairs that included M1 showed a significant difference (PD > Dys and PD > ET), and only low gamma and high gamma bands showed this difference. (D) Lack of a ‘stun effect’ of lead insertion on resting state cortical power in subjects with Parkinson’s disease. Thick red line = mean log power spectral density prior to lead insertion; thin black line = mean log power spectral density following insertion of 1.2 mm diameter deep brain stimulator lead through the motor territory of subthalamic nucleus.
Figure 4 (A) Example local field potential (LFP) recordings from individual subjects with Parkinson’s disease (PD, left), dystonia (centre) and essential tremor (ET, right). The local field potential (top row) is shown with simultaneously recorded forearm EMG (bottom row). Recording duration is 4 s, centred on the start of movement. (B) Time varying log power spectral density for the same subjects as in A, averaged over five stop/move epochs. The colour scale represents the change in power spectral density from the baseline period, defined as 2 to 1 s prior to onset of EMG activity. Vertical dotted line indicates the start of movement. (C) Time-varying power spectral density during the elbow movement task, showing data pooled across all subjects in each disease group (nine subjects per group) and represented as a Z-score. For visual clarity, the Z-scores are thresholded so that Z-scores between −1 and 1 are all assigned the neutral (grey) colour. (D) Movement related change in power (log power move phase-log power stop phase), over the 4–100 Hz range, utilizing the 2 s epochs beginning 0.5 s after the start of the move or stop phases. The red, blue and green lines show the mean log power change in subjects with Parkinson’s disease, dystonia and essential tremor, respectively. The dotted lines (and colour shading) indicate ±SEM. The asterisks indicate the frequencies at which the disease groups differed, at a significance threshold of $P = 0.002$ (corresponding to an uncorrected threshold of 0.05, with Bonferroni correction). (E) Mean power 13–30 Hz normalized to baseline (2 to 1 s prior to the EMG-defined start of movement) as a function of time (time resolution of 50 ms), in an individual subject with Parkinson’s disease. The onset of beta band power decrease (vertical arrow) was defined as the time at which mean beta power crossed the threshold of 3 SD of the mean power during the reference period (horizontal red-dotted lines). (F) Mean (±SEM) time of onset of movement-related beta decrease, relative to start of EMG activity, did not differ between groups (one-way ANOVA $P = 0.909$). NS = not significant.
field potential were similar, with a main effect of disease ($P = 0.005$) resulting from reduced movement-related power change in dystonia compared with the other groups ($P = 0.001$ for dystonia and $P = 0.054$ versus essential tremor). For movement-related gamma power changes, there was a main effect of body part for both M1 and S1, ($P = 0.05$ and $P = 0.001$, respectively) due to a much larger movement-related increase in gamma power in arm movements compared to foot movements. There was no main effect of disease and no disease x body part interaction, although there was a trend toward reduced movement-related M1 gamma activation in the Parkinson’s disease group (Fig. 5). The relatively modest movement-related change in M1 gamma activity for all disease states may reflect the simplicity of the motor task utilized. For hand, shoulder joint and jaw movements, there was no difference in movement kinematics, but for foot movements the Parkinson’s disease group was slightly faster (Supplementary Fig. 1).

**Beta and gamma band power during the stop and move phases**

The above analysis for task-related changes in cortical power specifically examined the change in log power during the move phase of the task, relative to the stop phase. We also analysed absolute differences in cortical log power between diseases, separately for the stop and move phases, for all four contact pairs (Fig. 6, elbow movement task). These indicate, as was true for rest (Fig. 3C), that broadband gamma spectral power was greater in Parkinson’s disease both during the stop and move phases, and this difference was specific for contact pairs covering M1. In addition, the difference in high beta log power between Parkinson’s disease and both other disease groups was significant in the stop phase, but this was not true for the move phase (Fig. 6). Similar results were found for hand and shoulder joint movements (data not shown). We extended the analysis of broadband gamma power up to the Nyquist frequency of 500 Hz, and showed that the difference in broadband spectral power in M1 remained significant up to 220 Hz in the stop phase (Supplementary Fig. 2). Within the Parkinson’s disease group, we examined each frequency band for a correlation of log power with disease duration, but found no statistically significant correlations ($P = 0.06$ for low beta, $P = 0.07$ for high beta, $P = 0.09$ for low gamma and $P = 0.17$ for high gamma).

