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The oscillatory activity in the Parkinsonian subthalamic nucleus investigated using the macro-electrodes for deep brain stimulation

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Abstract

Objectives: To investigate the oscillatory activity in the Parkinsonian subthalamic nucleus using the macro-electrodes for deep brain stimulation.

Methods: During bilateral deep brain stimulating electrode implantation, spontaneous and evoked field potentials were recorded from the subthalamic nucleus (STN) in two patients with Parkinson's disease (PD) during spontaneous resting tremor, passive manipulation of the wrist, and following electrical stimulation of the contralateral STN.

Results: Frequency analysis of the STN field potentials recorded during spontaneous resting tremor showed significant coherence with electromyographic activity in the contralateral arm, suggesting a close involvement of the STN in the generation of resting tremor in PD. The STN responded to passive movement of the contralateral wrist, but not to ipsilateral movement. High frequency (100 Hz) electrical stimulation of the STN induced tremor (4 Hz) in both forearms, and also oscillation of the contralateral STN (4 Hz). In contrast, low frequency (5 Hz) stimulation induced contralateral arrhythmic involuntary movement (3 Hz), but without altering the contralateral STN activity.

Conclusions: We propose that the functional connection between the STN and arm muscles is mainly contralateral, but cross talk may occur between bilateral STN via a frequency-dependent pathway. © 2002 Published by Elsevier Science Ireland Ltd.

Keywords: Subthalamic nucleus; Deep brain stimulation; Field potential; Parkinson's disease

1. Introduction

Chronic deep brain stimulation (DBS) has been shown to be an effective treatment for all major symptoms of Parkinson's disease (PD) (Aziz and Bain, 1999; Bejjani et al., 2000; Benabid et al., 1993, 1994, 1998; Brown et al., 1999; Krack et al., 1998; Kumar et al., 1998; Limousin et al., 1995a; Starr et al., 1998). It also provides a unique opportunity to investigate the role of basal ganglia nuclei in the pathogenesis of Parkinsonian symptoms by recording neuronal activity from the nuclei in which the DBS electrode being implanted. By recording and correlating single-unit activity across cells, it has been shown that synchronised tremor-related activity appears in the major basal ganglia nuclei: the ventral thalamic nuclear group (Lenz et al., 1994; Levy et al., 2000), the internal segment of the globus pallidus (Hurtado et al., 1999) and the subthalamic nucleus (STN) (Levy et al., 2000). However, single-unit recording can only sample limited numbers of cells in each patient during electrode implantation. It is still unclear that to what extent the larger population of cells is unified by the increased oscillatory activity. The overall activity of a nucleus can be better represented by focal field potentials, which are mostly generated by synaptic potentials from a population of cells in the nucleus. It was shown that intrinsic focal field potentials (FPs) could be recorded from an intended subcortical nucleus (Spiegel and Gildenberg, 1982). If synchronised tremor-related activity was present across a population of cells, then it would sum up to generate focal FPs which could be recorded using the implanted DBS electrode (Brown et al., 2001). To identify the synchronised movement-related activity in the STN, recordings of FPs in the STN via the DBS electrode were carried out in 7 PD patients during implantation. The primary purpose of recording was to functionally localise the STN so that the placement of the electrode can be optimised (Liu et al., 2000, 2001). FPs were correlated to surface electromyographics (EMGs) simultaneously recorded from the

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contralateral arm during resting tremor, and during passive and active wrist movements in comparison with rest.

In this paper we report two cases of bilateral STN implantation, where evoked FPs were recorded following electrical stimulation of the contralateral STN at different frequencies together with surface EMGs. We aimed to investigate the frequency-dependent effects of STN stimulation on Parkinsonian symptoms (Limousin et al., 1995b, 1996) and to examine a possible interaction between the two STNs.

2. Patients and methods

2.1. Patients

Intraoperative recordings were obtained from two male patients (aged 56 and 60 years) with PD who were undergoing bilateral STN DBS electrode implantation. Both patients had expressed symptoms of PD for at least 10 years. Medication proved insufficient in controlling their symptoms for as much as 70% of the day and dyskinesia was observed during 'on' phases. Both patients gave their consent for the intraoperative recordings to take place and ethical approval was given.

