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Desynchronization of temporal lobe theta-band activity during effective anterior thalamus deep brain stimulation in epilepsy

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ABSTRACT

Background: Bilateral cyclic high frequency deep brain stimulation (DBS) of the anterior nucleus of the thalamus (ANT) reduces the seizure count in a subset of patients with epilepsy. Detecting stimulation-induced alterations of pathological brain networks may help to unravel the underlying physiological mechanisms related to effective stimulation delivery and optimize target engagement.

Methods: We acquired 64-channel electroencephalography during ten ANT-DBS cycles (145 Hz, 90 μs, 3–5 V) of 1-min ON followed by 5-min OFF stimulation to detect changes in cortical activity related to seizure reduction. The study included 14 subjects (three responders, four non-responders, and seven healthy controls). Mixed-model ANOVA tests were used to compare differences in cortical activity between subgroups both ON and OFF stimulation, while investigating frequency-specific effects for the seizure onset zones.

Results: ANT-DBS had a widespread desynchronization effect on cortical theta and alpha band activity in responders, but not in non-responders. Time domain analysis showed that the stimulation induced reduction in theta-band activity was temporally linked to the stimulation period. Moreover, stimulation induced theta-band desynchronization in the temporal lobe channels correlated significantly with the therapeutic response. Responders to ANT-DBS and healthy-controls had an overall lower level of theta-band activity compared to non-responders.

Conclusion: This study demonstrated that temporal lobe channel theta-band desynchronization may be a predictive physiological hallmark of therapeutic response to ANT-DBS and may be used to improve the functional precision of this intervention by verifying implantation sites, calibrating stimulation contacts, and possibly identifying treatment responders prior to implantation.

1. Introduction

Epilepsy is a well-described neurological condition which affects individuals of all ages and approximately 1% of the global population (Kwan and Brodie, 2000). Seizures originating in the temporal lobe(s) are most common in adults (Téllez-Zenteno and Hernández-Ronquillo, 2012). While antiepileptic drugs, which primarily work through the enhancement of inhibitory neurotransmission and attenuation of excitatory transmission (Löscher et al., 2013; Vajda and Eadie, 2014) can be efficacious, up to 30% of patients continue to experience recurrent seizures despite optimal medical therapy (Halpern et al., 2008; Kwan and Brodie, 2000). For these patients, bilateral deep brain stimulation (DBS) of the thalamic anterior nuclei (ANT) is a therapeutic option (Fisher et al., 2010; Laxpati et al., 2014; Lim et al., 2007; Salanova et al., 2015; Sitnikov et al., 2018). The clinical efficacy of ANT-DBS was systematically evaluated in the "Stimulation of the Anterior Nucleus of the Thalamus for

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Epilepsy" (SANTE) study and revealed median seizure reduction rates of 40.4% in the in the double-blinded phase 3–4 months after surgery (Fisher et al., 2010). Moreover, it was determined that treatment efficacy was greatest in patients with seizures originating in one or both temporal regions. During the unblinded phase, the authors reported that patients experienced a median seizure reduction rate of 56%, and that 54% of the patient population had seizure reductions of at least 50% (at 2 years postoperatively). However, there is still a lack of a reliable functional marker for therapy response (Son et al., 2016; Sweeney-Reed et al., 2016). While the therapeutic potential of ANT-DBS is promising, the efficacy is widely variable. As such, further efforts are warranted in order to understand the variability in clinical benefit, and in order to define functional markers/readouts. Furthermore, the therapeutic mechanisms of ANT-DBS are not well-understood (Fisher and Velasco, 2014). The selection of ANT as a target for DBS was justified by its central connectivity and possible role in propagation of epileptiform activity (Wyckhuys et al., 2009). Several studies in rat models have shown that bilateral high-frequency stimulation or lesions of the ANT reduced seizure frequency (Child and Benarroch, 2013; Hamani et al., 2004; Mirski et al., 1997; Takebayashi et al., 2007). As such, it was hypothesized that ANT stimulation or lesions may work to suppress the amplification, propagation, and/or synchronization of seizure activity (Takebayashi et al., 2007). Animal studies at the cellular/microcircuit level have suggested that ANT stimulation may work to restore the balance between excitatory and inhibitory neurotransmission, with findings of increased levels of GABA in the hippocampus in response to ANT-DBS (Child and Benarroch, 2013; Liu et al., 2012; Shi et al., 2015). At the subcortical network level, one study in humans with multiple intracerebral depth electrodes has demonstrated that high-frequency ANT stimulation decreased electrical activity over a broad frequency range, and reduced interictal spikes in the hippocampus (Yu et al., 2018), while a single case study demonstrated that ANT-DBS reduced the power of hippocampal delta and theta activity (Zumsteg et al., 2006). However, the synergistic use of human brain mapping techniques and ANT-DBS is scares.

