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

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1 A B S T R A C T

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.

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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 Friedt, 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
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 internus (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, yells, blinks, snorting, shuffling, 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 subdural 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 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 r2 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 r2 analysis.

Coefficient of determination (r2) analysis was performed between movement-free baseline data and the test conditions (voluntary left hand movement, right hand movement, or tics). The r2 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 r2 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 r2 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 r2 value.

2.4.2. Support vector machine.

A support vector machine (Suykens, 1999) was trained on 30s of tic-free baseline and 30 s of tic data collected at the beginning of each
follow-up visit. LFPs were band pass filtered into non-overlapping 10 Hz bins in the 1–100 Hz range, rectified, down-sampled to 10 Hz, and smoothed with a 40 Hz low pass filter prior to training and classification. The 40 Hz low pass filter improved detection rates without greatly distorting the data under visual inspection. We used the top 3 discriminating features from the original 20 (10 spectral bins each from CM-PF and motor cortex). The most significant features were selected by identifying the top 3 bins from CM-PF and/or motor cortical features that had the highest $r^2$ statistic comparing baseline and tic training data. The input to the support vector machine was the power from the top 3 bands and the output was a binary decision of “tic” or “not a tic.” Feature selection and the support vector machine were retrained with each follow-up visit. Detection was evaluated using recall (i.e., sensitivity) and precision, which are defined below.

Recall = \frac{\text{True Positives}}{\text{True Positives} + \text{False Negatives}}

Precision = \frac{\text{True Positives}}{\text{True Positives} + \text{False Positives}}

Recall is identical to sensitivity, but precision (also known as positive predictive value) was chosen over specificity because the former does not depend upon true negatives (i.e., when absence of tics did not lead to detection). Tics are paroxysmal events, and thus the occurrence and absence of tics are unbalanced. A detector applied to an unbalanced dataset evaluated with specificity could detect zero events, but still achieve a high rating because the large number of true negatives would falsely inflate the scores. We calculated recall and precision for simple tics (single muscle group), complex tics (multiple muscle group), and long complex tics (multiple muscle group and lasting longer than 5 s). A true positive was defined as detection at the beginning of the tic, or occurring for at least 70% of the duration of the tic. A false positive was defined as a detection that was not concurrent with a tic, or within 2 s of the onset/endpoint of a tic. A false negative was defined as a tic with no detections at its onset, or <70% detection of the tic duration.

3. Results

3.1. Intraoperative recordings

We observed statistically significant low– (1–10 Hz) and high– (30–100 Hz) frequency CM-PF activity during tics, which were not present during volitional movements ($p < 0.05$). Statistically significant high-frequency activity within premotor and motor contacts was observed during volitional movements, but no statistically significant activity was observed within CM-PF contacts ($p < 0.05$) (Fig. 2B). We observed similar patterns of statistically significant CM-PF and motor cortex activity in TS02 ($p < 0.05$) (Fig. 2D). Statistically significant cortical activity from the hand motor region during volitional movement and tics in both patients were more clearly observed in the most posterior contacts ($p < 0.05$).

3.2. Postoperative recordings

Fig. 3 shows examples of tics and volitional movements as captured by EMG activity, along with neural recordings. Data were collected monthly for 6 months following implantation in a bipolar configuration. Stimulation was disabled during data collection. Low-frequency (1–10 Hz) CM-PF activity was observed during tics in postoperative data from both subjects (Figs. 3 and 4). An increase in the low-frequency CM-PF LFP was observed concurrent with or preceding the desynchronization of motor cortex beta activity at the onset of tics. Volitional movements involving the same body regions as tics did not evoke low-frequency CM-PF activity. High-frequency (40–100 Hz) changes in CM-PF activity were not observed postoperatively during tics. This was most likely due to the higher noise floor of the implanted devices or high-frequency attenuation that was potentially caused by the bipolar electrode configuration (see Supplementary Materials).