2.2. FPs and EMGs recording via the DBS electrode

A target at the centre of the STN was selected on the basis of the fused imaging procedure described previously (Liu et al., 2000a). The quadripolar DBS electrodes (Medtronic, 3389™) were positioned at the calculated stereotactic coordinates and once secured, field potentials were recorded from adjacent pairs of the 4 electrode contacts. EMG activity was recorded with surface electrodes (Neotrode, Conmed Corporation) placed on the extensor (*carpi ulnaris*) and the flexor (*digitorum profundus*) of the arm contralateral to the DBS electrode selected for FP recording. Both FP and EMG signals were filtered between 0.5 Hz and 1 kHz, amplified with a gain of $\times 1000$ (CED1902, Cambridge, UK), digitised at a sampling rate of 250 Hz, and displayed online with an adjustable time scale of seconds to minutes. Recordings were repeatedly made during rest, resting tremor, passive and active movement of the wrist, during which simultaneous changes in amplitude and frequency of FPs and EMGs were observed to identify the functional correlation between the two signals.

2.3. Data analysis

The neurophysiological data segments of 20–40 s duration were selected for each movement condition for frequency analysis. The selected segments were first band-pass filtered (0.5–40 Hz) to cover the frequency range of tremor. The power at each frequency up to 20 Hz was then calculated in sequential 10 s windows, non-overlapping, using the fast Fourier transform. In order to test for functional correlation between pallidal and EMG activity, the cross-spectral density, coherence estimates and phase were calculated using MATLAB (The MathWorks, Inc.). Details of these analyses were described previously (Liu et al., 2002) and summarised here. Coherence is a statistical function used to estimate the probability that two independent signals are correlated at a given frequency, and it ranges from 0 to 1. A coherence of zero indicates that the two signals are not linearly related, and a coherence of 1 means that the two are identical. These calculations were previously described by (Zihr et al., 1998) and recently by (Hurtado et al., 1999). In order to assess the significance level of the coherence function, the 95% confidence interval was calculated according to the expression described by (Rosenberg et al., 1989; Marsden et al., 2000) taking the number of non-overlapping data windows into account. Phase was defined by the 4 quadrant arctangent of the real parts of the signals of A and B within $\pm \pi$.

3. Results

Comparing with rest condition, increased oscillatory activity was seen in the FPs of the STN contralateral to the arm with resting tremor. Clear correlation in amplitude and frequency between STN activity and the surface EMG of the contralateral forearm was observed on-line during recording (Fig. 1). Off-line frequency analysis showed significant coherence of the STN field potentials with contralateral EMG activity at the tremor frequency with a stable phase difference of 180° although tremor frequency ranged from 4 to 8 Hz among these two patients. Resting tremor could be often induced by moving the wrist passively. However, no significant increase in STN activity was recorded in response to passive movements of either the contralateral wrist (Data segment 4 in Fig. 2) or the ipsilateral wrist. These findings suggest that the STN primarily projects contralaterally, and the increased STN oscillation likely contributes to generation of resting tremor, rather than it responds to the proprioceptive feedback from the tremulous arm.

In these patients, electrical stimulation at 5 Hz (similar to the frequency of resting tremor) was applied unilaterally to the STN, which induced chorea-like involuntary movements of the contralateral arm at around 3 Hz (Data segment 3 in Fig. 2). No corresponding activity could be recorded from either the contralateral STN or the ipsilateral arm. No significant coherence was found between FPs of the contralateral STN and the EMG contralateral to the stimulated STN.

High frequency (100 Hz) electrical stimulation of the STN induced 4 Hz tremor in both forearms, gradually increasing in magnitude, and also oscillation of the contralateral (unstimulated) STN at the same frequency (Fig. 3). The induced oscillatory activity in the unstimulated STN was significantly coherent with the contralateral EMG at the tremor frequency. The phase relationship between two signals was varied across the frequency range of 2–12 Hz with a clear change at 8 Hz. The tremulous activity in both STN and EMG could