Detecting stimulation-induced alterations of pathological brain networks may unravel the underlying physiological mechanisms related to effective stimulation delivery and optimize target engagement. To the best of our knowledge, this is the first study to assess network/macrocircuit effects of ANT-DBS at the level of cortical oscillatory networks related to epilepsy and therapy response. The study of the cortical mechanisms of ANT-DBS in this context may help to explain the variability in therapeutic efficacy, to refine patient selection criteria, and to define functional therapeutic markers which can guide electrode placements and the calibration of stimulation parameters.

2. Methods

2.1. Patients

This study included n = 14 individuals, seven of whom were patients who had undergone ANT-DBS surgeries ($n_{patients} = 7$) and an additional seven who were healthy control subjects ($n_{controls} = 7$); all provided written informed consent. All patients had a prolonged history of epilepsy and were refractory to conventional pharmacological therapy. Patient demographics are presented in Table 1. All patients had undergone bilateral, image-guided implantations of Medtronic 3389 leads (Medtronic, MN, USA) into the ANT using an extra-ventricular trajectory (Fig. 1; postoperative images for all patients are available in supplementary material). Stimulation parameters followed the SANTE protocol (145 Hz, 90 μs and 3–5 V; Fisher et al., 2010). Patients kept a seizure diary before and after surgery counting the number of seizures they experienced. The clinical benefit was quantified by counting the number of seizures they experienced from the beginning of the second month postoperatively (when the stimulation was turned on) to the end of the fifth month (four-month period) in comparison to the mean preoperative status. The first postoperative month was excluded due to the possibility of micro-lesion effects (Lane et al., 2017).

Table 1
Patient demographics.

ID	Age	EEG Seizure onset foci	Seizure history (years)	Avg. seizures/ month (before DBS)	Median seizure reduction rate in % (4 months)	Maximum likelihood estimation
1	51	Right temporo-parieto-occipital	Childhood	28	5.5	non-responder
2	22	Multifocal Left > Right	5	13	8	non-responder
3	45	Left temporal	10	7	71	responder
4	48	Bitemporal, independent	5	80	42	responder
5	26	Multifocal Left > Right	16	174	25	non-responder
6[a]	31	Bitemporal, independent	4	15	77	responder
7	25	Right > Left temporo-parieto-occipital	17	57	−3.5	non-responder

[a] Patient with bilateral periventricular heterotopia.

Out of the seven subjects of this study, two could clearly be identified as responders (seizure reduction rates: 77% and 71%) and three as non-responders (5.5%, 8% and −3.5%). The two remaining subjects (seizure reduction rates: 42% and 25%) were classified based on whether they are more likely to belong to the responder (mean seizure reduction rate = 74%) or the non-responder (mean seizure reduction rate = 3.33%) clusters within our cohort, i.e. by a maximum likelihood approach. Assuming a Gaussian distribution with uniform variance for responder and non-responder populations, it was determined that the patient with a seizure reduction rate of 42% was a responder and the patient with a seizure reduction rate of 25% was a non-responder.

In total, three patients were classified as responders (nresponders = 3) and four as non-responders (nnon-responders = 4). Two of the responders presented with bilateral mesial temporal lobe epilepsy and the third responder presented with temporal lobe type seizures due to bilateral periventricular heterotopia, whereas the non-responders all presented with extratemporal or multifocal seizure origins. Some of the patients were part of the European registration study (Lehtimäki et al., 2018). This study was approved by the ethics committee of the Medical Faculty Tübingen.

