Changes in Cortical and Pallidal Oscillatory Activity during the Execution of a Sensory Trick in Patients with Cervical Dystonia

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Running Title
Recordings during Sensory Trick

Abstract

We examined the effects of a sensory trick (SeT) on cortical EEG and globus pallidus (GP) local field potentials in four cervical dystonia patients, two of whom had an effective SeT and two who did not. The application of an effective SeT was associated with bilateral desynchronization in the 6 - 8 Hz and β bands in the GP and sensorimotor cortical regions. In contrast, mimicking a SeT led to a worsening of dystonia, which was associated with desynchronization of the β band and synchronization in the 4 - 6 Hz range. These preliminary findings suggest a role for 4-8 Hz frequency synchronization in the pathophysiology of dystonia.

Keywords: Geste Antagoniste, Spasmodic Torticollis, Basal Ganglia, Electroencephalography, Wavelet Analysis

Introduction

A unique feature of cervical dystonia (CD) is the use of a sensory trick (SeT) to alleviate dystonic contractions. The SeT usually involves the patient touching his or her chin with the hand that is contralateral to the direction of head turn. It is not simply a counterpressure phenomenon since relaxation of dystonic muscles can precede the actual touch (Wissel et al., 1999). The only previous study to examine the mechanism underlying the SeT in CD reported on the basis of H_2^{15}O positron emission tomography that the SeT is associated with activation of the superior and inferior parietal lobule on the side ipsilateral to the head turn as well as deactivation of the supplementary motor area and the primary sensorimotor area on the contralateral side (Naumann et al., 2000).

The pathophysiology giving rise to CD is unknown, but it has been suggested that abnormal oscillatory activity in the basal ganglia might be involved in the generation of dystonic contractions (Silberstein et al., 2003; Liu et al., 2002). Previous studies of local field potentials (LFPs) recorded in the globus pallidus internus (GPi) of dystonic patients revealed increased 4-10 Hz oscillatory activity compared to PD patients (Silberstein et al., 2003) and an increase in 4 Hz oscillations during dystonic episodes in a patient with myoclonic dystonia (Liu et al., 2002). These findings suggest that the 4-10 Hz activity might have a role in dystonia, and led us to hypothesize that the application of a SeT would lead to desynchronization of the 4-10 Hz LFP activity in GPi. In this paper we report the results of a preliminary study that examined the effects of a SeT on cortical electroencephalographic (EEG) activity in 4 CD patients and the simultaneously recorded LFP activity recorded from deep brain stimulation (DBS) electrodes in the GPi of 2 of these patients. The findings reported here were briefly described in an abstract (Mahant et al., 2005).

Methods

Four CD patients of the Movement Disorders Clinic at the Toronto Western Hospital were included in this study. Two had an effective SeT (SeT+) and two did not (SeT-). In each group, one patient underwent surgery for the implantation of DBS electrodes into the GPi and the remaining one attended the Movement Disorders clinic to receive periodic botulinum toxin treatment. All patients had prior botulinum toxin injections. Details of their clinical features are outlined in the Table (additional clinical details for patients A and B can be found in Hung et al., in press, as patients 3 and 8).

The study was approved by the local ethics committee and patients gave informed consent.

In patients A and B who underwent surgery, bilateral LFP and EEG recordings were made two to three days after surgery, before the internalization of the implantable pulse generator. Bilateral DBS electrodes were implanted following microelectrode recordings for the localization of the GPi target as described in (Lozano et al., 1996). LFP recordings were made from Model 3387 DBS quadripolar electrodes (Medtronic, Minneapolis, MN), i.e. with four contacts of 1.3 mm in diameter, 1.5 mm in length and spaced 1.5 mm apart. In the other two CD patients, EEG recordings were performed prior to their scheduled botulinum toxin injection. In these patients, the clinical effects from their previous injection had worn off by the day of the recordings. EEG recordings were made with silver-silver chloride electrodes (impedance $\leq 5\text{k}\Omega$) arranged according to the International 10-20 System. In addition, EMG activity of the sternocleidomastoid and the splenius capitis muscles was simultaneously recorded with surface electrodes. A contact-sensing device was placed on the index finger to identify the times at which finger contact with the face was made.

