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Thalamic deep brain stimulation for tourette syndrome increases cortical beta activity

Thomas Schüller [a,*], Daniel Huys [a], Sina Kohl [a], Veerle Visser-Vandewalle [b], Till A. Dembek [c], Jens Kuhn [a,d], Juan Carlos Baldermann [a,c,e,1], Ezra E. Smith [f,1]

[a] University of Cologne, Faculty of Medicine and University Hospital Cologne, Department of Psychiatry and Psychotherapy, 50935, Cologne, Germany
[b] University of Cologne, Faculty of Medicine and University Hospital Cologne, Department of Stereotactic and Functional Surgery, 50935, Cologne, Germany
[c] University of Cologne, Faculty of Medicine and University Hospital Cologne, Department of Neurology, 50935, Cologne, Germany
[d] Johanniter Hospital Oberhausen, Department of Psychiatry and Psychotherapy & Psychosomatic Medicine, 46145, Oberhausen, Germany
[e] University of Freiburg, Faculty of Medicine and University Hospital Cologne, Department of Psychiatry and Psychotherapy, 79104, Freiburg, Germany
[f] Tucson VA Medical Center, Tucson, AZ, USA

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ABSTRACT

Background: Deep brain stimulation (DBS) of the thalamus can effectively reduce tics in severely affected patients with Tourette syndrome (TS). Its effect on cortical oscillatory activity is currently unknown.
Objective: We assessed whether DBS modulates beta activity at fronto-central electrodes. We explored concurrent EEG sources and probabilistic stimulation maps.
Methods: Resting state EEG of TS patients treated with thalamic DBS was recorded in repeated DBS-on and DBS-off states. A mixed linear model was employed for statistical evaluation. EEG sources were estimated with eLORETA. Thalamic probabilistic stimulation maps were obtained by assigning beta power difference scores (DBS-on minus DBS-off) to stimulation sites.
Results: We observed increased beta power in DBS-on compared to DBS-off states. Modulation of cortical beta activity was localized to the midcingulate cortex. Beta modulation was more pronounced when stimulating the thalamus posteriorly, peaking in the ventral posterior nucleus.
Conclusion: Thalamic DBS in TS patients modulates beta frequency oscillations presumably important for sensorimotor function and relevant to TS pathophysiology.

1. Introduction

Tourette syndrome (TS) is a hyperkinetic neurodevelopmental disorder characterized by motor and vocal tics. Tics are typically preceded by a premonitory urge, an unpleasant sensation that ceases with tic execution (Brandt et al., 2016 [1]; Ganos et al., 2013). While the underlying neuropathology of TS remains incompletely understood, it is associated with a hyperdopaminergic state [2,3] and aberrant activity in cortical – basal ganglia networks including the cingulate cortex, supplementary motor area (SMA), insula, putamen and thalamus [4–8]. Most patients that seek treatment for their tics benefit from behavioral interventions, neuroleptic medication or a combination of both (Bate et al., 2011; Huys et al., 2012). For those patients who do not respond sufficiently and remain severely affected, deep brain stimulation (DBS) is a viable treatment option [9]. High-frequency DBS of the thalamus can alleviate tics and improve quality of life [10,11]. Structural and functional magnetic resonance imaging (MRI) studies have pointed to a dispersed network including the cingulate cortex, insula, and sensorimotor cortex, that mediates clinical efficacy of thalamic DBS ([12]; Johnson et al., 2020).

The putative electrophysiological changes associated with clinically effective DBS have yet to be elucidated. Oscillatory activity in the beta frequency (13–30 Hz) may play a decisive role, as it has been linked to maintaining the current state of the sensorimotor system, exerting top-down control to prevent interference from noise within the system [13,14]. In TS, cortical and thalamic beta activity has been negatively

* Corresponding author. University of Cologne, Faculty of Medicine and University Hospital Cologne, Department of Psychiatry and Psychotherapy, Kerpener Straße 62, 50937, Cologne, Germany.
E-mail address: thomas.schueller@uk-koeln.de (T. Schüller).
[1] Denotes shared last authorship.