Since many of the subjects in the dystonia group had been taking oral benzodiazepines or baclofen up to 1 day preoperatively (Table 1), and because these medications can affect beta power in sensorimotor cortex (Hall et al., 2011), we compared log beta power during stop and rest phases in subjects who were not taking any benzodiazepines or baclofen, with the group averages for dystonia subjects as a whole (Supplementary Fig. 3). The few study subjects not taking preoperative benzodiazepines or baclofen did not represent outlier data, providing evidence that medication effects did not have a major impact on the data collected.

**Discussion**

In this study, we utilized intra-operative subdural electrocorticography to record sensorimotor cortex local field potentials in patients with rigid-akinetic Parkinson’s disease, primary craniocervical dystonia and essential tremor, both during rest and an alternating stop/move task. We show disease specific patterns in the cortical local field potential power spectrum as follows: (i) patients with Parkinson’s disease have greater broadband gamma spectral power...
power in M1 than the other disease groups in all behavioural conditions tested, which is anatomically specific to M1. The band of increased spectral power included the high beta range for one behavioural condition tested, the stop phase of the movement task; (ii) in patients with Parkinson’s disease, the M1 and S1 alpha–beta spectral peak occurs in the high beta range, in contrast to the low beta range for other disorders; and (iii) patients with primary craniocervical dystonia have reduced movement-related beta band desynchronization, compared with the other two disorders.

**Primary motor cortex broadband spectral power is increased in Parkinson’s disease**

In Parkinson’s disease, power spectral density was increased over a very broad frequency range, from as low as 20 Hz to >200 Hz. Broadband spectral power changes are thought to reflect asynchronous spiking activity in the region underlying the recording electrode (Manning et al., 2009; Miller et al., 2009). Cortical broadband local field potential power also correlates with the
blood oxygen level-dependent (BOLD) signal on functional MRI studies (Scheeringa et al., 2011). Thus, increased broadband power in M1 in subjects with Parkinson’s disease may indicate increased M1 spiking activity and increased metabolic activation relative to other disease states. Since all subjects with Parkinson’s disease had longstanding disease it is not clear if this reflects a primary abnormality versus a compensatory mechanism. The original ‘rate model’ of basal ganglia and cortical function in Parkinson’s disease posited resting state cortical hypoactivity, driven by excessive inhibitory basal ganglia output (DeLong, 1990). However, functional imaging studies reveal a ‘Parkinson’s disease-related motor pattern’ in which M1 has increased metabolic activity compared with normal controls (Tang and Eidelberg, 2010), and the expression of this pattern increases as disease progresses (Huang et al., 2007). Our results also support an alternative mechanism for the increased subthalamic nucleus single unit discharge that is characteristic of the parkinsonian state: subthalamic nucleus hyperactivity may be driven by an overactive M1, via the corticosubthalamic ‘hyperdirect’ pathway.

Prior work has shown that basal ganglia local field potential beta power is increased in the parkinsonian OFF medication state compared to the ON medication state (Hammond et al., 2007) and (in one study of globus pallidus local field potentials) compared to non-Parkinson’s disease patients (Silberstein et al., 2003). We did not study patients with Parkinson’s disease in the ON medication state, but the comparison of Parkinson’s disease OFF medication to two other disease groups showed evidence for a relative increase in beta power only in the high beta range, and the finding was only significant in one behavioural state tested, the stop phase of an alternating stop/move task. The increase in high beta power was not a narrowband increase, but was associated with a broadband increase from 20 to 220 Hz. Our findings thus help to refine the ‘beta synchrony’ hypothesis of Parkinson’s disease: increased beta power in the basal ganglia does not appear to induce a large, narrowband increase in M1 or S1 beta power; suggesting more subtle derangements in beta oscillatory activity at the cortical level. Other aspects of beta synchrony that have been proposed as important in the genesis of impaired motor function are spectral bandwidth or ‘complexity’ of the beta signal (Chen et al., 2010), and alterations in the coupling between beta oscillations and higher frequencies (Lopez-Azcarate et al., 2010). Consistent with our findings, a recent magnetoencephalography study of patients with Parkinson’s disease ON and OFF medication showed no increase in cortical beta power in the OFF medication state (compared with ON medication state), but did show that high beta band synchrony between the cortex and subthalamic nucleus is modulated by levodopa (Litvak et al., 2011).

