NeuroImage: Clinical 31 (2021) 102746

Contents lists available at ScienceDirect

NeuroImage: Clinical

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

Performance monitoring in obsessive–compulsive disorder: Insights from internal capsule/nucleus accumbens deep brain stimulation

Thomas Schüller [a,*], Theo O.J. Gruendler [b], Ezra E. Smith [c], Juan Carlos Baldermann [a,d], Sina Kohl [a], Adrian G. Fischer [e,f], Veerle Visser-Vandewalle [g], Markus Ullsperger [e,h], Jens Kuhn [a,i], Daniel Huys [a]

[a] University of Cologne, Faculty of Medicine and University Hospital Cologne, Department of Psychiatry and Psychotherapy, Cologne, Germany
[b] Center for Military Mental Health, Military Hospital Berlin, Berlin, Germany
[c] Division of Translational Epidemiology, New York State Psychiatric Institute, New York, NY, USA
[d] University of Cologne, Faculty of Medicine and University Hospital Cologne, Department of Neurology, Cologne, Germany
[e] Otto von Guericke University, Center for Behavioral Brain Sciences, Magdeburg, Germany
[f] Freie Universität Berlin, Center for Cognitive Neuroscience, Berlin, Germany
[g] University of Cologne, Faculty of Medicine and University Hospital Cologne, Department of Stereotactic and Functional Neurosurgery, Cologne, Germany
[h] Otto von Guericke University, Institute of Psychology, Magdeburg, Germany
[i] Johanniter Hospital Oberhausen, Department of Psychiatry, Psychotherapy and Psychosomatic, Oberhausen, Germany

ARTICLE INFO

Keywords:
Obsessive-compulsive disorder
Deep brain stimulation
Internal capsule/nucleus accumbens
Performance monitoring
Theta frequency

ABSTRACT

Background: Symptoms of obsessive–compulsive disorder (OCD) are partly related to impaired cognitive control processes and theta modulations constitute an important electrophysiological marker for cognitive control processes such as signaling negative performance feedback in a fronto-striatal network. Deep brain stimulation (DBS) targeting the anterior limb of the internal capsule (ALIC)/nucleus accumbens (NAc) shows clinical efficacy in OCD, while the exact influence on the performance monitoring system remains largely unknown.
Methods: Seventeen patients with treatment-refractory OCD performed a probabilistic reinforcement learning task. Analyses were focused on 4–8 Hz (theta) power, intertrial phase coherence (ITPC) and debiased weighted Phase-Lag Index (dwPLI) in response to negative performance feedback. Combined EEG and local field potential (LFP) recordings were obtained shortly after DBS electrode implantation to investigate fronto-striatal network modulations. To assess the impact of clinically effective DBS on negative performance feedback modulations, EEG recordings were obtained pre-surgery and at follow-up with DBS on and off.
Results: Medial frontal cortex ITPC, striatal ITPC and striato-frontal dwPLI were increased following negative performance feedback. Decreased right-lateralized dwPLI was associated with pre-surgery symptom severity. ITPC was globally decreased during DBS-off.
Conclusion: We observed a theta phase coherence mediated fronto-striatal performance monitoring network. Within this network, decreased connectivity was related to increased OCD symptomatology, consistent with the idea of impaired cognitive control in OCD. While ALIC/NAc DBS decreased theta network activity globally, this effect was unrelated to clinical efficacy and performance monitoring.

1. Introduction

Obsessive-compulsive disorder (OCD) is characterized by distressing intrusive thoughts (obsessions) and often time consuming repetitive behaviors (compulsions). These symptoms are related to aberrant activity in cortico-basal ganglia-thalamo-cortical (CBGTC) loops (Milad and Rauch, 2012). A classic heuristic for functional imbalance in in OCD is the hyperactive/-connected (ventral) emotional loop and the hypoactive/-connected (dorsal) cognitive loop (van den Heuvel et al., 2016). The ventral loop is closely related to symptom severity via emotional processing (Harrison et al., 2009; Thorsen et al., 2018), while the cognitive loop relates to symptom severity via impaired cognitive

* Corresponding author at: 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).

https://doi.org/10.1016/j.nicl.2021.102746
Received 5 March 2021; Received in revised form 23 June 2021; Accepted 24 June 2021
Available online 29 June 2021

flexibility and goal directed behavior (Chamberlain et al., 2008; Vaghi et al., 2017). First line treatment of OCD by cognitive behavioral therapy and pharmacotherapy modulate these networks effectively, leading to symptom alleviation for a majority of patients (Hirschtritt et al., 2017; Norman et al., 2021; Shin et al., 2014). Yet, some patients do not sufficiently respond to first line treatments and remain severely affected. For those patients, deep brain stimulation (DBS) has emerged as a treatment option with symptom reduction and responder rates around 50% (Denys et al., 2020; Huys et al., 2019).

