Neurobiology of Disease 86 (2016) 177–186

Contents lists available at ScienceDirect

Neurobiology of Disease

journal homepage: www.elsevier.com/locate/ynbdi

Electrocorticography reveals beta desynchronization in the basal ganglia-cortical loop during rest tremor in Parkinson's disease☆

Salman E. Qasim [a,*], Coralie de Hemptinne [b], Nicole C. Swann [b], Svjetlana Miocinovic [c], Jill L. Ostrem [c], Philip A. Starr [b]

[a] Department of Biomedical Engineering, Columbia University, USA
[b] Department of Neurological Surgery, University of California San Francisco, San Francisco, CA, USA
[c] Department of Neurology, University of California San Francisco, San Francisco, CA, USA

ARTICLE INFO

Article history:
Received 13 September 2015
Revised 24 November 2015
Accepted 26 November 2015
Available online 27 November 2015

Keywords:
Parkinson's disease
Electrocorticography (ECoG)
Tremor
Basal ganglia
Deep brain stimulation (DBS)

ABSTRACT

The pathophysiology of rest tremor in Parkinson's disease (PD) is not well understood, and its severity does not correlate with the severity of other cardinal signs of PD. We hypothesized that tremor-related oscillatory activity in the basal-ganglia-thalamocortical loop might serve as a compensatory mechanism for the excessive beta band synchronization associated with the parkinsonian state. We recorded electrocorticography (ECoG) from the sensorimotor cortex and local field potentials (LFP) from the subthalamic nucleus (STN) in patients undergoing lead implantation for deep brain stimulation (DBS). We analyzed differences in measures of network synchronization during epochs of spontaneous rest tremor, versus epochs without rest tremor, occurring in the same subjects. The presence of tremor was associated with reduced beta power in the cortex and STN. Cortico-cortical coherence and phase–amplitude coupling (PAC) decreased during rest tremor, as did basal ganglia-cortical coherence in the same frequency band. Cortical broadband gamma power was not increased by tremor onset, in contrast to the movement-related gamma increase typically observed at the onset of voluntary movement. These findings suggest that the cortical representation of rest tremor is distinct from that of voluntary movement, and support a model in which tremor acts to decrease beta band synchronization within the basal ganglia-cortical loop.

1. Introduction

Parkinson's disease (PD) is a movement disorder characterized by severe loss of dopaminergic neurons in the midbrain. This manifests in several cardinal symptoms including a 4–7 Hz tremor at rest, rigidity, bradykinesia, and postural instability (Hoehn and Yahr, 1967). Though many early studies searched for a single "generator" of tremor activity, it is now thought that rest tremor emerges from changes in the network dynamics of the basal ganglia-thalamocortical loop and cerebello-thalamocortical loop (Helmich et al., 2012). Tremor related oscillatory activity has been observed throughout these networks, through single unit recording (Hutchison et al., 1997; Levy et al., 2002; Levy et al., 2000 2002b) and local field potentials in the subthalamic nucleus (Reck et al., 2009; Weinberger et al., 2009), and in mapping of cortical connectivity through the use of magnetoencephalography (MEG) (Hirschmann et al., 2013; Timmermann et al., 2003; Volkmann et al., 1996) and electroencephalography (EEG) (Hellwig et al., 2000). However, most previous studies have recorded only from basal ganglia or cortex rather than studying the simultaneous activity necessary to observe network changes corresponding to rest tremor.

An understanding of the pathogenesis of rest tremor may provide insight into several mysteries related to the clinical presentation of tremor in patients with PD. Unlike other PD symptoms, such as bradykinesia or rigidity, the severity of tremor does not correlate with dopaminergic cell death in the striatum (Pirker, 2003). It also does not correlate with the severity of the other motor symptoms (Deuschl et al., 2000, 2001). Tremor-dominant patients have slower progression of disability and better prognosis than patients without tremor (Hoehn and Yahr, 1967). These characteristics suggest a pathophysiological distinction between PD with rest tremor and PD without rest tremor. Recent authors have postulated that these distinctions may indicate a compensatory role for rest tremor (Zaidel et al., 2009; Helmich et al., 2012). One theory of parkinsonian bradykinesia implicates excessive neuronal synchronization in the beta (13–30 Hz) band within and between structures of the motor network (Hammond et al., 2007), and detailed examination of the network changes underlying rest tremor would

☆ Authors' contributions and conflict of interest disclosures: Authors report no conflict of interest.