The high beta band (20–30 Hz) in the parkinsonian state

We found that the frequency at which the cortical alpha–beta peak occurs is higher in Parkinson’s disease, in all behavioural states tested. The presence of a particular cortical beta band frequency range that is characteristic of the parkinsonian state is consistent with the predictions of prior studies. Modelling the basal ganglia–thalamocortical circuit as a damped oscillator, Eusebio et al. (2009) analysed EEG responses to single pulse stimulation of the subthalamic nucleus in patients with Parkinson’s disease, and calculated a circuit ‘resonance frequency’ of 20 Hz. Their predicted oscillation frequency is similar to the median frequency of the peak M1 local field potential spectral power found here for Parkinson’s disease in the resting state (22.5 Hz), in contrast to the median frequencies for peak power for essential tremor and dystonia, which were <15 Hz. Several lines of evidence support the idea that the frequency range of oscillations within the beta band in the basal ganglia–thalamocortical circuit may be increased in the parkinsonian state. In a study of rodents at rest or engaged in a motor task (treadmill walking), the induction of Parkinsonism was associated with a narrowband increase in high beta oscillations in the basal ganglia (Avila et al., 2010), similar to our results for M1 in humans. Mathematical modelling of striatal circuitry also predicts that the induction of Parkinsonism should produce a shift to higher frequency local field potential oscillations (McCarthy et al., 2011). The role of high versus low beta band activity is not entirely clear, although in humans these rhythms can be modulated differently during motor tasks depending on context (Marceglia et al., 2009). In the normal state, M1 beta oscillations may serve to mediate task-specific cortico-cortical information transfer (Rubino et al., 2006), with beta phase modulating the timing of M1 spikes during motor tasks (Reimer and Hatsopoulos, 2010). These mechanisms could be altered by shifts in the ‘carrier frequency’ within the beta band.

In contrast to our findings, some prior magnetoencephalography studies indicate a slowing of cortical oscillatory activity in the parkinsonian state (Bosboom et al., 2006; Stoffers et al., 2007; Vardy et al., 2011). The apparent conflicts are likely accounted for by differences in symptom profile, medication state (ON medication in several studies), behavioural state and source localization. Unlike the present study, these prior studies did not specifically exclude subjects with prominent tremor. Since parkinsonian tremor is associated with cortical activity at twice tremor frequency (~10 Hz, in the alpha band) (Timmermann et al., 2003), the inclusion of subjects with tremor could alter the frequency components of the alpha–beta spectral peak.

Increased cortical beta activity during movement in primary dystonia

Two prior studies utilizing scalp EEG in patients with writer’s cramp (a form of task specific focal hand dystonia) showed evidence for impaired cortical beta desynchronization during the dystonic posture (Toro et al., 2000; Kristeva et al., 2005). Our results extend this finding as follows: (i) we show that reduced movement-related beta desynchronization is an important feature of primary cranio cervical dystonia, not just task specific hand dystonia and (ii) utilizing the higher spatial resolution technique of electrocorticography compared with EEG, we show that impaired movement-related beta desynchronization is present in both M1 and S1. The involvement of S1 is consistent with the fact that abnormalities in sensory function are ubiquitous in many types of dystonia.
(Tinazzi et al., 2009). As pointed out in a prior EEG study (Toro et al., 2000), impaired movement-related beta desynchronization in dystonia likely represents a physiological ‘endophenotype’ rather than a response to abnormal movement, since it is present in arm motor cortex in a patient group whose dystonia did not involve the arm. We cannot determine definitively whether the impaired beta band desynchronization is due to reduced beta power at rest or increased beta power during movement, but it seems more likely to be the latter, since in both M1 and S1, beta power was relatively low during the stop phase of the task (similar to the essential tremor group) while during movement, it was relatively high (similar to the Parkinson’s disease group) (Fig. 6).

Normally, during fluid alternating contraction/relaxation movements, cortical beta band power is decreased throughout the movement, whereas tonic muscular contraction produces only a transient decrease in beta power at the onset of movement (Crone et al., 1998b; Miller et al., 2007). Thus, an impairment of beta desynchronization during fluid movements could result in a physiological state promoting sustained contractions, leading to dystonic postures. Interestingly, an opposite alteration in movement-related M1 beta power (excessive desynchronization) has been found in patients with motor tics (Franzkiowiak et al., 2010).