2.2. Data acquisition

64-channel resting-state electroencephalography (EEG) data were collected from each subject via two synchronized BrainAmp DC Amplifiers (Brain Products, Munich, Germany) and sampled at ≥1000 Hz. The EEG electrodes were placed according to the extended 10–20 system. For the duration of the examination, the subjects and patients alike were instructed to lay flat, but awake, on a bed with their eyes closed. The experimenter a) periodically confirmed wakefulness during the experiment and b) asked the patients after the measurements whether they had fallen asleep, which was denied by all of them. Furthermore, the qualified examiner was always present and verified that none of the patients experienced a seizure during the recording sessions. In patients, recordings encompassed 10 stimulation trials at 140 Hz, 90 μs and 3–5 V. Each trial consisted of a period of 5-min OFF stimulation, followed by 1-min ON stimulation. This paradigm (stimulation parameters and periodic stimulation delivery) is based on the chronic stimulation delivery paradigm of the SANTE study. Stimulation was always delivered bipolarly using the two dorsal-most electrode contacts. In controls, only resting-

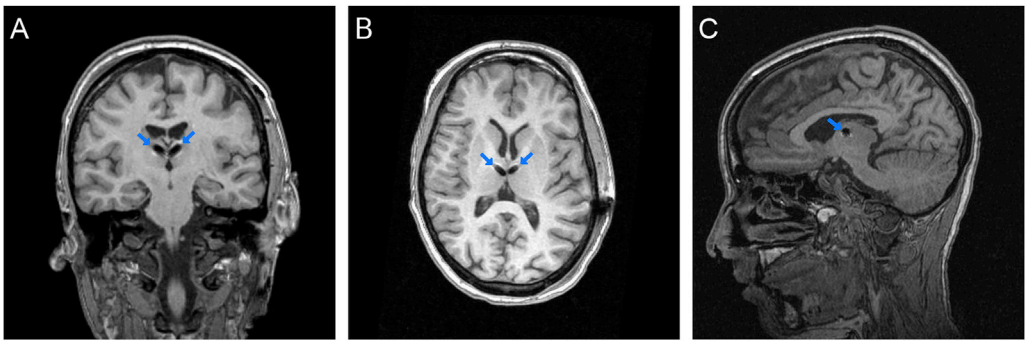

Fig. 1. Postoperative MRI images from a representative patient. Representative coronal (A), axial (B), and sagittal (C) MRI images from a single patient demonstrating lead placement (highlighted by arrows).

state data were acquired.

2.3. Pre-processing

The EEG data were visually inspected for large scale artifacts (e.g. movement artifacts). Bad channels were removed from the analysis. The data were low-pass filtered (45 Hz) for anti-aliasing using a finite-impulse-response filter with a high suppression factor. The ripple pass-band suppression was chosen as 10e-5 and the stopband suppression as 10e-7. Subsequently, the data were down-sampled to 100 Hz, common average re-referenced and cut into 40-s epochs. ON data were taken from the central 40s of a stimulation period, while OFF (resting-state) data were selected as the period from 50 to 10 s prior to stimulation onset. Each epoch consisted of 4000 samples. Visual inspection was applied to detect bad epochs (i.e. corrupt channels or moved EEG cables). These were excluded from any further analysis. Each epoch was high-pass filtered (2 Hz) to remove movement artifacts. Afterwards, a power spectrum density was calculated using Welch's method with a Hamming window, 1 Hz bins, 50% overlap, and 1s segment size. To analyze frequency-specific power in each block, the bins of each frequency band were summed up. The analyzed frequency bands included the theta (4–7 Hz), alpha (8–12 Hz), beta (13–32 Hz) and low gamma (33–45 Hz) bands. Furthermore, the power was calculated for smaller 2 Hz-wide sub-bands, starting from 4 to 6 Hz, 5–7 Hz and so on, up to 10–12 Hz (as theta and alpha were identified as frequency bands of interest during later steps of the analysis).