3.3. Tic detection

We constructed a tic detector and examined the consistency and reproducibility of the clinical tic signatures over the course of a 6-month period. Detection results for both subjects are available in Table 1. The most effective signal for tic detection varied with time. This was likely a result of variable signal quality, changes in tic appearance, patient stress, stimulation efficacy, or physiological factors. The CM-PF signal was in general more robust with TS01. TS01 had more long complex tics than TS02 and this type of tic seemed to be the most detectable. Simpler tics may not be associated with as large of a signal in CM-PF and are easier to see as changes in M1 activity. Long complex tics were concurrent with a highly detectable thalamocortical signature with average recall 88.6%, average precision 96.3% in both patients. Complex tics were detected with an average recall of 63.9% and precision of 36.6%, and simple tics were detected with an average recall of 39.3% and precision of 37.9% across both patients. In total, long complex tics accounted for 54% of all tics, complex tics accounted for 31% of all tics, and simple tics accounted for 15% of all tics. 79% (139/176) of all positive detections were within a 100-ms window of tic onset. 14% of all positive detections were observed before tic onset (on average...
800 ms before tic onset) and 7% of positive detections were observed after tic onset (on average 500 ms after tic onset). A video illustrating the temporal dynamics between tics, motor cortex beta activity, raw CM-PF activity, and detection in TS01 is provided in Supplementary Video 1.

Feature selection varied from month to month across both patients. CM-PF low-frequency bands (1–30 Hz) were the most discriminating features in months 2, 3, 5, and 6 for TS01 and months 1 and 5 for TS02. A combination of CM-PF activity in the low-frequencies (1–20 Hz) and motor cortex activity in multiple bands (1–10 Hz, 20–40 Hz), including beta, were the most discriminating features in month 4 for TS01 and in months 2, 3, 4, and 6 for TS02. The patients were under open-loop DBS for the entirety of the study. DBS was only disabled during data recordings to eliminate artifacts resulting from stimulation during the study. False positives were not observed during volitional movements. Most false positives did not coincide with any particular event or motion; others coincided with yawning, moments where patients described their reaction as surprised, or itching sensations. We also tested detection using the features obtained from the first month, which were 1–30 Hz CM-PF for both patients. The detection of long complex tics was preserved even when the detector was not retrained (see Table 1).

Fig. 2. Intraoperative $r^2$ analysis of tics and volitional movements. (AC) Placement of electrodes in TS01 and TS02 are shown in X-rays. (BD) Intraoperative data were recorded in a unipolar configuration from all 16 contacts simultaneously. Significant ($p < 0.05$) contralateral broadband gamma activity was observed for volitional movements and tics (localized primarily to right side of body in TS01) in premotor (TS01) and motor contacts (TS01 and TS02). Significant ($p < 0.05$) high-frequency activity was observed in CM contacts only during the tic condition (TS01 and TS02) (two column figure).

Fig. 3. CM is associated with tics and not volitional movements. Data from follow-up visit month 2: neural activity from M1 and CM-PF (top two rows), EMG activity from various locations. Subject TS01 was instructed to tic freely. Tic onset denoted by red dotted line: (1) A neck-wrenching tic (simple), (2) rapid arm throwing tic (complex long), (3) arm-wrenching tic (complex), (4) arm-throwing and neck-twisting tic (complex long). In a separate trial, the subject was asked to perform a series of volitional movements. Movement onset denoted by red dotted line: (5) talking and opening/closing hands rapidly, (6, 7) opening/closing hands, (8, 9) rapidly shaking hands. No tics were observed during the volitional movement condition (1 column figure).
4. Discussion

4.1. Signal or motion artifact?

Data collected intraoperatively from both subjects exhibited properties that demonstrate that tic-related signals are not movement artifacts. Intraoperative $r^2$ analysis revealed high amplitude activity within thalamic and cortical structures contralateral to tic, but less activity within structures ipsilateral to tics. These intraoperative recordings were taken prior to the tunneling of cables through the neck and while the patients’ heads were securely mounted with a head frame. The largest source of artifact, in this case, would be from movement generated at the tissue electrode interface. Therefore, if the tic-related signal was driven by movement artifact, there would have to be more force delivered to the hemisphere of the brain contralateral to movement than the ipsilateral hemisphere. The dampening of forces through tissue would suggest that it is unlikely for a force traveling a longer distance to be larger than a force traveling a shorter distance. Therefore, the increase in activity within contralateral structures cannot be reduced to only movement artifact.