* Corresponding author at: Columbia University, 116th St & Broadway, New York, NY 10027, USA.
E-mail addresses: salman.qasim@columbia.edu (S.E. Qasim), Coralie.Dehemptinne@ucsf.edu (C. de Hemptinne), Nicole.Swann@ucsf.edu (N.C. Swann), Svjetlana.Miocinovic@ucsf.edu (S. Miocinovic), Jill.Ostrem@ucsf.edu (J.L. Ostrem), Philip.Starr@ucsf.edu (P.A. Starr).

Available online on ScienceDirect (www.sciencedirect.com).

http://dx.doi.org/10.1016/j.nbd.2015.11.023
0969-9961/

clarify whether rest tremor is acting to counter this pathological synchronization.

In this study we examined the hypothesis that transient spontaneous epochs of rest tremor may reflect a state of desychronization in frequency bands other than tremor frequency, within and between nuclei of the basal ganglia-thalamocortical motor loop. We approached this using the technique of electrocorticography (ECoG) of sensorimotor cortex, combined with subthalamic nucleus (STN) local field potential (LFP) recording, during spontaneous epochs of rest tremor and rest without tremor, in PD patients undergoing surgical implantation of deep brain stimulator (DBS) leads in the awake state. We found that tremor is associated with a reduction in cortical and subthalamic beta power, cortico-cortical coherence, cortical–subthalamic coherence and cortical cross frequency coupling. These findings suggest that tremor acts to counter the excessive beta synchronization associated with parkinsonian bradykinesia. Our findings also have implications for the development of closed-loop stimulation algorithms that rely on biomarkers modulated by tremor.

2. Materials and methods

2.1. Subject recruitment

The subjects in this study were recruited from a population of patients undergoing DBS implantation at one of two campuses: the University of California, San Francisco (UCSF), or the San Francisco Veteran Affairs Medical Center (SFVAMC). Each subject had a diagnosis of idiopathic Parkinson's disease confirmed by a movement disorders neurologist. Informed consent for the temporary intra-operative placement of the cortical strip was obtained prior to surgery under a protocol approved by the Institutional Review Board, according to the Declaration of Helsinki. Data from some of the same subjects in this study were also used, for different analyses, in other publications (Crowell et al., 2012; de Hemptinne et al., 2013, 2015; Shimamoto et al., 2013).

2.2. Surgery and placement of subdural ECoG electrodes and STN DBS lead

ECoG was recorded using either a 6-contact (n = 22) or 28-contact (n = 5) ECoG strip temporarily placed over the sensorimotor cortex (Panov et al., 2015). The ECoG strip was inserted under the dura through the burr hole used for the DBS lead placement and advanced in the direction of the intended target location, the arm area of motor cortex (3 cm from the midline, on the medial aspect of the “hand knob”) (Yousry et al., 1997). Six-contact electrodes were composed of platinum contacts of 4 mm total diameter, 2.3 mm exposed diameter and 10 mm spacing between contacts (Integra NeuroScience, Plainsboro, NJ, or Ad-Tech, Racine WI). Twenty-eight-contact electrodes were composed of platinum contacts of 2 mm total diameter, 1.2 mm exposed diameter and 4 mm spacing between contacts (Ad-Tech, Racine, WI).