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correlated with tic severity [15,16]. Reduced beta desynchronization in TS patients is normalized by voluntary tic suppression, and beta power increases preceding tics that may relate to increased motor inhibition [17,18]. Interestingly, the administration of antidopaminergic medication, which is commonly used for the treatment of TS, can lead to elevated cortical beta power [19,20]. Investigations into Parkinson's disease have also substantially contributed to the current understanding of beta power in the sensorimotor system. Parkinson's diseases is, contrary to TS, a hypokinetic and hypodopaminergic disorder with robustly elevated beta activity in the basal ganglia [21,22]. Excessive beta activity is closely linked to the hypokinetic motor state [9] and can be normalized through treatment with dopaminergic replacement therapy [23] and high-frequency DBS of the subthalamic nucleus [24–26]. Therefore, modulation of the hyperkinetic motor state in TS may be likewise mediated by the modulation of the sensorimotor beta system. Here, we aimed to elucidate the effect of thalamic DBS on cortical beta power. To this aim, TS patients chronically treated with DBS were repeatedly assessed with DBS-on or DBS-off.

2. Methods

We recruited eleven TS patients receiving continuous thalamic DBS as treatment (see Table 1 for demographic and clinical information). The thalamic target region was either located in the ventral anterior/ventral lateral nuclei (VA/VAL) or the centromedian nucleus - nucleus ventrooralis internus (CM-Voi). For details of the surgical procedure we refer to Huys et al. [11] and Baldermann et al. [10]. Clinical assessment included the Yale Global Tic Severity Scale (YGTSS), the Premonitory Urge for Tics Scale (PUTS), the Beck Depression Inventory (BDI–II), the Wender Utah Rating Scale (WURS-K) and the Obsessive-Compulsive Inventory - Revised (OCI-R). We recorded EEG resting state activity in 6-min blocks with 1-min segments of eyes open/eyes closed instructions. Six open-label blocks alternating between DBS-on (patients' clinical amplitude, frequency and pulse width settings) and DBS-off were recorded. One patient's (Patient 8) EEG recording had to be discarded due to poor data quality. One patient aborted the study after four blocks were recorded, this data was included in the subsequent analyses. This study was registered in the German Clinical Trials Register (DRKS00018838), approved by the Ethics Committee of the Medical Faculty of the University of Cologne (No. 19–1310) and performed in accordance with the Declaration of Helsinki.

EEG was recorded from 63 electrodes (actiCAP, Brain Products GmbH, Gilching, Germany) with a sampling rate of 5000 Hz. All processing steps were performed with EEGLAB [27] and custom Matlab scripts (The Mathworks Inc., Natick, MA, USA). Data were filtered with a zero-phase finite impulse response filter (2–45 Hz) and with a frequency-domain Hampel filter to remove residual DBS artifacts (Allen et al., 2010). Segments with artifacts affecting more than 25% of the channels were removed (*clean_rawdata*). When necessary, electrodes were reconstructed by spherical spline interpolation. Online reference FCz was re-created. All data were down-sampled to 100 Hz and submitted to independent component analysis. Artifactual components were automatically removed by the classifier MARA (Winkler et al., 2011). For statistical analysis, we performed a linear mixed model (*fitlme*) for a fronto-central electrode cluster (FC4, C4, FCz, Cz, C3, C4) with z-scored data and predictors Stimulation (on, off) and Repetition: (1, 2, 3) with subjects modeled as random intercepts. EEG generators were estimated using eLORETA (Pascual-Marqui, 2007). Here, voxel-wise linear mixed models as described above were performed with $p < .005$ considered significant. Also, we performed Spearman correlations between electrode cluster difference scores (DBS-on minus DBS-off) and psychometric scales with false discovery rate correcting for multiple ($n = 6$) comparisons. Likewise, we also checked whether the stimulation effect was associated with the total electric energy delivered (current amplitude^2 * frequency * pulse width * impedance).