Postoperative data collection showed high specificity for tic-related signals. Out of the various combinations of bipolar signal pairs, only a few channels showed a strong signal when tics were present in both patients. Multiple, if not all, electrode pairs should have exhibited changes in activity if the tic signal was actually a movement artifact or the result of cable twisting within the neck. Again, for TS01, whose tics were highly lateralized, tic signatures were present only in the contralateral hemisphere. The recordings in the hemisphere ipsilateral to the tic motions should have been contaminated with these features had they been motion artifacts.

4.2. Tics and DBS

It has been hypothesized that thalamocortical basal ganglia dysfunction is a key component of Tourette syndrome and tic genesis. DBS of CM-PF and globus pallidus are associated with favorable therapeutic outcomes in TS. Tic-related electrophysiological activity of globus pallidus has been observed and reported and we now present evidence of tic-related electrophysiological activity within the CM-PF. In our analysis, we observed that low-frequency CM-PF activity increased and beta motor cortex activity decreased during tics. Changes in CM-PF activity were not observed during volitional movements, but decreases in beta amplitude in motor cortex activity were associated with both tics and volitional movements (see Figs. 3 and 4). A large increase in M1 beta activity was sometimes observed prior to a tic, which helped in differentiating tics from volitional movements. These observations, as well as the observations from previous studies (Maling et al., 2012), imply that increased low-frequency CM-PF activity is associated with undesired motor patterns. In addition, this evidence suggests that tics may have a specific biomarker that could be tied to the pathophysiological mechanisms underpinning tics.

Using video obtained at each month’s visit, we detected long complex tics with an average recall of 88.6% and the average precision 96.3%. These results are promising; however, a tic detector should also be able to run without retraining. We retested our detector using features obtained at the first month’s visit, which were 1–30 Hz CM-PF for both patients and found that the detection of long complex tics was preserved (Table 1). This is important as long complex tics are considered to be the most disabling type of tic in Tourette syndrome patients and, as we observed, could be the most appropriate for invasive therapies such as DBS or ablative interventions (Cheung et al., 2007). We found detection of simple tics to be difficult as a change in cortical or thalamic signals was only observed 39.3% of the time; likewise,
Detection of tics of varying durations evaluated by precision and recall. Long complex tics demonstrated a higher detectability. Tic and baseline data were not available for month 1 in TS01. Shown are detection results using features that were retrained each month and detection results using features obtained in the first month's visit.
Obeso et al. found that simple tics were generally not associated with cortical premotor potentials (Obeso et al., 1981).

The features selected in the tic detector to attain best performance were not stationary over subsequent months. Chronic DBS therapy could have modulated neural activity and led to the changes in the features selected across the months. The waxing/waning nature of tics and their temporal evolution may also be responsible for changes in the feature selection process. Still, just like the clinical programming that needs to be optimized over subsequent months, feature selection for the design of an optimal tic detector may have to be optimized across several months.

In the baseline condition, we asked the subjects to suppress their tics. It is possible that suppression of tics differs from a natural baseline condition when no tics are occurring. One might suggest that the urge to tic may still be present in these patients even though they are not ticcing. We asked our patients to indicate when they had an urge to tic and we found no changes in activity during urges in comparison to baseline conditions. We therefore concluded that for this preliminary paper, using the tic-free baseline as a control for tics was a fair comparison.

Careful measurement of the neural correlates of tics allowed for quantitative assessment of tic onset and frequency in this study. This information is the prerequisite to developing advanced treatment strategies such as closed-loop (“adaptive”) deep brain stimulation. In the future, we plan to use the tic-associated neurophysiologic features that we identified to enable chronic closed-loop DBS in our TS patients. Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.nicl.2016.06.015.