2.4. Effects of stimulation and responsiveness on cortical activity

Since this study was exploratory, the first objective was to identify the presence of any effects related to the response-type (responder, non-responder), stimulation-condition (ON, OFF), and the interaction of these factors. Thus, the two-way ANOVA model represents the most statistically appropriate method, in which we furthermore used a rather conservative multiple comparisons correction (Bonferroni-Holm method). Beyond the initial exploratory results, the subsequent analyses were discovery-driven, and performed in a systematic manner.

More specifically, a mixed-model two-way ANOVA was used to identify frequency bands of interest on the patient group level in the theta, alpha, beta and lower gamma frequency-bands, and subsequently to identify sub-bands of interest. Frequency bands were identified as being of interest if the ANOVA revealed a significant effect within a particular frequency band, after multiple comparison correction (Bonferroni-Holm). The two fixed factors (main effects) of the ANOVA-model were stimulation-condition (ON/OFF; within subject factor) and response-type (responder/non-responder; between-subjects factor), and subject-ID was included as a random factor (as each subject was measured repeatedly and a general offset between subjects was expected; random-intercept per subject). The gradient of the main effects determined their respective effect (increasing/decreasing). The interaction between the two fixed factors was also modeled in the ANOVA. The stimulation-condition main effect was used to model the measured change in cortical power (i.e. synchronization or desynchronization) when DBS was ON compared to OFF, irrespective of response-type. The response-type main effect was used to model the difference in cortical power between responders and non-responders, irrespective of the stimulation-condition. The interaction effect was used to model a conditional change in cortical activity depending on both main effects (for example a larger effect size of stimulation-condition in responders compared to a smaller effect size in non-responders). Information regarding interpretation of ANOVA results is summarized in supplementary fig. 1.

In the two-way ANOVA, the presence of an interaction effect between stimulation-condition and response-type may be the result of (1) a cortical power change in responders (but not non-responders) due to a change in the stimulation-condition, (2) a cortical power change in non-responders (but not responders) due to a change in the stimulation-condition, (3) a difference in cortical power during stimulation ON (but not OFF) due to differences between responders and non-responders (4) a difference in cortical power during stimulation OFF (but not ON) due to differences between responders and non-responders. Since the mixed-model two-way ANOVA only determines the presence or absence of an interaction effect, subsequent one-way ANOVAs were performed in order to determine potential causes of this interaction. As such, four subsequent mixed-model one-way ANOVA analyses were computed to determine (i) the main effect of stimulation-condition in responders only, (ii) the main effect of stimulation-condition in non-responders only, (iii) the main effect of response-type during stimulation ON, and (iv) the main effect of response-type during stimulation OFF. For all ANOVA analyses, in order to compensate for the type-1 error inflation, multiple comparison corrections were applied to correct the significance threshold using the Bonferroni-Holm method with a hypothesis count of 63, which was derived based on the number of non-overlapping frequency bands investigated (the theta and alpha sub-bands 4–6 Hz; 5–7 Hz; 6–8 Hz; 7–9 Hz; 8–10 Hz; 9–11 Hz; 10–12 Hz; and broad-band beta (13–32 Hz) and gamma (33–45 Hz), which were also assessed in preliminary analyses, i.e. 9 in total) and the number of brain regions (temporal left, temporal right, frontal left, frontal right, parietal left, parietal right, occipital; i.e. 7 in total).

2.5. Stimulation and seizure reduction

After determining frequency bands of interest by using the aforementioned ANOVA analyses, we investigated whether stimulation-induced changes of these frequencies were of clinical relevance. For this purpose, we defined cortical regions of interest based on the seizure-onset zones of the patients, i.e., effects on the temporal lobe channels (FT7, T7, TP7, FT8, T8, TP8) and widespread areas were investigated. Since Pearson's definition assumes a linear relationship, the Spearman correlation coefficient was used for this estimation as it does not assume a specific shape of the investigated relationship. The correlation analyses

(Fig. 3) indeed confirmed that decreases in theta activity correlated with seizure reductions (this finding is expanded upon in the results section, but mentioned here since it informed the subsequent analyses).