To investigate the association between beta power modulation and respective thalamic stimulation sites, we calculated probabilistic stimulation maps [28]. To this end, we reconstructed each pair of electrodes in standard MNI space following the default pipeline of Lead-DBS (Version 2.6, www.lead-dbs.org) [29]. Based on the individual stimulation settings, the electric fields were determined in patient's native space using FastField and then transformed into standard space [30]. Then, a recently introduced sigmoid transformation was applied to each electric field activation threshold to create a probabilistic stimulation site model for each patient and hemisphere, where the probability of activation (ranging from 0 to 100 %) for each voxel was determined according to published activation thresholds (see Jergas et al. [31] and Åström et al. [32] for a more detailed description). Left-hemispherical stimulation site models were then non-linearly flipped to the right hemisphere since no laterality effects were assumed. Finally, the fronto-central cluster beta difference scores were assigned to their stimulation site and weighted by the respective activation probability. Probabilistic stimulation maps were then calculated as the voxel-wise weighted-average stimulation-dependent beta modulation and displayed over maps of thalamic nuclei [33]. To control for outliers, voxels with a cumulative probability of activation below 350 % were discarded. This criterion ensures that only voxels targeted by at least three distinct stimulation sites were considered (Fig. S2). Postoperative images were not available for three patients, limiting this analysis to a subset of seven patients with a total of 14 stimulation sites.

3. Results

Beta power in the fronto-central electrode cluster was significantly modulated by stimulation ($t_{55} = 6.45$, $p < .001$) with increased beta power during DBS-on. Also, a significant effect of repetition ($t_{55} = 2.37$, $p = .02$) indicated increased beta power for later repetitions (Fig. 1 a, b). Beta power EEG generators were located bilaterally in the midcingulate cortex (MCC), extending into the supplementary motor area (SMA)/premotor cortex (Fig. 1 c) with peak voxels in the MCC in both

Table 1
Demographic and clinical information. YGTSS: Yale Global Tic Severity Scale; PUTS: Premonitory Urge for Tic Scale; OCI-R: Obsessive Compulsive Inventory – Revised; WURS-K: Wender Utah Rating Scale; BDI-II: Beck Depression Inventory – II; VA/VL: Ventral Anterior/Ventral Lateral nuclei; CM-Voi: centromedian nucleus - nucleus ventrooralis internus.

	Age	Sex	YGTSS total	YGTSS tic	PUTS	OCI-R	WURS-K	BDI-II	DBS Target	Stimulation Settings
Patient 01	41	M	89	39	28	40	55	46	CM-Voi	0-, 1-, c+/8-, 9-, c+; 3.9 V; 180 ms; 70 Hz
Patient 02	31	M	20	10	18	1	9	0	CM-Voi	2-, 3-, c+/10-, 11-, c+; 2.1 V; 60 ms; 130 Hz
Patient 03	27	M	4	4	9	0	9	0	VA/VL	0-, 1-, c+/8-, 9-, c+; 5.2 V; 90 ms; 110 Hz
Patient 04	23	M	65	25	24	16	22	9	CM-Voi	0-, 1-, c+/8-, 9-, c+; 2.2 V; 150 ms; 70 Hz
Patient 05	30	F	31	11	28	20	28	19	CM-Voi	2-, 3-, c+/10-, 11-, c+; 4.6 V; 150 ms; 80 Hz
Patient 06	35	M	24	14	24	16	37	6	VA/VL	0-, 1-, c+/9-, 10-, c+; 2.4 V; 120 ms; 60 Hz
Patient 07	26	M	18	18	25	1	26	0	CM-Voi	1-, 2-, c+/9-, 10-, c+; 4.4 V; 210 ms; 90 Hz
Patient 09	34	M	48	28	19	16	44	47	VA/VL	1-, 2-, c+/9-, 10-, c+; 3.8 V; 90 ms; 120 Hz
Patient 10	25	M	16	6	24	34	24	3	CM-Voi	0-, 1-, c+/8-, 9-, c+; 3.8 V; 90 ms; 130 Hz
Patient 11	26	M	67	37	35	36	7	29	CM-Voi	0-, 1-, c+/8-, 9-, c+; 5 mA; 60 ms; 120 Hz