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References
Ackermann, L., Duits, A., Linden van der, C., Tijssen, M., Schuens, K., Ternel, Y., et al., 2011. Double-blind clinical trial of thalamic stimulation in patients with Tourette syndrome. Brain 134 (3), 832–844 (Mar 1).
Aronow-Wener, S.P., Adams, H., Verhicle, A., Thatcher, A., Mink, J., Augustine, E., 2014. Social functioning in youth with Tourette syndrome (P449). Neurology 82 (10 Supple-ment), 4006 (Apr 8).
Boroojerdi, B., Follys, H., Kriing, T., Spetzger, U., Thron, A., Tipper, R., 1999. Localization of the motor hand area using transcranial magnetic stimulation and functional magnetic resonance imaging. Clin. Neurophysiol. 110 (4), 699–704 (Apr 1).
Bour, L.J., Ackermans, I., Foncke, E.M.J., Cath, D., van der Linden, C., Visser Vandewalle, V., et al., 2015. Tic related local field potentials in the thalamus and the effect of deep brain stimulation in Tourette syndrome: report of three cases. Clin. Neurophysiol. 126 (8), 1578–1588 (Aug).
Bronfeld, M., Bar-Gad, I., 2013. Tic disorders: what happens in the basal ganglia? Neuroscientist 19 (1), 101–108 (Feb 1).
Cath, D.C., Hedervely, T., Ludolph, A.G., Stem, J.S., Murphy, T., Hartmann, A., et al., 2011. European clinical guidelines for Tourette syndrome and other tic disorders. Part I: assessment. Eur. Child Adolesc. Psychiatry 20 (4), 155–171 (Mar 29).
Cedzich, C., Taniguichi, M., Schaffer, S., Schramm, J., 1996. Somatosensory evoked potential phase reversal and direct motor cortex stimulation during surgery in and around the central region. Neurosurgery [Internet] 38 (5) (Available from:http://journals.lww.com/neurosurgery/Fulltext/1996/05000/Somatosensory_Evoked_Potential_Phas reversal_and.23.aspx).
Cheung, M.Y.C., Shahed, J., Janjic, J., 2007. Malignant Tourette syndrome. Mov. Disord. 22 (12), 1743–1750 (Sep 15).
Goertz, C.G., Tanner, C.M., Stebbins, G.T., Leipzig, G., Carr, W.C., 1992. Adult tics in Gilles de la Tourette’s syndrome: description and risk factors. Neurology 42 (4), 784 (Apr 1).
Hill, N.J., Gupta, D., Brunner, P., Gunduz, A., Adamo, M.A., Ritaccio, A., et al., 2012. Recording human electrocorticographic (ECoG) signals for neuroscientific research and real-time functional cortical mapping. J. Vis. Exp. JOVE (46) ([Internet], Jun 26 [cited 2015 Dec 4], Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3471287/).
Jankovic, J., Kurlan, R., 2013. Tourette syndrome: evolving concepts. Mov. Disord. 28 (6), 1149–1156 (May 1).
Lebowitz, E.R., Motlagh, M.G., Katsovich, L., King, R.A., Lombroso, P.J., Grantz, H., et al., 2012. Tourette syndrome in youth with and without obsessive compulsive disorder and attention deficit hyperactivity disorder. Eur. Child Adolesc. Psychiatry 21 (8), 451–457 (Apr 28).
Maling, N., Hashemiyoon, R., Foote, K.D., Okun, M.S., Sanchez, J.C., 2012. Increased thalamic gamma band activity correlates with symptom relief following deep brain stimulation in humans with Tourette’s syndrome. PlaS One 7 (9), e44215 (Sep 6).
McGuire, J.F., Placentini, J., Brennan, E.A., Levin, A.B., Murphy, T.K., Small, B.J., et al., 2014. A meta-analysis of behavior therapy for Tourette syndrome. J. Psychiatri. Res. 50, 106–112 (Mar).
Mink, J.W., 2001. Basal ganglia dysfunction in Tourette’s syndrome: a new hypothesis. Pediatr. Neurol. 25 (3), 190–198 (Sep).
Miocinovic, S., Somayajula, S., Chitnis, S., Viet, J.L., 2013. History, applications, and mechanisms of deep brain stimulation. JAMA Neurol. 70 (2), 163–171 (Feb 1).
Obeso, J.A., Rothwell, J.C., Marsden, C.D., 1981. Simple tics in Gilles de la Tourette’s syndrome are not prefixed by a normal premovement EEG potential. J. Neurol. Neurosurg. Psychiatry 44 (8), 735–738 (Aug 1).
Okun, M.S., Foote, K.D., Wu, S.S., et al., 2013. A trial of scheduled deep brain stimulation for tourette syndrome: moving away from continuous deep brain stimulation paradigms. JAMA Neurol. 70 (1), 85–94 (Jan 1).
Porta, M., Servello, D., Zanaboni, C., Sanasiotti, F., Menghetti, C., Sassl, M., et al., 2012. Deep brain stimulation for treatment of refractory Tourette syndrome: long-term follow-up. Acta Neurochir. 154 (11), 2029–2041 (Sep 9).
Roesner, V., Plessen, K.J., Rothenberger, A., Ludolph, A.G., Rizzo, R., Skow, L., et al., 2011. European clinical guidelines for Tourette syndrome and other tic disorders. Part II: pharmacological treatment. Eur. Child Adolesc. Psychiatry 20 (4), 173–186 (Mar 29).
Rousse, A.G., Stanislas, S.R., Cong, P., Jensen, R.M., Afshar, P., Ullstedt, D., et al., 2011. A chronic generalized bi-directional brain–machine interface. J. Neural Eng. 8 (3), 036018.
Scharf, J.M., Miller, L.L., Mathews, C.A., Ben-Shlomo, Y., 2012. Prevalence of Tourette syndrome and chronic tics in the population-based Avon Longitudinal Study of Parents and Children cohort. J. Am. Acad. Child Adolesc. Psychiatry 2 (Feb) 51, 192–201.e5.