Localization of the M1 contact was determined both anatomically and functionally. Anatomical localization was determined using either intraoperative computed tomography (iCT) merged with preoperative MRI or lateral fluoroscopy as previously described (Crowell et al., 2012). Functional localization was performed with somatosensory potentials evoked by median nerve stimulation and used to select contacts for the subsequent analyses (frequency = 2 Hz, pulse width = 200 μs, pulse train length = 160 μs, amplitude 25–40 mA). The central sulcus was localized using the N20 reversal technique (Crowell et al., 2012). The most posterior contact pair showing a reversed N20 potential was defined as the closest electrode pair to M1, the contact pair immediately posterior to that was defined as covering the central sulcus, and the contact pair posterior to that with an upward N20 waveform was defined as the closest electrode pair to primary somatosensory cortex (S1). These methods are illustrated in Fig. 1.

DBS electrodes were placed in the STN as previously described (Starr et al., 2002). Targeting was confirmed by evaluation of stimulation induced symptom improvement and adverse effects, as well as by visualization of DBS lead location on an iCT scan computationally fused to the preoperative MRI (Shahlaie et al., 2011).

2.3. Intraoperative data collection

ECoG potentials were recorded using the Guideline 4000 system (FHC Inc., Bowdoin, ME) (n = 7), the Alpha Omega Microguide Pro (Alpha Omega, Inc., Nazareth, Israel) (n = 14), or the PZ5 Neurodigitizer (Tucker Davis Technologies, Inc., Alachua, FL) (n = 6). ECoG potentials recorded with the 6-contact strips were recorded in a bipolar configuration referencing the five most posterior contacts (contacts 1–5) to the most anterior one. With the 28-contact strip, ECoG potentials were referenced to a scalp needle electrode.

Subcortical local field potentials were recorded using a 4-contact cylindrical DBS lead (Model 3389, Medtronic, Inc., Minneapolis MN). Each contact was 1.5 mm in height and 1.2 mm in diameter, with 0.5 mm intercontact spacing. With contact 0 as the most ventral contact and contact 3 as the most dorsal contact, LFPs were recorded using contacts 1 and 2. Subcortical LFPs from subjects implanted with the 6-contact ECoG strips were recorded in a bipolar configuration while subcortical LFPs from subjects implanted with the 28-contact strips were recorded in a monopolar configuration and re-referenced in a bipolar configuration in post-processing.

Six-contact ECoG and subcortical LFP signals were bandpass filtered 1–500 Hz, amplified × 7000. All signals were recorded at a sampling rate of minimum 1 KHz and up to 3 KHz. All data recordings after lead insertion were performed 5 to 60 min after insertion in order to minimize the contribution of acute effects related to electrode placement (Mann et al., 2009; Tykocki et al., 2013). The Guideline system had slight attenuation up to 20 Hz due to the slow roll-off characteristics of an intrinsic 1 Hz high pass filter, and this was compensated for using an empirically determined correction factor (Crowell et al., 2012). Even so this did not consistently correct for attenuation below 4 Hz. When results were analyzed separately for data collected with the GS4000, no differences were found in any condition. Nevertheless, we discarded frequencies below 4 Hz for group comparisons.

Additional channels were used to record analog signals from surface electromyography (EMG) from the arm contralateral to the cortical strip over the extensor carpi radialis (ECR) and/or biceps brachii. We also recorded the same hand's movement in three-dimensional space with a tri-axial accelerometer affixed to the wrist (AX2300-365, FHC, Inc., Bowdoin, ME). These data were recorded at a sampling rate of minimum 1 KHz and up to 25 kHz.

Subjects were lying in a semi-supine position in the operating room for the duration of surgery and data collection, and instructed to keep their eyes open and refrain from speech or voluntary movements during recordings. Data were recorded in two conditions: during rest tremor and rest without tremor.

2.4. Pre-processing

All data were processed and analyzed offline in MATLAB (Mathworks, Inc). All the data were downsampled to 1 kHz and notch filtered for power line noise (60 Hz) and its harmonics (at 120, 180, 240 Hz).

3. Data analysis

3.1. Identification of tremor epochs

In order to identify epochs of tremor, we collected surface EMG and accelerometry data from subjects' contralateral arm. Due to a high signal