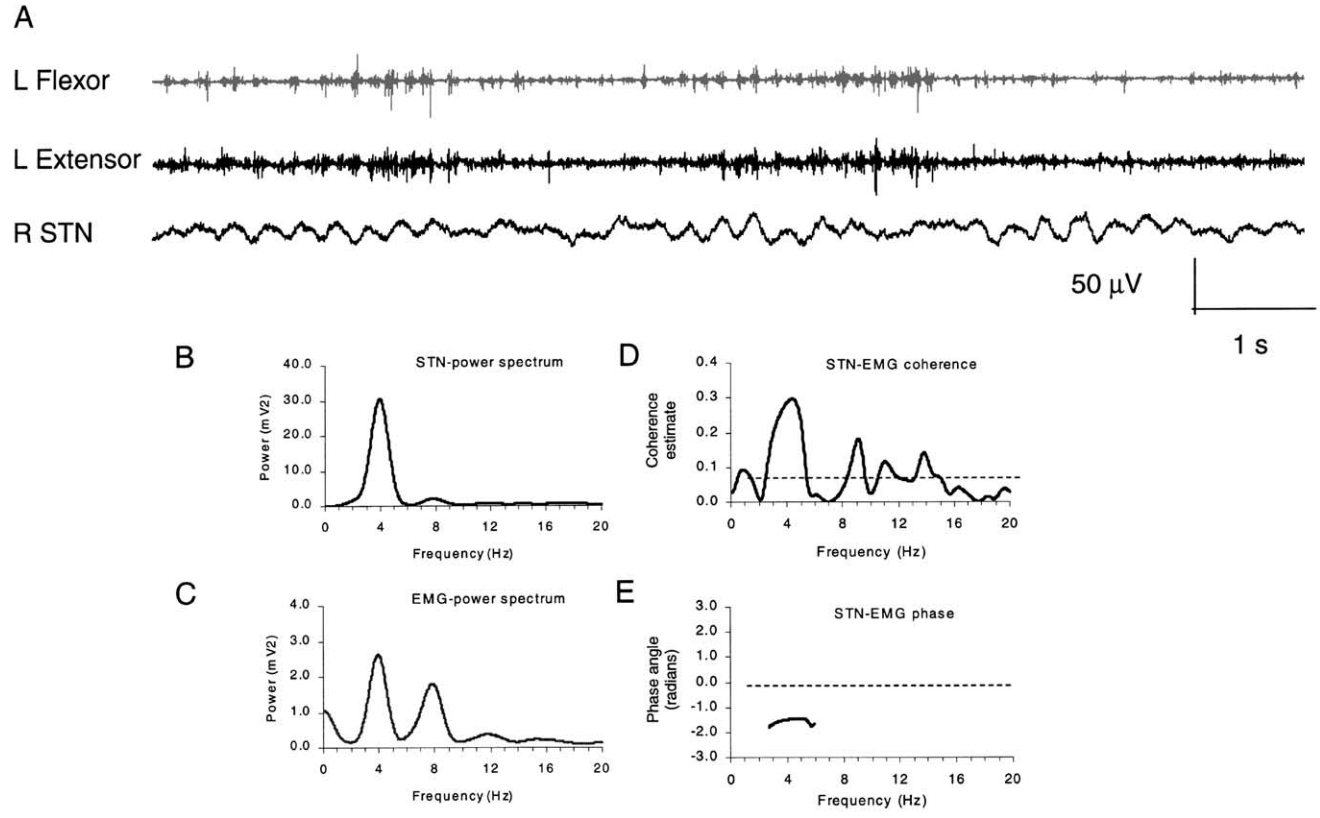

Fig. 1. (A) Ten-second segments of simultaneous recording of FPs of the right STN (R STN) and surface EMGs of the wrist flexor (L Flexor) and extensor (L Extensor) from the left forearm during resting tremor. Frequency analyses, coherence and phase calculations of the data segments of STN FPs and the flexor EMGs illustrated in section A. Power spectra of the STN FPs (B); and the flexor EMGs (C) showed that both signals had similar frequency components peaking predominantly at the tremor frequency of 4 Hz. Coherence between FPs and EMGs was highly significant around 4 Hz (D) with a fairly stable phase difference of 180° (2π radians, E). 95% confidence level in the coherence estimates is indicated by the dotted line (D).

be significantly suppressed by the active wrist movements in a similar fashion to suppression of spontaneous resting tremor by active wrist movements. In contrast, at higher frequency of 130 Hz, electrical stimulation completely suppressed tremor in both arms, and oscillatory activity in the contralateral STN completely disappeared.

4. Discussion

We recorded focal FPs from the STN and surface EMGs from the extensor and flexor in the forearm in two Parkinsonian patients during bilateral DBS electrode implantation. In comparison with rest, recordings were carried out during resting tremor, passive and active wrist movements, and following electrical stimulation to the contralateral STN at different frequencies. Our major findings are: (1) the functional correlation between the STN and arm muscles is mainly contralateral, and no significant increase in the FPs responding to passive wrist movements was found; (2) increased oscillation occurred during resting tremor, and such oscillation was significantly coherent with the contralateral EMGs at the tremor frequency with a stable phase difference; and (3) involuntary movements and increases in STN activity could be induced and suppressed by electrical stimulation to the contralateral STN in a frequency-dependent manner.