Schröck, L.E., Mink, J.W., Woods, D.W., Porta, M., Servello, D., Visser-Vandewalle, V., et al., 2015. Tourette syndrome deep brain stimulation: a review and updated recommendations. Mov. Disord. 30 (4), 448–471 (Apr 1).

Sudhyadhom, A., Haq, U.U., Foote, K.D., Okun, M.S., Bova, F.J., 2009. A high resolution and high contrast MRI for differentiation of subcortical structures for DBS targeting: the Fast Gray Matter Acquisition T1 Inversion Recovery (FGATIR). NeuroImage (Supplement 2), T44–T52 (Aug 47).

Suykens, J., 1999. a. K, Vandewalle J. Least Squares Support Vector Machine Classifiers. Neural. Process. Lett. 9 (3), 293–300 (Jun).

Verdellen, C., Grienert, J., van de Hartmann, A., Murphy, T., Group the EG, 2011 Mar 29. European clinical guidelines for Tourette syndrome and other tic disorders. Part III: behavioural and psychosocial interventions. Eur. Child Adolesc. Psychiatry 20 (4), 197–207.

Wilhelm, S., Peterson, A.L., Piacentini, J., et al., 2012. RAndomized trial of behavior therapy for adults with tourette syndrome. Arch. Gen. Psychiatry 69 (8), 795–803 (Aug 1).

Wonnacott, T.H., Wonnacott, R.J., 1972. Introductory Statistics. vol. 19690. Wiley New York.

Zhuang, P., Hallett, M., Zhang, X., Li, J., Zhang, Y., Li, Y., 2009. Neuronal activity in the globus pallidus internus in patients with tics. J. Neurol. Neurosurg. Psychiatry 80 (10), 1075–1081 (Oct 1).