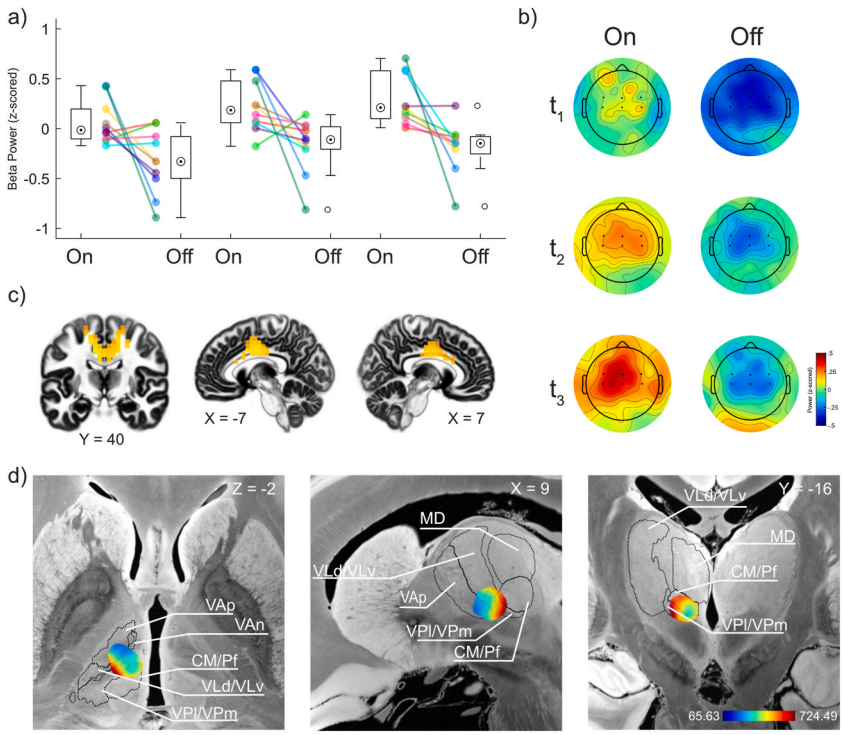

Fig. 1. Beta modulation. a) Boxplots represent fronto-central beta power. Colored lines show the beta modulation for individual patients. b) Topographies showing beta power on/off stimulation at all repetitions (t_1 – t_3). Black dots mark electrodes included in the fronto-central cluster used for statistical analyses. c) EEG generators determined with eLORETA showing peak modulation of beta power in bilateral midcingulate cortex. d) Probabilistic stimulation maps of beta modulation with a minimum of three overlapping stimulation sites. Borders of thalamic nuclei marked with black outlines. Hot colors indicate increased beta modulation and cold colors less beta modulation. CM/Pf: Centromedian/Parafascicular; MD: mediodorsal; VAn: ventral anterior nigral; VAp: ventral anterior pallidal; VLd/VLv: ventral lateral dorsal/ventral; VPl/VPm: ventral posterior lateral/medial. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

hemispheres (MNI: x = −15, y = 0, z = 40; x = 15, y = −10, z = 45). Correlations between symptoms scales and beta cluster difference scores (DBS-on minus DBS-off) were not significant ($p_{FDR} > .18$). Total electric energy delivered was not significantly related to beta modulation ($r = -0.50$, $p = .14$). Probabilistic stimulation maps indicate that within the thalamus, more pronounced MCC beta modulation was associated with a postero-lateral gradient, peaking in the ventral posterior nucleus (Fig. 1 d). The specificity of beta modulation was validated by post hoc analyses of the fronto-central electrode cluster in additional delta (2–4 Hz), theta (4–8 Hz) and alpha (8–12 Hz) frequency bands (Fig. S1). There was a significant decrease in delta power in response to stimulation ($t_{55} = -5.73$, $p < .001$). To investigate a potential interrelation of the stimulation effects in delta and beta power, an exploratory correlation was performed on power difference scores (DBS-on minus DBS-off). However, this correlation was not significant ($r = 0.01$, $p = .97$). Both theta ($t_{55} = 3.27$, $p = .001$) and alpha power ($t_{55} = 3.96$, $p < .001$) showed significant increases in subsequent repetitions. No EEG generators were detected for any of the additional frequency bands.