4.1. Tremor-related synchronised oscillation in the STN

In N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) treated monkeys, periodic oscillatory neuronal activity was found in the STN (Bergman et al., 1994). The existence of tremor-related activity in the STN was further supported by single-unit recordings in PD patients (Hutchison et al., 1998; Krack et al., 1998; Rodriguez et al., 1998) during DBS electrode implantation. Increased synchronisation of the STN neuronal activity in PD patients was evident in other studies using coherence functions on paired-unit activity during tremor (Levy et al., 2000) and using focal field potential recording in response to dopamine (Brown et al., 2001). Off medication, two major oscillatory frequency bands were found in the STN: one occurred in the β range, with a peak centred at ~20 Hz, and was altered by dopaminergic input, whereas the other appeared at the frequency of the on-going tremor at 4–6 Hz. In the present study, oscillatory FPs significantly increased in amplitude during tremor and were coherent with the EMG activity at

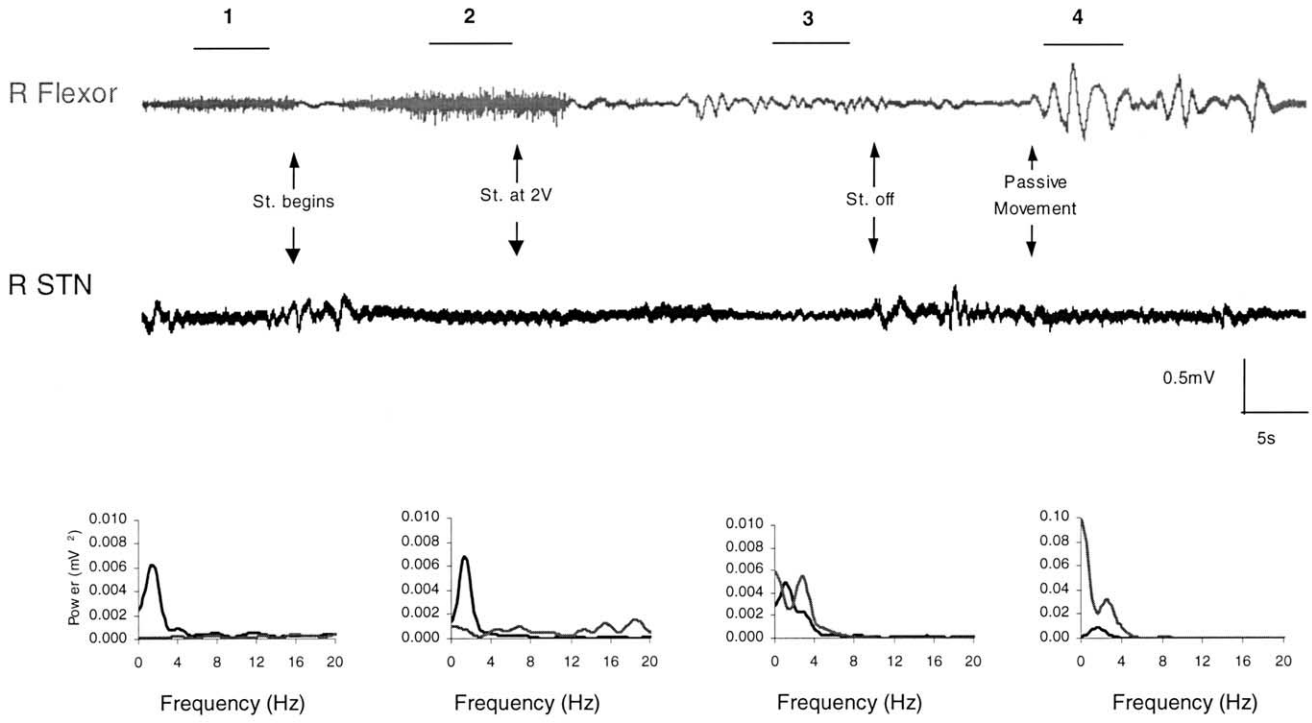

Fig. 2. Continuous 40 s recording of EMGs from the right forearm flexor (grey trace) and FPs from the right STN (black trace) during rest, stimulation at 5 Hz to the left STN, and passive movements of the right wrist. Four 5 s data segments (numbered, length indicated by a line over the traces) were analysed in frequency. (1) At rest, EMGs showed low amplitude activity of spontaneous resting tremor without identifiable component in the power spectrum; (2) the tremor activity gradually increased in amplitude when stimulation intensity gradually increased; (3) slow irregular involuntary chorea-like arm movements of 3 Hz were evoked by the stimulation 5 s after its intensity reached at 2 V and stopped when the stimulation ceased; and (4) the patient's wrist was moved passively at a rate of 3 Hz. Across the whole recording session, FPs showed a slow rhythmic activity of 2 Hz which was hardly affected by either electrical stimulation to the contralateral STN or the passive movements of the ipsilateral wrist. No significant correlation was seen between the EMGs and the ipsilateral FPs during the above motor conditions.