Clinically efficient DBS of the anterior limb of the internal capsule (ALIC) and nucleus accumbens (NAc) has been linked to modulation of fronto-striatal networks (Figee et al., 2013; Smith et al., 2019). Furthermore, the stimulation of fibers connecting the prefrontal cortex with the subthalamic nucleus and medial dorsal thalamus is closely associated with symptom reduction (Baldermann et al., 2019; Li et al., 2020). While ALIC/NAc DBS likely impacts both emotional and cognitive control processes, its mechanism of action remains incompletely understood (Fridgeirsson et al., 2020; Grassi et al., 2018). Performance monitoring is one feature of cognitive control that is especially relevant for OCD (Endrass and Ullsperger, 2014; Fontenelle et al., 2020; Ullsperger et al., 2014). Negative performance feedback robustly enhances power and phase consistency in theta frequencies (4 – 8 Hz) in medial-frontal brain regions (Cavanagh et al., 2010; Cohen et al., 2007). These findings have been extended to striatal local field potentials (LFP) that also show enhanced theta activity following negative feedback (Cohen et al., 2009b; 2009c). Furthermore, connectivity between medial frontal cortex (MFC) and the striatum is enhanced for cognitive control processes (Cohen, 2011; Cohen et al., 2009b; 2012;; Horschig et al., 2015). These findings support the notion that theta perturbations in a fronto-striatal network reflect the recruitment of cognitive control to adjust subsequent behavior (Cavanagh and Shackman, 2014; Cavanagh et al., 2012). Specifically, cortical activity in response to negative performance feedback seems to be diminished in OCD and related to symptom severity (Endrass et al., 2013; Gründler et al., 2009).

Here, we assessed OCD patients treated with ALIC/NAc DBS performing a reinforcement learning task. The goal of the current study was twofold: First, we aimed to further characterize the fronto-striatal cognitive control network. To this aim, combined EEG and LFP recordings were performed shortly after electrode implantation. We expected theta modulations in MFC, LFP and fronto-striatal connectivity to be increased for negative performance feedback and tested for correlations with symptom severity. Second, we investigated the influence of clinical effective DBS on the cognitive control network. To this aim, we recorded EEG before DBS surgery and at follow-up with DBS on and off. We hypothesized theta perturbations to be modulated by DBS.

2. Methods

2.1. Participants

Seventeen participants (10 female; mean age: 44 ± 14.16) with treatment-refractory OCD received ALIC/NAc DBS as part of a clinical trial (Huys et al., 2019). Participants received bilateral quadripolar leads (Model 3387 or 3389; Medtronic; Minneapolis, MN, USA) with the two most distal contacts [left: 0,1; right: 8,9] targeting the NAc and two most proximal contacts [left: 2,3; right: 10,11] located in the ALIC. All participants gave written informed consent before the start of the experiment. Participants were assessed shortly after surgery with combined recordings from externalized leads (i.e. LFP recordings) and EEG (n = 15). To investigate the effects of DBS, EEG was also recorded before surgery (n = 14), and at six (n = 15) and twelve month (n = 2) follow-up. All patients performed the DBS-on post-surgery recordings (n = 17). Three patients refused to discontinue stimulation, thus DBS-off recordings were collected in fourteen patients. The sequence of on/off recordings was counterbalanced pseudo-randomly. This study was registered in the German Clinical Trials Register (DRKS00005316), approved by the Ethics Committee of the Medical Faculty of the University of Cologne (No.12–261) and performed in accordance with the Declaration of Helsinki.

2.2. Reinforcement learning task

Participants had to learn reward probabilities of 12 different stimuli. They could either choose to gamble on a specific stimulus or avoid the gamble, while each choice required a respective button press. In each trial, if participants had chosen to gamble, they could win or lose 10 points. If they avoided the gamble, no points were won or lost, but the counterfactual feedback still indicated the outcome they would have obtained if they had decided to gamble. Therefore, information guiding behavioral adaptation was also provided by the counterfactual feedback. The main task consisted of four blocks in which three stimuli were alternated. Each stimulus was presented 30 times. Four stimuli had a high (70/80%), four stimuli had a neutral (50%) and four stimuli a low (20/30%) win probability. Between each trial a random jitter between 300 and 700 ms was presented. Thereafter, the stimulus was shown until the participant responded or for a maximum duration of 2000 ms. If participants failed to respond during this time they were instructed to speed up. After a response the feedback was presented for 750 ms. The task was administered using Presentation 16.3 (Neurobehavioral Systems, Inc., Berkeley, CA, USA). Responses were given via a response pad (RB-840, Cedrus, San Pedro, CA, USA).

2.3. EEG recording and analyses

All recordings were performed in a dimly lit, electrically and acoustically shielded chamber. All data were continuously recorded with a sampling rate of 5000 Hz (BrainAmp MR plus amplifiers; Brain Products, Gilching, Germany) and impedances below 10 kΩ.

For EEG recordings to assert the effect of DBS (DBS-EEG) we used 63 Ag/AgCl (EASYCAP, Herrsching, Germany) electrodes placed according to the 10–20 system standard. Data were filtered using a zero-phase finite impulse response filter with cut-off frequencies of 1 and 40 Hz (6 dB/Octave) and subjected to a frequency-domain Hampel filter to correct for residual DBS artifacts (Allen et al., 2010). Data were downsampled to 500 Hz and feedback-locked epochs created ± 1500 ms. Epochs were removed if 5 standard deviations (SD) of the joint data probability were exceeded (removed epochs: 11.28 ± 4.54 SD). Data were then subjected to extended infomax independent component analyses and resulting independent components (ICs) were submitted to the fully automated artifact classifier MARA (Winkler et al., 2011).