4. Discussion

Thalamic DBS increased fronto-central beta activity which was localized to a MCC generator. This modulation was varied over repetitions: there was a decline in beta activity when continuous stimulation was initially switched off, and beta power increased when DBS was switched on again beyond the level of chronic stimulation. The observed pattern argues for an acute perturbation of fronto-central beta power across short DBS-on/-off recordings. We also observed post hoc effects of increased power in successive repetitions for theta and alpha power. Delta power showed a marked decrease during active DBS stimulation, which appears to be independent of the stimulation effect observed in beta power. The probabilistic stimulation peak associated with beta modulation was localized to the ventral posterior nucleus, which is a first-order thalamic nucleus that relays ascending somatosensory signals, including pain and proprioception, to the cortex [34]. Source localization revealed the bilateral MCC as a major contributing site of fronto-central beta modulation. The MCC has been conceptualized to be involved in short latency movements in response to aversive stimuli [35], accordingly it has been considered as an important hub for both tic and premonitory urge networks [1,36]. This idea received recent support by a study that showed an association of the cingulate gyrus with tics induced by brain lesions and clinical efficacy of DBS [5]. The modulation of MCC activity through thalamic DBS is in line with perturbation of the cingulo-opercular resting state network (CON) as the centromedian thalamus and the CON are robustly connected [37]. The CON has also been associated with non-pathological urges like blinking, yawning and scratching [38]. Moreover, there is substantial overlap between the CON and functional MRI patterns that predict increased tic reductions induced by thalamic DBS [12].

A recent study has shown that there is a convergence zone between the CON and sensorimotor networks in the thalamus in close vicinity of the stimulation site associated with beta modulation reported here [39]. Expanding the idea of sensory-motor thalamus as a convergence zone of executive control and the motor system even further, recent findings show inter-effector regions in primary motor cortex, thought to integrate motor control and higher executive functions, that are robustly functionally connected to the centromedian, ventral lateral and ventral posterior nuclei, closely aligning with the peak of our probabilistic stimulation maps [40]. Strikingly, connectivity of those convergence zones to cortical regions was most pronounced in MCC and supplementary motor area, again matching our current results [40]. This new conceptualization might be highly relevant for understanding the effects

of thalamic DBS and for new insights regarding the pathophysiology of TS.

While remaining speculative at this point, the up-regulation of beta activity may induce a hypokinetic effect, conversely to down-regulation of excessive beta activity by effective treatment of Parkinson's disease [41]. This idea is in line with a Bayesian model of sensorimotor beta activity, where beta power encodes the confidence in the feedforward model of the motor system, with high beta power indicating stable movements and low beta power indicating changes in movement induced by sensory feedback including proprioception [42,43]. Therefore, increased beta activity in the MCC might reduce the influence of sensory perceptions (i.e., premonitory urges) on movements (i.e., tics).

There are certain limitations to the conclusions that can be drawn from this study. First, due to the rarity of DBS treatment in TS we were limited to a small sample size. Therefore, we employed a repeated-measures design to increase statistical power. Second, we recognize that eLORETA source localizations are low-resolution, and it is possible that a different source estimation algorithm may have produced different results. However, the eLORETA approach performs adequately in validation studies [44,45] and is reliable across measurements [46,47]. Third, we did not record video during the EEG making it difficult to determine how EEGs were influenced by movement artifacts (including tics). Fourth, we used clinically determined stimulation settings that varied considerably between patients. This precludes more fine-grained analyses in comparison with standardized stimulation settings that provide similar electric fields across patients. Fifth, the normalization of individual images into standard space can lead to inaccuracies in electrode positions, typically measuring less than 1 mm [48]. Sixth, the small sample size precluded a meaningful statistical analysis of the probabilistic stimulation maps.

Together, our results show modulation of a sensorimotor beta network that may be useful in the ongoing search for predictors of successful DBS treatment and mechanistic pathophysiological models of TS. Whether the reported effect is causally linked to DBS induced clinical efficacy needs to be addressed in future studies.

CRediT authorship contribution statement

Thomas Schüller: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Project administration, Validation, Visualization, Writing – original draft, Writing – review & editing. **Daniel Huys:** Conceptualization, Investigation, Supervision, Writing – review & editing. **Sina Kohl:** Conceptualization, Resources, Writing – review & editing. **Veerle Visser-Vandewalle:** Resources, Supervision, Writing – review & editing. **Till A. Dembek:** Methodology, Software, Validation, Writing – review & editing. **Jens Kuhn:** Conceptualization, Supervision, Writing – review & editing. **Juan Carlos Baldermann:** Conceptualization, Formal analysis, Investigation, Methodology, Supervision, Visualization, Writing – original draft, Writing – review & editing. **Ezra E. Smith:** Formal analysis, Investigation, Methodology, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2024.01.011.

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