NeuroImage: Clinical 12 (2016) 165–172

Contents lists available at ScienceDirect

NeuroImage: Clinical

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

Thalamocortical network activity enables chronic tic detection in humans with Tourette syndrome

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ARTICLE INFO

Article history:
Received 31 January 2016
Received in revised form 17 May 2016
Accepted 20 June 2016
Available online 25 June 2016

Keywords:
Tourette syndrome
Centromedian thalamus
Motor cortex
Deep brain stimulation

ABSTRACT

Tourette syndrome (TS) is a neuropsychiatric disorder characterized by multiple motor and vocal tics. Deep brain stimulation (DBS) is an emerging therapy for severe cases of TS. We studied two patients with TS implanted with bilateral Medtronic Activa PC + S DBS devices, capable of chronic recordings, with depth leads in the thalamic centromedian–parafascicular complex (CM-PF) and subdural strips over the precentral gyrus. Low-frequency (1–10 Hz) CM-PF activity was observed during tics, as well as modulations in beta rhythms over the motor cortex. Tics were divided into three categories: long complex, complex, and simple. Long complex tics, tics involving multiple body regions and lasting longer than 5 s, were concurrent with a highly detectable thalamocortical signature (average recall [sensitivity] 88.6%, average precision 96.3%). Complex tics were detected with an average recall of 63.9% and precision of 36.6% and simple tics an average recall of 39.3% and precision of 37.9%. The detections were determined using data from both patients.

1. Introduction

Tourette syndrome is a neuropsychiatric disorder characterized by multiple motor and vocal tics (Cath et al., 2011) (Jankovic and Kurlan, 2011) (Lebowitz et al., 2012) (Scharf et al., 2012). Tics are involuntary or partially voluntary movements that complicate daily tasks and frequently result in social embarrassment, leading to decreased quality of life (Aronow-Werner et al., 2014). Tics generally begin in childhood and subside or lessen during puberty; however, in approximately 20% of cases, tics persist or even worsen (Goetz et al., 1992). Numerous pharmacological and behavioral therapy options exist for Tourette syndrome (Roessner et al., 2011; Wilhelm et al., 2012; Verdellen and Griendt, 2011 Mar 29), but in severe cases, there may be little or no relief (McGuire et al., 2014). Deep brain stimulation (DBS) is an emerging therapy for severe intractable cases of Tourette syndrome and is reserved as a last line of therapy after other pharmacological and behavioral therapies fail (Ackermans et al., 2011; Okun et al., 2013; Porta et al., 2012).

DBS is an invasive neuromodulatory therapy (Miocinovic et al., 2013), in which depth electrodes are placed within subcortical brain structures and high-frequency electrical stimulation is used in an effort to modulate pathological neural activity. DBS is currently being evaluated as a therapy for severe intractable Tourette syndrome and is yet to be approved by the FDA for this indication. It is estimated that approximately 120 Tourette syndrome patients worldwide have been treated with DBS since 1999, and almost all 48 published studies report some degree of motor tic reduction (Schrock et al., 2015). While initial trials have been promising, the mechanisms underpinning the success of DBS treatment in Tourette syndrome remain unknown. Current models of Tourette syndrome pathophysiology have hypothesized that thalamocortical basal ganglia dysfunction is as a key component leading to many of the symptoms in Tourette syndrome (Bronfeld and Bar-Gad, 2013; Mink, 2001). Inhibitory input from basal ganglia structures directed toward thalamic nuclei likely plays a role in suppressing unwanted motor patterns while activating desired motor patterns. It has been hypothesized that dysfunctional striatal activity decreases inhibitory projections from basal ganglia structures resulting in excessive disinhibition of thalamic nuclei. This excessive disinhibition in turn leads to the production of undesired motor patterns, also referred to as tics. To test this hypothesis, the electrophysiological correlates of tics must be studied. Presently, the available literature reports increases

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http://dx.doi.org/10.1016/j.nicl.2016.06.015

in low-frequency (2–13 Hz) local field potential (LFP) activity within the centromedian–parafascicular nucleus of the thalamus (CM-PF) (Bour et al., 2015) and a reduced mean frequency and irregular grouped firing during single-neuron recordings from the globus pallidus internis (GPi) (Zhuang et al., 2009) before and during tics. In a previous Tourette syndrome DBS study, our group showed that following 6 months of DBS therapy, 3 out of 5 patients with DBS in the CM-PF thalamic region had reductions in low-frequency activity that were coupled with an overall reduction in tic severity (Maling et al., 2012). Still, statistical evidence supporting the existence of electrophysiological tic-related activity within thalamocortical structures has yet to be shown. Understanding tic genesis and using this information to advance Tourette syndrome therapies, such as the development of closed-loop DBS, will require investigation into the chronic signatures underpinning tics. We sought to identify these electrophysiologic signatures using chronically implanted thalamic and cortical electrodes and to develop a tic detector that could initiate DBS when pathological activity is present.

2. Materials and methods

2.1. Subjects

The first subject (TS01) is a 23-year-old female, who was diagnosed with TS at the age of 8. Her tics are dystonic in appearance and take on a number of forms including full arm extensions, shoulder jerks, neck twisting, grimacing, forceful upward eye movements, barking, and occasionally, groans. A majority of this subject's tics were lateralized to the right side of her body. She demonstrated the ability to suppress her tics. The second subject (TS02) is a 25-year-old female who was also diagnosed with TS at the age of 8. Her tics included cursing, kissing sounds, yelling, blinking, snorting, shrugging, eye rolling, finger tapping, head bobbing, and hitting her own face. A majority of the tics were centralized to the face; tics involving the extremities were less frequent. This subject's tics tended to reduce in intensity and frequency when she focused on a task (e.g., singing). Both subjects provided informed consent as approved by the University of Florida Institutional Review Board (IRB-01) and by the US Food and Drug Administration (FDA) through an investigational device exemption (IDE).