Intracranial recordings were obtained using the implanted electrodes (Model 3387 or 3389; Medtronic Neurological Division, Minneapolis, MN, USA) and custom-build adapters. Scalp electrodes were individually placed according to the extended 10–20 system, but avoided regions of scalp near surgical lesions. All scalp montages (number of electrodes: 17.1 ± 3.1 SD) included Fz, FCz and mastoid reference electrodes. Data were filtered using a zero-phase finite impulse response filter with cut-off frequencies of 1 and 40 Hz (6 dB/Octave) and downsampled to 500 Hz. All channels were re-referenced to linked mastoids. Feedback-locked epochs were created ±1500 ms and removed if 5 standard deviations (SD) of the joint data probability were exceeded (removed epochs: 6.46 ± 3.6 (SD)). Scalp electrode data was decomposed with extended infomax independent component analyses (ICA) and independent components representing ocular artifacts were removed. LFP data were subjected to a separate ICA analysis in order to perform a data-driven referencing scheme. Briefly, independent components (ICs) with broad spatial distribution, indicating the influence of non-local sources, were removed and remaining ICs back-projected. This process results in local time series with higher sensitivity and specificity compared to a bipolar reference, and mitigates the influence of referencing on LFPs (Michelmann et al., 2018).

For all data phase measures were computed by convolution of the

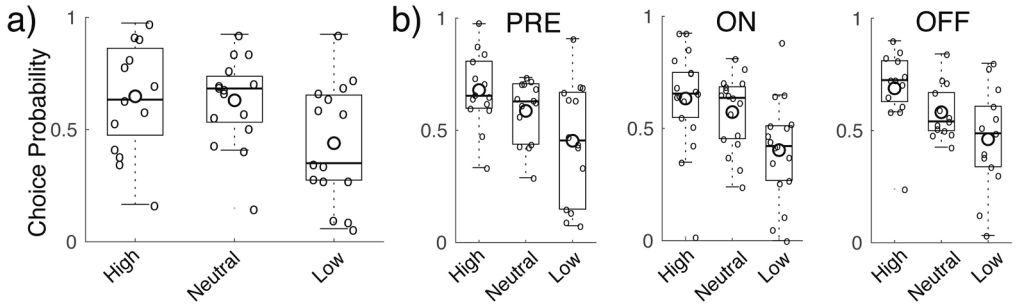

Fig. 1. Behavior. a) Proportion of gamble choices were adapted to the reward probability conditions (high = 70/80%; neutral = 50%; low = 20/30%) during the intracranial recordings. b) Proportion of gamble choices were adapted to different reward probabilities for pre-surgery, deep brain stimulation (DBS) on and off assessments. Behavior was not significantly modulated ($p > .55$) by DBS. Black circles denote individual participants' choices.

EEG signal with a series of complex Morlet wavelets between 1 and 50 Hz in 25 logarithmic steps and a wavelet width of 4 cycles (Cohen, 2014). For further analyses, feedback-locked epochs from −200 to 800 ms were created. Intertrial phase coherence (ITPC) was assessed reflecting the consistency of phase values over trials at each channel individually. ITPC can be considered as a phase-based functional configuration of a neural system to a relevant event (Cohen, 2014). Debiased weighted Phase-Lag Index (dwPLI) is a robust measure of phase synchronization in the presence of noise, volume conduction and sample size bias (Vinck et al., 2011). We employed dwPLI to measure connectivity between intracranial channels and a bipolar referenced Fz-FCz scalp channel (Smith et al., 2020b). The bipolar scalp channel was chosen to mitigate possible effects of volume conduction (Seeber et al., 2019). All data was baseline corrected to 200 ms pre-feedback.

DBS electrode location were reconstructed using the Lead-DBS toolbox (Horn and Kühn, 2015; Horn et al., 2019) following the pipeline described in Horn et al. (2017). Briefly, postoperative computer tomography scans were co-registered on preoperative magnetic resonance imaging using advanced normalization tools (ANTs; Avants et al., 2009). Subsequently, images were nonlinearly normalized into in