SynAmp amplifiers (NeuroScan Laboratories, El Paso, TX) were used for all recordings. On-line monitoring and data management were done with the Scan 4.1 software (NeuroScan Laboratories). The sampling rate was 2.5 kHz. Filters were set at 0.05-500 Hz for recordings from scalp and DBS electrodes, and 30-500 Hz for EMG signals.

All patients were seated during the experiments with their eyes closed. They were asked to execute their SeT or a SeT-like maneuver after a sound cue. Off-line analysis

was performed with the MatLab software (The MathWorks, Natick MA). DBS recordings were transformed into a bipolar montage between two consecutive contacts, and scalp EEG recordings were transformed into bipolar montages of Cz-Fz, Cz-Pz, F3-C3, F4-C4, C3-P3, and C4-P4. All EMG recordings were rectified off-line. Segments of recordings from 0.5 s prior to 10 s after the presentation of each cue were designated as test epochs (10.5 s in duration). The baseline epochs were the 5 s periods immediately preceding the test epochs. Segments of recordings with movement artifacts were excluded from analysis. The bipolar LFP, EEG and rectified EMG recordings were digitally convolved with the Morlet wavelet (refer to Torrence and Compo (1998) for details), yielding a continuous measure of frequency-specific power over time. Segments of test epoch were aligned with the time of cue presentation as time 0 and averaged. The frequency components of the baseline periods were averaged by the construction of a power spectrum of the entire period. The baseline power was subtracted from the wavelet transformation of the averaged test epochs and a statistical comparison of changes in power in the averaged test epochs from the baseline was performed; a cutoff t value of 3 (equivalent to $p < 0.05$) was used.

Results and Discussion

Both SeT+ patients had markedly decreased EMG activity in the recorded neck muscles with the use of their SeT (Figure A, C). There was a significant bilateral event-related desynchronization (ERD) in the EEG and deeper GPi contacts LFPs in the 6 - 8 Hz band in patients A and C (EEG only in C), as well as in the β frequency band (~ 30 Hz in patient A; ~ 20 Hz in patient C; Figure A, C). These changes were intermittently present

throughout the execution of the SeT. There was no immediate time-locked change in the EEG or GP LFP to contact between hand and face.

In the two SeT- patients, execution of SeT-like movements led to a marked increase in neck EMG activity in patient B and a small increase in patient D (Figure B, D). There was significant ERD in the β band (20 Hz; $p < 0.05$) in the left GPi (side contralateral to the hand used for the SeT) during the task while event-related synchronizations (ERS) in the 4 - 6 Hz range were present in the right GPi contacts (Figure B). Unfortunately, EEG recordings made in the surgical SeT- patient, patient B, were obscured by movement artifacts.

The oscillatory activity recorded from the non-surgical SeT- patient, patient D, was more temporally and spatially variable. At the beginning of the SeT maneuver (left hand used), ERDs in 5 Hz, 10 Hz and β (20 Hz) frequencies were detected over the left hemisphere, whereas ERDs in the ~ 12 Hz range were detected on the left side during termination of the maneuver. Between the beginning and end phases of the maneuver, ERDs in ~ 12 Hz and β (~ 20 Hz) frequencies were detected on the side contralateral to the hand used for the SeT (in C4-P4; data not shown) while ERSs in the ~ 5 Hz range were found in C3-P3 and C4-P4.

This is the first study to investigate the effect of SeTs on basal ganglia LFP activity. Due to the low number of CD patients undergoing implantation of DBS electrodes for treatment, we were limited by the number of surgical patients that could be included in the study. Although we have a small patient number, the EEG results found in the surgical patients could largely be replicated in the non-surgical CD patients. From our observations, alleviation of dystonia was accompanied by ERD in the 6 - 8 Hz range

while worsening of dystonia was associated with ERS in 4 – 6 Hz range. Furthermore, most of these changes began prior to the contact between the hand and face and similar changes were detected over various GP and scalp contacts in patient A. On the other hand, ERD in the β range was found in both patient groups, which indicates that this change may be movement-related as is well-documented in other studies (see Brown and Williams (2005) for current review) and not directly related to the dystonia-relieving effect of the SeT.