2.2. Implantation and localization of electrodes

High-resolution T1 + Gad and FGATIR MRI (Sudhyadhom et al., 2009) coupled with a deformable (patient-specific) brain atlas were used to plan the targets and trajectories of both the bilateral 4-contact CM-PF thalamic DBS leads (Medtronic 3387, Medtronic, LLC, Minneapolis, MN) and the bilateral 4-contact motor cortical subdural strip electrodes (Medtronic Resume II) through one frontal burr hole on each side of the skull. This MR-based plan was fused to a stereotactic CT acquired the morning of surgery after application of a CRW head frame. No sedation was used for head frame application or during the operative procedure. Burr holes and dural incisions were placed at the stereotactically identified sites after local anesthesia and the subcortical electrode arrays were placed over the hand motor cortex, since many motor tics involve involuntary movements of the hands and/or arm. The strips were positioned over the structural motor hand knob (Boroojerdi et al., 1999), and the hand sensorimotor cortex was localized intraoperatively using somatosensory-evoked potentials (SSEP) (Cedzich et al., 1996) and real-time functional mapping (Hill et al., 2012). After implantation of the subdural strips, a microelectrode was advanced using a micropositioner (FHC, Bowdoin, ME) along the planned thalamic trajectory to allow for physiological monitoring. The advancing electrode was held steady at multiple depths through the trajectory in order to allow for consistent recordings of single neurons at specified depths along the DBS lead trajectory. DBS leads were implanted and intraoperative macrostimulation was performed to assure that thresholds for stimulation-induced side effects were acceptable. A single Medtronic Stimloc cap (countersunk flush with the skull and modified to allow the egress of two leads) was used on each side to secure both the DBS leads and the cortical leads in place and intraoperative fluoroscopy was used to ensure that the leads were not displaced during this process. We co-registered pre-op MRI + patient-specific atlas images with (1-month) delayed post-op high-resolution CTs to precisely identify the anatomic locations of each of the 16 implanted electrodes.

2.3. Experimental design

Subjects were instructed to rest (suppress their tics to the best of their ability), to tic freely, and then to perform volitional movements (while suppressing tics); see Fig. 1.

Intraoperative LFPs were collected in a unipolar configuration from all 16 implanted contacts by using an external amplifier (Neuroscan Synamps 2, Compumedics, Charlotte, NC), and these LFPs were referenced to a subdermal electrode placed in the scalp. Postoperative LFPs were recorded in a bipolar configuration with the Activa PC + S (Medtronic, Inc., Minneapolis, MN) at 800 or 422 Hz. The Activa PC + S is a first-generation DBS device that is capable of recording and transferring neural data through telemetry, as well as stimulation (Rouse et al., 2011). There was at least 30 min between when stimulation was turned off when the patient arrived at the clinic and when "baseline" data were recorded. One channel of data from CM-PF depth contacts and one channel of data from cortical motor cortex contacts were collected simultaneously in 8-min segments in bipolar configuration. Postoperative recordings were taken from the empirically determined best contacts from intraoperative data collection. The empirically derived contacts were determined by identifying the electrodes with the highest r^2 value between the tic and baseline conditions. Surface EMG recordings, without accelerometers, were collected with TS01 (Ag/AgCl electrodes, Neuroscan Synamps 2). Accelerometers and surface EMG were used with TS02 (Delsys wireless EMG/accelerometer system, Natick, MA, at 1925.93 and 148.15 Hz, respectively). EMG/accelerometers were placed bilaterally on the forearm, bicep, and neck. Stimulation from the Activa PC + S was observed on neck EMG, which was used to synchronize the LFP and EMG/acceleration signals. Synchronization of video and EMG was achieved with a signal-syncing device developed in house. Our initial behavioral paradigms had instructed subjects to voluntarily mimic their tics as the control condition. However, subjects indicated that this inadvertently led to real tic initiation and may have biased a clear delineation between tic and voluntary movements. Therefore, subjects were instructed to perform naturalistic volitional movements that did not necessarily appear like their tics.

2.4. Statistical analysis

2.4.1. Intraoperative r^2 analysis.

Coefficient of determination (r^2) analysis was performed between movement-free baseline data and the test conditions (voluntary left hand movement, right hand movement, or tics). The r^2 measure represents the proportion of the signal feature that is accounted for by the test condition. The larger this value, the larger the proportion of the signal feature that can be accounted for by the test condition (Wonnacott and Wonnacott, 1972). Significance was calculated by determining the probability that a given r^2 value would be observed within an F-cumulative density function defined by the number of data points in the baseline and task (e.g., ticing or volitional movement) condition. A p-value of 0.05 was used to determine statistical significance of the calculated unsigned r^2 value between the baseline and testing conditions. The null hypothesis is that the signal feature does not account for differences between the baseline and the task condition for the given r^2 value.

2.4.2. Support vector machine.

A support vector machine (Suykens, 1999) was trained on 30 s of tic-free baseline and 30 s of tic data collected at the beginning of each