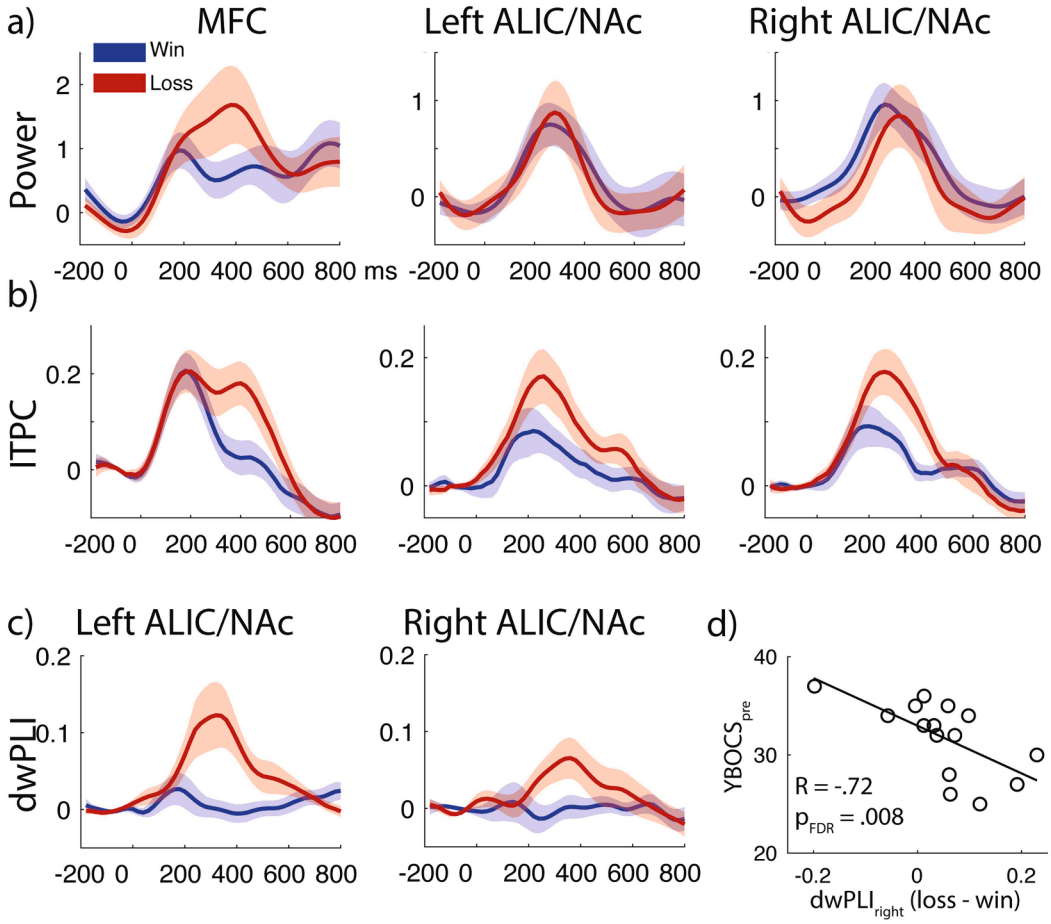

Fig. 2. Results of the intracranial recording session. Theta perturbations in response to performance feedback. a) Power perturbations were enhanced for negative feedback above medial frontal cortex (MFC) but not for striatal LFPs. b) Intertrial phase coherence (ITPC) was enhanced for negative feedback at MFC and at striatal LFPs. c) Debiased weighted phase-lag index (dwPLI) increases for negative feedback indicate increased connectivity between MFC and striatal LFPs. d) Correlation between right hemispheric dwPLI and pre-operative YBOCS scores. For statistical analyses quantifications see Fig. S2. Shaded areas represent standard error of the mean.