tremor frequency (4–5 Hz). In contrast, in the rest condition without tremor, the focal FPs were much lower in amplitude with a rhythm at 2 Hz and there was no significant coherence with the EMGs. In addition, the tremor-related oscillatory FPs in the STN and the tremor activity in EMGs were both suppressed by active wrist movements. These findings provide further evidence that the low frequency oscillatory activity in the STN is tremor-related (Brown et al., 2001). Our observation that no significant responses were recorded in the STN FPs during passive movements of the contralateral wrist supports the claim that the tremor-related oscillatory activity in the STN contributes to the generation of the tremor rather than it being driven by sensory feedback of the on-going tremor (Levy et al., 2000).

4.2. Frequency-dependent effects of electrical stimulation to the STN in PD

Effects of electrical stimulation to the STN in PD patients were clearly frequency-dependent: Stimulation at 5 Hz induced contralateral chorea-like involuntary movements peaking at 2–3 Hz, while tremor (around 5 Hz) could be triggered by stimulation between 20 and 100 Hz, and tremor could be completely suppressed when stimulation frequency increased to 130 Hz. Two interesting facts are: (1) it seems that low frequency stimulation induces involuntary movements, whereas high frequency stimulation inhibits excessive movements; and (2) there is a dissociation between frequencies of the applied stimulation and of the induced involuntary movements. The former has been observed previously in STN stimulation in PD patients (Limousin et al., 1995b) and in stimulation to the STN (Benazzouz et al., 2000) or the pedunculopontine nucleus (PPN) (Nandi et al., 2001) in normal monkeys. The mechanisms of such frequency-dependency are still largely unclear yet. We have also observed the dissociation in frequencies in an animal experiment in which electrical stimuli of 5–30 Hz to the pedunculopontine region via a chronically implanted electrode induced a proximal arm tremor stabilised at 5 Hz (Nandi et al., 2001). We propose that the applied stimulation may have far reaching effects and act as a trigger to excite a tremor generating circuit outside the STN which has its own preferred oscillation frequency (McAuley and Marsden, 2000). The low frequency oscillation of the STN FPs coherent with EMGs with a stable phase difference at the tremor frequency in the absence of electrical stimulation may indicate that the STN may be a part of the tremor generating circuit or may have a direct influence on the tremor generating circuit via the basal ganglio-thalamo-cortical pathway. Tremor is also influenced by cortical output (Parker et al.,