Limitations in analysis and interpretation

We studied the effect of disease group on the absolute magnitude of broadband spectral power. Studies of absolute (non-normalized) spectral power could be confounded by spurious variations in signal strength related to the size of the subarachnoid space separating the local field potential electrode from the underlying cortical signal generators. Specific patterns of cortical atrophy have been found in Parkinson’s disease (Burton et al., 2004; Tinazzi et al., 2011). The arguments against this as a confounder of our results are: (i) the finding was specific to M1, which would not be the case if generalized brain atrophy were a factor; (ii) cortical atrophy in Parkinson’s disease, when it occurs, tends not to involve M1 (Tinazzi et al., 2011); and (iii) if M1 atrophied in Parkinson’s disease to a greater extent than other disorders, it would be expected to reduce the amplitude of broadband power (due to an increase in the subarachnoid CSF space) rather than increase it, as was found here.

Given the invasive nature of direct brain recordings, it is not possible to study a control group of subjects that are neurologically normal. Here, we used essential tremor as a comparison group for Parkinson’s disease and dystonia, as essential tremor is thought to arise from the cerebellothalamic system, rather than the basal ganglia (Louis, 2010). Cerebellothalamic abnormalities could nevertheless alter neuronal activity in M1 (Schnitzler et al., 2009), so it is possible that the alpha and low beta frequency distribution of M1 and S1 spectral power seen in patients with essential tremor is itself pathological. However, previous electrocorticography studies have shown M1 power spectral peaks at similar alpha and low beta frequencies in subjects without movement disorders (Crone et al., 1998b; Aoki et al., 1999; Miller et al., 2007). It is also possible that chronic treatment with levodopa is responsible for the changes observed here (Picconi et al., 2003). However, one of the subjects with Parkinson’s disease (Case PD-5) had been OFF levodopa for 6 months prior to surgery, and that subject’s cortical oscillatory activity was very similar to that of the group as a whole. Data collected during the movement task were collected after insertion of the deep brain stimulator lead, and are therefore subject to a possible ‘stun’ or ‘microlesion’ effect in which the physiology of the basal ganglia-thalamocortical loop is changed by acute oedema in the target nucleus. For resting state data, however, we showed no change in cortical power spectral density from early recordings (during initial entry of the first microelectrode into dorsal 0.5 mm of the target) versus later recordings after full microelectrode recording and deep brain stimulator lead insertion.

In generalized dystonia, prior basal ganglia local field potential studies have shown a predominance of low frequency (theta–alpha) activity (Silberstein et al., 2003; Chen et al., 2006; Tang et al., 2007; Liu et al., 2008). Our data are not optimized to study the very low frequency range of the power spectrum, due to a hard-wired single pole 1 Hz high pass filter in our clinical recording equipment, whose slow roll-off attenuates very low frequencies. Although this attenuation was precisely measured to provide a ‘correction factor’ for the lowest frequencies in the spectrum, post hoc corrections of power spectral density for filter effects are inexact. Our dystonia patient group also differs from those of prior basal ganglia local field potential studies in that our subjects were not symptomatic in the homotopic region (arm area) of the structure where local field potentials were recorded.

Finally, the movement task we employed was optimized for the study of movement-related beta desynchronization, but less so for movement-related gamma band increases. The gamma band increase is smaller in magnitude and would therefore benefit from more task repetitions, which were precluded by intra-operative constraints. Further, a more cognitively complicated task than the one performed here would likely be a produce a stronger movement-related increase in gamma (Miller et al., 2011), allowing for a greater possibility of distinguishing gamma changes between disease groups.

Conclusion

Direct recording of cortical local field potentials by subdural electrocorticography during movement disorders surgery represents a powerful new technique for the study of the basal ganglia-thalamocortical circuit. Using this technique, we show that the rigid-akinetic parkinsonian state is associated with an increase in broadband spectral power in M1, and a relative increase in the frequency at which the sensorimotor cortex alpha-beta peak occurs. Primary dystonia is associated with reduced movement-related desynchronization. The findings refine and extend the ‘oscillation model’ of movement disorders pathophysiology.
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Supplementary material

Supplementary material is available from Brain online.

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