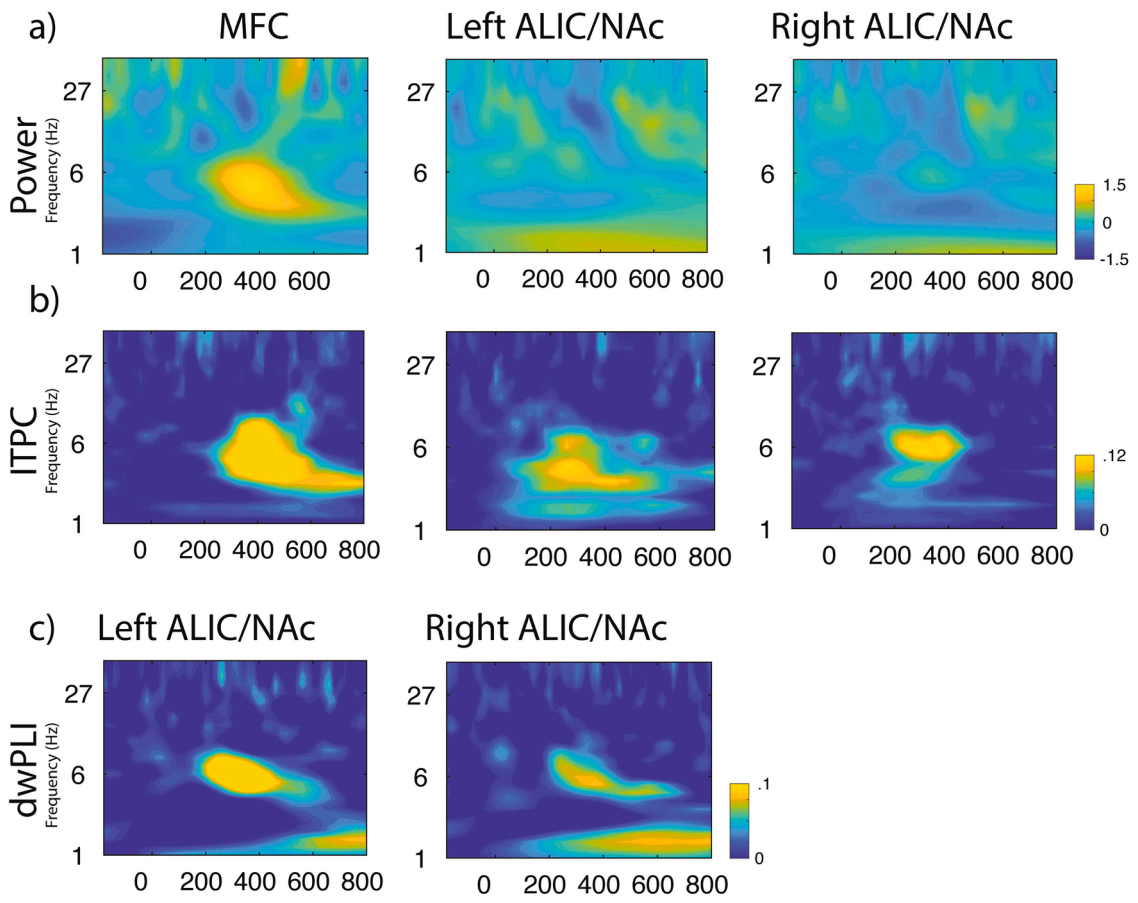

Fig. 3. Results of the intracranial recording session. Time-frequency (loss – win) plots are shown with logarithmically spaced frequencies (1 – 50 Hz). a) Theta power perturbations are apparent in MFC but not ALIC/NAc. b) Intertrial phase coherence (ITPC) shows modulation in the theta frequency at MFC and ALIC/NAc. c) Debiased weighted phase-lag index (dwPLI) shows theta and delta (1–4 Hz) frequency modulation.

standard space (ICBM 2009b NLIN, Asym) and DBS electrodes were reconstructed using the PaCER-algorithm (Husch et al., 2018). If required, electrodes were manually refined and corrected for post-operative brain shift.

2.4. Statistical analyses

All statistical analyses were performed using SPSS 25 (IBM Corp., New York, NY, USA). A time window from 200 to 500 ms (Fischer and Ullsperger, 2013) after feedback onset including frequencies from 4 to 8 Hz were chosen for statistical analyses. Electrode Fz and intracranial channels bordering NAc and ALIC (also see 2.1; left hemisphere: 15 participants channel 2; right hemisphere: 14 participants channel 10, one participant channel 9) were chosen for further analyses. Only trials where the participants had gambled and therefore won or lost points were included in the analyses. All variables were tested for normal distribution with the Kolmogorov-Smirnov test ($p > .05$).

Intracranial LFP data were analyzed using repeated-measures ANOVAs including the factors valence (win, loss) and hemisphere (right, left). Fz data was analyzed using a two-tailed one-sample *t*-test. Behavioral data was analyzed with repeated-measures ANOVA including the factor reward probability (high, neutral, low).

DBS-EEG data were analyzed using mixed-effect models with valence (win, loss) and stimulation (pre, on, off) as fixed factors. Behavioral data were analyzed using a mixed-effect model with reward probability (high, neutral, low) and stimulation (pre, on, off) as fixed factors. Interactions were included in all models. Planned comparisons were performed for pre/on, pre/off and on/off ($p < .05$).

To test for associations of task related modulations (negative – positive feedback theta) with pre-surgery symptom severity scores ($YBOCS_{pre}$) indicating baseline symptom severity and the 12-month follow-up percentage difference score ($YBOCS_{diff}$) indicating DBS induced symptom change. To correct for multiple comparisons p-values were corrected using false discovery rate (FDR; Benjamini and Hochberg, 1995).

3. Results

3.1. Intracranial recording session

Choices were significantly modulated by reward probability indicating adaptive behavior ($F_{2,28} = 5.02$, $p = .01$; Fig. 1a; Fig. S1a).

Theta power was increased for negative performance feedback at MFC ($t_{14} = 2.15$, $p = .04$; Fig. 2a) but not at the intracranial electrodes (all $p > .31$). In contrast, ITPC was increased for negative feedback both at MFC ($t_{14} = 4.33$, $p < .001$; Fig. 2b, Fig. 3b) and at the intracranial electrodes ($F_{1,14} = 18.26$, $p = .001$; Fig. 2b, Fig. 3b). The effect of hemisphere ($p = .84$) and the valence × hemisphere interaction ($p = .69$) were not significant. We also observed increased connectivity following negative feedback ($F_{1,14} = 6.45$, $p = .02$; Fig. 2c, Fig. 3c), with increased connectivity values in the left hemisphere ($F_{1,14} = 11.26$, $p = .005$) but no significant interaction ($p = .24$). Furthermore, lower dwPLI connectivity between sensors over MFC and right ALIC/NAc electrodes was related to more pre-DBS OCD symptoms ($YBOCS_{pre}$, $R = -0.72$, $p_{FDR} = 0.008$; Fig. 2d). This finding was robust when removing the participant with considerable more connectivity for positive feedback ($R = -0.66$, $p_{FDR} = 0.03$). There were no further associations between dwPLI, ITPC and power with $YBOCS_{pre}$ (all $p_{FDR} > 0.16$) or $YBOCS_{diff}$ (all $p_{FDR} >$