2.6. Theta activity differences in temporal lobe channels

In regions where spatio-spectrally localized clinical relevance was found (from above correlations), the DBS induced cortical-activity changes were investigated further. At the group level, cortical-activity was investigated for five individual groups; responders and non-responders in both stimulation ON and stimulation OFF, and healthy controls. Since multiple measurements were utilized for each patient (i.e. data from 10 trials for each patient, from multiple EEG channels), one-way ANOVA analyses were performed to compare activity between these groups, using subject-id and channel-id as random factors. At the single subject level, the same was done, except using only channel-id as a random factor. Subjects (subject-id) were modeled as a random factor due to multiple measurements within subjects; the same reasoning applies to EEG channels (channel-id) within regions since neighboring EEG channels carry mutual information.

2.7. Time-domain analysis of identified effects in single subjects

In order to investigate the temporal relationship between the onset of DBS and the incurred changes in cortical activity, the complete recording sessions were filtered in accordance to spatio-spectral regions of interest. The complete recording sessions were windowed (1s window size; 10 ms step width) and each segment was transformed into the frequency domain using Welch's method (Hanning window, 0.5 s fast Fourier transform window size, and 50% overlap). Afterwards, the amount of relative theta-activity was calculated by dividing the sum of the theta-band bins (4–6 Hz) by the sum of all frequency bins (2–45 Hz). In order to reduce temporal smearing, post-process smoothing was limited to a rolling mean filter with a window width of 1000 samples.

3. Results

3.1. Effects of stimulation and responsiveness on cortical activity

Stimulation induced a significant desynchronization in the temporal lobe channels area in responders only. The mixed-model two-way ANOVA revealed significant main effects of response-type on cortical activity in the theta-band (i.e. there were significant differences in cortical activity between responders and non-responders, regardless of whether stimulation was ON or OFF). The theta-band power was overall lower (desynchronized; negative gradient) in responders compared to non-responders, without spatial specificity. There were no significant effects of stimulation when responders and non-responders were pooled together. Furthermore, the two-way ANOVA analyses also revealed significant interaction effects between stimulation-condition and response-type, which were significant in the alpha-band after multiple comparison correction (meaning that changes of cortical activity were dependent on both stimulation-condition and response-type simultaneously.

This observation implicates that either the effect of stimulation on cortical activity was dependent on whether the individual was a responder and non-responder, or that the cortical differences between responders and non-responders were dependent upon whether stimulation was ON or OFF. In order to discern which of these phenomena was true, and to investigate these effects in greater detail, subsequent one-way ANOVA analyses were performed for the theta and alpha frequency bands (frequency bands of interest based on the two-way ANOVA results). The subsequent one-way ANOVA analyses were done for 2 Hz wide sub-bands of the theta and alpha frequency bands.

With regards to the effects of stimulation-condition, the one-way ANOVA analyses did not reveal significant main effects of stimulation in the non-responders' sub-group (i.e. cortical activity did not change when stimulation was changed from OFF to ON in non-responders; Fig. 2A). However, the one-way ANOVA analyses did reveal significant main effects of stimulation-condition in responders, which were present without spatial specificity in the theta and alpha bands (Fig. 2A). The negative gradient is suggestive of a desynchronization of activity in these frequency bands (i.e. cortical theta and alpha-band activity were desynchronized when stimulation was changed from OFF to ON in responders). Taken together, these analyses reveal ANT-DBS desynchronized theta and alpha-band activity in responders, but had no effect on cortical activity in non-responders; these differences between responders and non-responders were the reason for the interaction effect in the previous two-way ANOVA analyses.

With regard to the effects of response-type, the one-way ANOVA analyses revealed significant main effects of response-type both when stimulation was ON and when it was OFF, localized to the theta-frequency band (Fig. 2B). Taken together, these analyses suggest that there was an overall lower level the theta-band activity in responders compared to non-responders both when stimulation was ON and OFF; which validates the significant main effect of response-type in the previous two-way ANOVA analyses. Detailed statistical figures for one-way ANOVAs are available in Fig. 2.