The oscillatory deep brain LFPs recorded in this study are most likely recorded and generated within the GPi. The target for the ventral contacts (contacts 0 and 1) was in the GPi and the location of the target was confirmed prior to implantation of the DBS electrode by microelectrode recordings and stimulations. Furthermore, in both patients stimulation through contact 1 was effective in alleviating the dystonia and the locations of these effective contacts were confirmed to be within the GPi by postoperative MRI (Hung et al., in press). This conclusion is also consistent with the findings of a recent study by Chu Chen et al. (2006) showing that oscillatory 3-12 Hz oscillations were maximal in the GPi of dystonic patients and that there was synchronization of neuronal activity and oscillatory field potentials within the GPi.

Pallidal oscillatory activity in the 4-10 Hz range has previously been associated with dystonia (Liu et al., 2002; Silberstein et al., 2003; Chu Chen et al., 2006), and we found that activity in the 6 - 8 Hz range was desynchronized when the dystonia was reversed by the use of the SeT. In the SeT- patients, execution of SeT-like movements led to desynchronization in this frequency range only during the beginning and end of the maneuver, suggesting that desynchronization of this frequency range can also be

movement-related. The worsening of dystonia, especially in patient B, was accompanied by an increase in cortical and pallidal oscillatory activity in the same frequency band. Such changes in activity were detected in some of the EEG channels in both SeT-patients, even in the one without head tremor. Hence, the ERS was unlikely to have been caused by sensory feedback from head tremor during the worsening of dystonia. This finding is consistent with the increase in 4 – 8 Hz pallidal activity during myoclonic episodes (Liu et al., 2002), as well as the increased 5 – 7 Hz activity in the dystonic muscles of CD patients (Tijssen et al., 2002).

In summary, our preliminary results suggest that oscillatory activity in the 4 – 8 Hz band may be involved in the pathophysiology of dystonia, as oscillatory power at these frequencies increased with worsening of dystonia, and decreased with improvement related to the performance of the SeT. Finally, our results affirm that SeTs are not necessarily sensory-triggered, since touching the face did not lead to a noticeable change in neuronal or dystonic activity and moreover, the neck EMG activity decreased before contact was made with the face.

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Legends:

Figure 1. Average rectified EMG and time–frequency wavelet spectrograms of EEG and pallidal local field potentials (LFPs) in each of the 4 patients during sensory trick or sensory trick-like movements. Panels A–D correspond to patients A–D respectively. All traces are aligned to cue presentation at time 0 (N=number of task repeats). In each panel, the top trace shows the average rectified EMG recording of the average rectified EMG recording of the left sternocleidomastoid muscle (LSCM). The subsequent plots show the average wavelet spectrograms of the selected EEG channels, and in panels A and B the average wavelet spectrograms of the LFP recordings from three pairs of pallidal contacts are also included. Periods of power reduction from baseline appear as blue areas (event-related desynchronizations) and periods of power increase (event-related synchronizations) appear as red areas. Areas of significant difference ($p < 0.05$) are enclosed by black contour lines. The vertical dashed lines marked “B+” and “B-” respectively denote the time of onset or offset of biceps muscle activation, as indicated by EMG recordings; whereas the lines marked “C+” and “C-” respectively indicate the time at which a contact was made or removed between the hand and face. In the labeling of the LFP contacts, the numbers (0 to 3) represent the locations of the contacts, with 0 being the most ventral and 3 the most dorsal. Abbreviations: L = left; R = right; GP = globus pallidus.

Table

Clinical details of patients involved in this study. SeT+: SeT user; SeT-: non-SeT user.

Patient	Sex	Age	Duration of Symptoms (years)	Description of Torticollis	Description of Trick / Trick-Like Maneuver	Last Injection of Botulinum Toxin	Medications
<u>Surgical:</u>							
A (SeT+)	F	62	5	Head rotation to right, anterocollis	Left hand touched face	> 1 year	Clonazepam, diazepam, lorazepam, meperidine, tizanadine
B (SeT-)	M	25	12	Head rotation to left, anterocollis	Right hand touched back of neck	>1 year	Trihexiphenidyl, clonazepam, tetrabenazine, baclofen
<u>Non-Surgical:</u>							
C (SeT+)	F	73	20	Head rotation to left	Right hand touched face	3 years	—
D (SeT-)	F	65	16	Head tilts to the left; left shoulder elevation; head tremor	Left hand touched face	3 months	Clonazepam, Sertraline

Figure