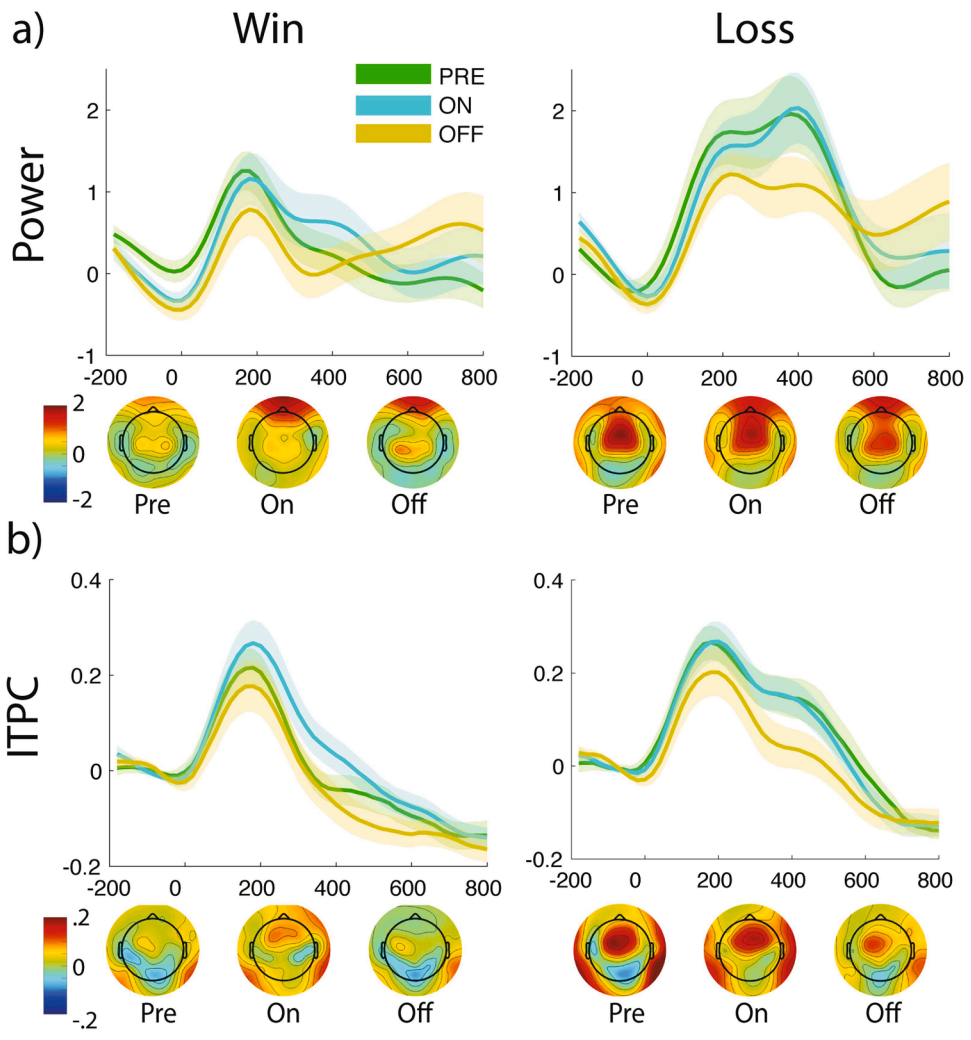

Fig. 4. Deep brain stimulation recording sessions. Theta perturbations in response to positive (left) and negative (right) performance feedback and corresponding topographies before electrode implantation (pre), with ongoing stimulation (on) and with discontinued stimulation (off). a) Theta power modulation were increased for negative feedback but not altered by DBS. b) Theta intertrial phase coherence (ITPC) was increased for negative feedback. ITPC was diminished for DBS-off affecting both positive and negative feedback modulations. For statistical analyses quantifications see Fig. S3. Topographies show mean activation 200 – 500 ms. Shaded areas represent standard error of the mean.