3.2. Stimulation and seizure reduction

Seizure reduction correlated with DBS induced activity reduction in the theta-band only. As were interested in determining whether the stimulation-induced desynchronization of cortical activity might be associated with seizure reduction. For this purpose, we correlated the strongest desynchronization of cortical activity in seizure onset zones with seizure reduction. Using the previous one-way ANOVA analyses, it was quantitatively determined that the 4–6 Hz and 10–12 Hz sub-bands were the theta and alpha sub-bands most strongly modulated in the temporal lobe channels. Same applied to the 5–7 Hz and 10–12 Hz frequency sub-bands in the rest of the cortex. To select the respective sub-bands, the EEG channels with the greatest power change were selected and then pooled into a) the temporal area channels only and b) all channels (i.e. widespread). Theta is henceforth defined as 4–6 Hz for temporal lobe channels. A significant correlation was found between seizure reduction and reduction of 4–6 Hz theta-band activity for the temporal lobe channels only ($r = 0.82$; $p = 0.023$; Fig. 3).

3.3. Theta activity differences in temporal lobe channels

Group and single subject level evaluations revealed significantly greater levels of theta band activity in non-responders (during stimulation ON and OFF) compared to both responders and healthy controls (i.e. temporal lobe channel theta activity was greater for non-responders compared to responders and healthy controls). Temporal lobe theta activity did not differ between responders and healthy controls. Furthermore, the difference in temporal lobe channels theta band activity between stimulation ON and stimulation OFF was significant for responders, whereas this difference was not significant for non-responders. Detailed statistical figures are available in Fig. 4 for the group level and for the individual subject level in Fig. 5.

Subsequently, the stimulation-induced effects (ON vs. OFF) on temporal lobe channels theta activity were also investigated at the single-subject level. These analyses revealed that indeed, temporal lobe channels theta activity was in general greater for non-responders compared to responders and healthy controls, and that temporal lobe channels theta activity was consistently reduced during stimulation ON in responders, but not in non-responders.

3.4. Time-domain analysis of identified effects in single subjects

We furthermore investigated whether the reduction of temporal lobe channel theta power coincided with the period of DBS activation. In