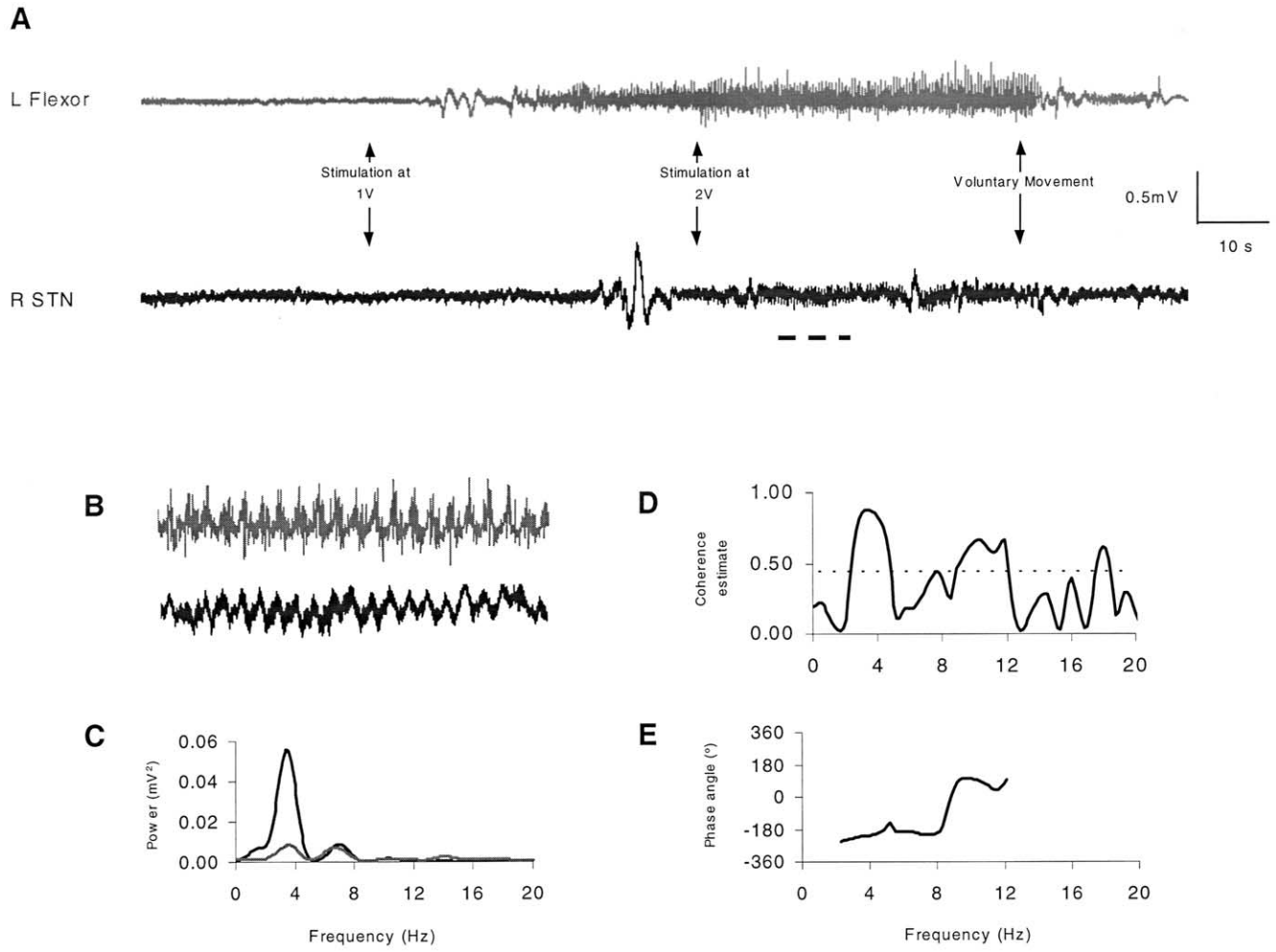

Fig. 3. (A) Continuous 100 s recording of EMGs from the left forearm flexor (grey trace) and FPs from the right STN (black trace) during rest, stimulation at 100 Hz to the left STN, and movement of the left arm. Comparing with rest, electrical stimulation at 100 Hz to the right STN induced bilateral wrist tremor. Correlated to that, oscillatory activity appeared in the contralateral FPs and ipsilateral EMGs. Frequency analysis of the selected data segment (B, and indicated by a dotted line under the traces in A) showed that oscillatory activity in FPs and EMGs had similar frequency components (C) and were significantly coherent around the tremor frequency of 4 Hz (D) with a phase difference of approximate 180° (E). Tremor and the oscillatory activity in the FPs and EMGs were suppressed by the voluntary movements while the stimulation was still on 95% confidence level in the coherence estimate is indicated by the dotted line (D).

1992) since resting tremor can be diminished by voluntary movements. Our evidence to support this is that the stimulation-induced oscillation in the STN FPs and consequent tremor could be 'reset' by voluntary movements even before the stimulation ceased. In comparison with the spontaneous resting tremor which has a stable phase difference between STN and EMG signals, the electrically induced tremor had a varied phase across the frequency range of interest, suggesting that generation of the tremor induced by electrical stimulation may involve wider circuits of different time delays.

4.3. Bilateral interaction of the STNs

It has been observed clinically that unilateral STN stimulation has predominantly contralateral but also ipsilateral effects on Parkinsonian symptoms. In the present study, evoked FPs at the tremor frequency were recorded from the unstimulated STN following stimulation of the contralateral STN at 100 Hz, which induced bilateral tremor. Unilateral stimulation at 130 Hz clearly suppressed the tremor in both sides. In contrast, unilateral stimulation at the tremor frequency of 5 Hz provoked low-frequency involuntary movements only in the contralateral limb and no significant changes in the STN FPs could be recorded in the contralateral STN. We conclude that cross talk might occur between bilateral STNs via a frequency-dependent pathway. This frequency-dependent pathway could contribute to the bilateral effects of unilateral high-frequency STN stimulation.

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