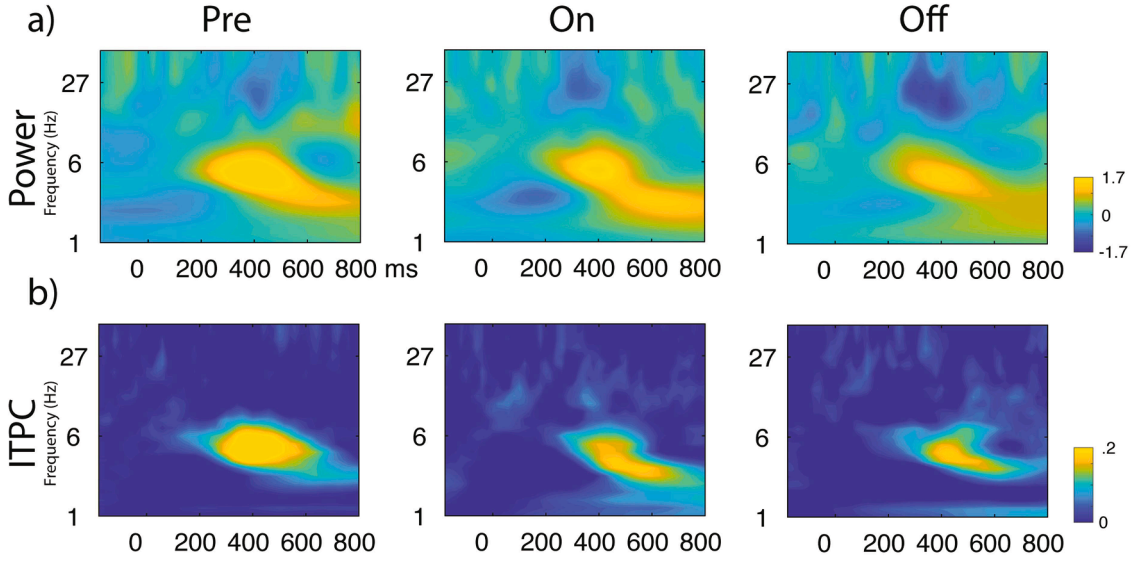

Fig. 5. Deep brain stimulation recording sessions. Time-frequency (loss – win) plots are shown with logarithmically spaced frequencies (1 – 50 Hz). a) Theta power perturbations are apparent in all sessions b) Intertrial phase coherence (ITPC) also shows theta frequency modulations in all sessions.

0.64).

3.2. Deep brain stimulation recording sessions

Participants' choices reflected the different reward probabilities indicating adaptive behavior ($F = 14.91$, $p < .001$; Fig. 1b) with no significant effect of stimulation (main effect: $F = 0.59$, $p = .55$; interaction: $F = 0.08$, $p = .98$).

Theta power was increased for negative feedback ($F = 17.1$, $p < .001$; Fig. 4a, Fig. 5a) but not modulated by stimulation (main effect: $F = 1.61$, $p = .2$; interaction: $F = 0.26$, $p = .76$). Furthermore, ITPC was increased for negative feedback ($F = 11.26$, $p < .001$; Fig. 4b, Fig. 5b) and reduced during DBS-off ($F = 3.28$, $p = .04$). Importantly, the DBS effect was not specific to negative feedback modulation (interaction: $F = 0.16$, $p = .63$). Planned comparisons revealed a significant difference between on and off stimulation (0.09 mean difference (MD), 0.03 standard deviation (SD), $p = .01$) but not between pre and on (−0.03 MD, 0.03 SD, $p = .37$) or pre and off (0.06 MD, 0.03 SD, $p = .11$). We observed no significant correlations between theta modulations in phase and power (on – off) and symptom severity or DBS-induced symptom change ($p_{FDR} > 0.44$).

4. Discussion

We examined theta modulations related to negative performance feedback in OCD patients treated with ALIC/NAc DBS. Our findings corroborate the notion of a theta-mediated fronto-striatal cognitive control network and findings are in line with previous studies showing increased MFC and striatal activity in response to negative performance feedback (Cavanagh et al., 2010; Cohen et al., 2009c; 2009a). Our findings suggest that theta phase perturbations are an important metric of the performance monitoring network showing local modulations in the striatum and MFC, and also connectivity between both structures. Furthermore, weaker connectivity (for cortical specificity of this finding see Fig.S4) for negative performance feedback was related to increased pre-surgery OCD symptomatology. This finding may be specifically related to a hypoactive cognitive loop in OCD transmitting a reduced signal to implement cognitive control, which may manifest in compulsive behavior (e.g. checking if the door is locked). This cognitive deficit might become most apparent in ambiguous situations in the training stages of reinforcement learning tasks (Remijnse et al., 2006; 2009). Nonetheless, we would like to point out that correlations in small samples have to be regarded with caution and no causality assumptions are implied.

Moreover, there is also evidence for hyperactive performance monitoring in OCD. The error-related negativity is elicited by erroneous responses in speeded reaction time task and is consistently increased in OCD (Endrass and Ullsperger, 2014). In this regard, increased pre-surgery symptoms in OCD were related to fronto–striatal resting state delta (1 – 4 Hz) connectivity, possibly linked to increased internal monitoring (Smith et al., 2020a; 2020b). Both hyper- and hypoactive performance monitoring processes likely add to the symptomatology of OCD. Hyperactive performance monitoring produces a sense of incompleteness (i.e. just-not-right feeling) while hypoactive performance monitoring fails to provide a sufficient signal to redirect behavior in a goal-directed manner (Gründler et al., 2009).

Regarding the influence of ALIC/NAc DBS on performance monitoring we observed no alteration of adaptive choice behavior. Theta phase consistency was diminished during DBS-off compared to DBS-on but did not alter the theta valence signal specifically. Also, the modulation by DBS was not related to symptom severity or symptom change. In contrast, clinical efficacy of ALIC/NAc DBS in OCD is associated by increased resting state delta activity in MFC (Smith et al., 2019) and cognitive control improvements and subsequently modulated theta activity are linked to alleviation of depressive symptoms (Widge et al., 2019). Furthermore, modulation of frontal low-frequency activity has been found to be specific for symptom-provoking stimuli (Figee et al., 2013). Here, we found no evidence that the processing of negative performance feedback is specifically altered by clinical effective ALIC/NAc DBS. No definite conclusions can be drawn as to whether the general theta modulation by DBS was related to an upregulation by active DBS or down-regulation by DBS discontinuation in comparison to the pre-surgical recordings. Nevertheless, great caution is needed when interpreting findings without pre-surgical recordings as our results could have easily been mistaken for upregulation of theta phase consistency as a result of DBS.

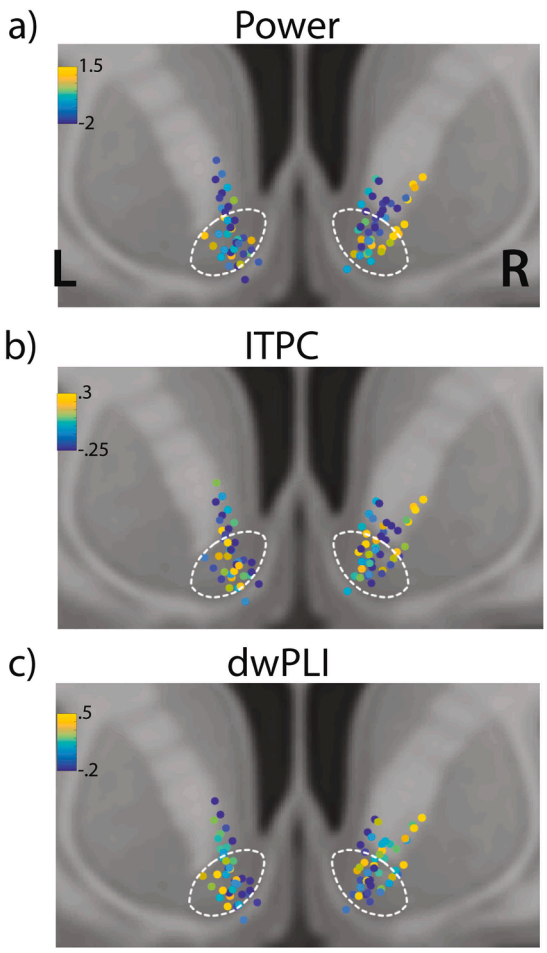

Fig. 6. Spatial distribution of intracranial electrodes. Point clouds represent individual intracranial electrodes color-coded by electrophysiological measures. a) Theta power b) Intertrial phase coherence. c) Debiased weighted phase-lag index. White dashed lines denote the nucleus accumbens.

Importantly, several limitations of the study have to be acknowledged. First, the number of available participants limits statistical power and also the generalizability of the findings. Studies with larger sample sizes are warranted to confirm our negative findings, i.e. no behavioral effect of ALIC/NAc DBS. Second, it is important to note that the generalizability of our results to a healthy population is subject to uncertainty. While our results are in line with a fronto-striatal performance monitoring network that is not specific to OCD patients, we cannot preclude a systematic influence of the disorder. Third, the task included counterfactual feedback that was not analyzed in the current study. Counterfactual feedback differs from factual feedback in a meaningful way since both factual wins and counterfactual losses indicate a favorable choice (factual losses and counterfactual wins indicate an unfavorable choice) while both factual and counterfactual wins indicate a positive stimulus value update (factual and counterfactual losses indicate a negative stimulus value update). Fourth, we diverged from the standard bipolar referencing approach, which may limit comparability across studies.

While referencing by subtraction of independent components may seem counterintuitive, both bipolar referencing and independent components can essentially be regarded as spatial filters. The advantage of the ICA approach is the lack of a priori assumptions about signal and noise distributions (Michelmann et al., 2018). This might be particularly beneficial considering the variability of electrode orientation compared to recordings from more narrowly defined DBS targets such as the subthalamic nucleus. Importantly, intraindividual variance across intracranial electrodes argues for maintained spatial specificity (Fig. 6). Nevertheless, the relatively sparse array of electrodes precludes the precise localization of the sources.

In conclusion, we observed a fronto-striatal performance monitoring network mediated by theta phase coherence. This network does not seem to be functionally affected by clinically effective DBS as evident by unaltered behavior and non-specific theta modulation. Additionally, decreased fronto-striatal connectivity in response to negative performance feedback was related to OCD symptom severity.

CRediT authorship contribution statement

Thomas Schüller: Formal analysis, Investigation, Methodology, Data curation, Visualization, Writing - original draft. **Theo O.J. Gruendler:** Conceptualization, Investigation, Software, Writing - review & editing. **Ezra E. Smith:** Formal analysis, Methodology, Software, Writing - review & editing. **Juan Carlos Baldermann:** Investigation, Data curation, Visualization, Writing - review & editing. **Sina Kohl:** Investigation, Data curation, Writing - review & editing. **Adrian G. Fischer:** Methodology, Software, Writing - review & editing. **Veerle Visser-Vandewalle:** Supervision, Resources, Writing - review & editing. **Markus Ullsperger:** Conceptualization, Funding acquisition, Writing - review & editing. **Jens Kuhn:** Conceptualization, Supervision, Funding acquisition, Resources, Writing - review & editing. **Daniel Huys:** Project administration, Supervision, Resources, 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.

Acknowledgements

This study was funded by the German Research Foundation (KFO-219, KU 2665/1-2; Project-ID 431549029 – SFB 1451). We would like to thank Elena Sildatke for her help with data acquisition.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2021.102746.

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