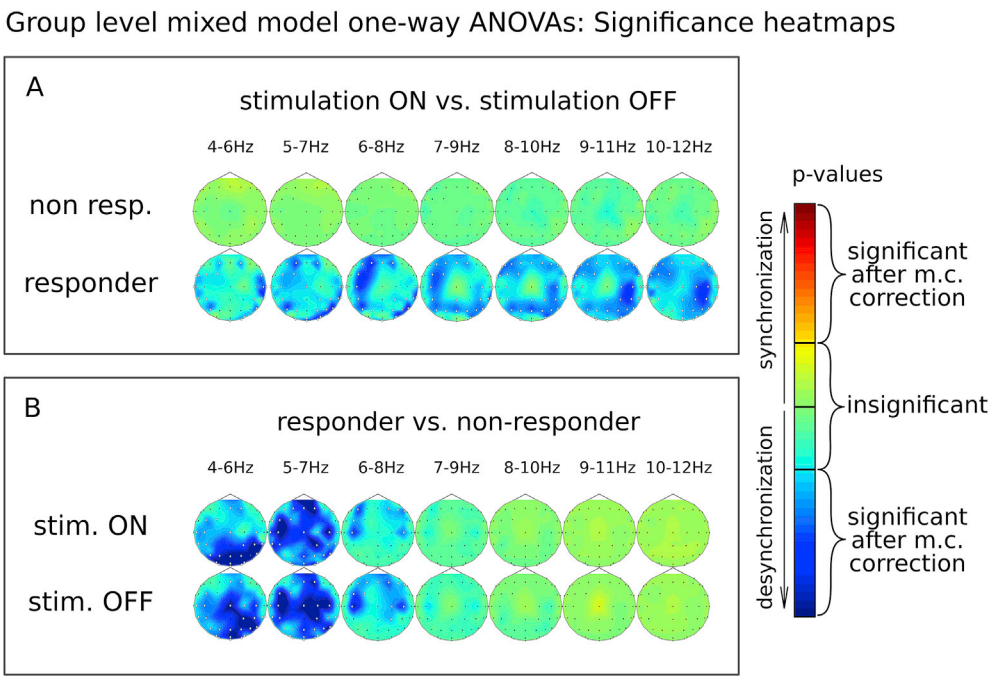

Fig. 2. Mixed model one-way ANOVA results with narrower frequency bands. In order to interrogate the reason for the significant interaction effects from the previous two-way ANOVA analyses, subsequent one-way ANOVA analyses were performed. These analyses were done for 2 Hz wide sub-bands of the theta and alpha frequency bands. (A) Significant main effects of stimulation-condition were found for the responder sub-group only, and were present in both the theta and alpha frequency bands. The negative gradient is suggestive of a desynchronization of activity in these frequency bands (i.e. cortical theta and alpha-band activity were desynchronized when stimulation was changed from OFF to ON in responders). Significant main effects of stimulation-condition in the non-responder sub-group were not found (i.e. cortical activity did not change when stimulation was changed from OFF to ON in the non-responders). Taken together, these analyses reveal ANT-DBS desynchronized theta and alpha-band activity in responders, but had no effect on cortical activity in non-responders; these differential effects were the reason for the interaction effect in the previous two-way ANOVA analyses. (B) Significant main effects of response-type were found both when stimulation was ON and when it was OFF, localized to the theta-frequency band. Taken together, these analyses suggest that there was an overall lower level the theta-band activity in responders compared to non-responders; which validates the significant main effect of response-type in the previous two-way ANOVA analyses. Note: EEG channels are marked by black dots, white dots represent channels which were significant ($p < 0.05$) after multiple comparison corrections.

Fig. 6, stimulation ramping is highlighted in yellow, whereas fully activated DBS is highlighted in green. These analyses were done at the single-subject level for all patients, and revealed a rapid theta power decrease with DBS activation in responders. Non-responders and responders showed temporary and lasting reduction of ANT-DBS related theta power, respectively. The effects of ANT-DBS on theta activity were always present in the two patients with bitemporal lobe epilepsy, but were less pronounced in the single patient with left temporal lobe epilepsy.

3.5. Classification of responders and non-responders

In this study, we grouped patients based on a maximum likelihood approach into responders and non-responders (see methods section). However, when reanalyzing the stimulation-induced theta band reduction and considering the patient with a 42% seizure reduction as a non-responder instead of a responder (following the community standards of a 50% threshold), the results remained unchanged. To investigate the robustness of our findings independent of these grouping issues (see supplementary fig. 3). Importantly, neither correlations nor individual subject level theta-band findings were affected by the classification approach, since the seizure reduction rate was used as a continuous metric.

3.6. Electrode locations of responders and non-responders

The position of the active DBS-lead contacts was compared between the responder and non-responder groups. Relative positions were calculated as the 1) lateral distance from the midline, 2) distance superior to the AC/DC line and 3) distance posterior to the AC normalized with respect to the AC/PC length. Hemispheres were averaged within patients prior to averaging patients. No systematic difference was found between the two groups ($p < 0.42$ – lateral; $p < 0.98$ – superior; $p < 0.83$ – posterior).

4. Discussion

This study revealed marked differences in cortical activity between ANT-DBS responders and non-responders. Non-responders presented with greater overall oscillatory power in the theta frequency band compared to responders and healthy controls. Furthermore, cortical activity depended both on stimulation-condition (ON/OFF) and response-type (responders/non-responders). Specifically, there was a significant ANT-DBS effect in the responder (but not the non-responder) sub-group with a desynchronization of cortical theta and alpha activity during StimOn (but not StimOff). Taken together, these findings suggest that non-responders had higher overall levels of theta-band activity compared to responders and healthy controls. However, non-responders and responders showed a different response to ANT-DBS with temporary and lasting reduction of theta power, respectively.

Due to the anatomical variability of DBS targets in stereotactic space from subject to subject, and the importance of lead positioning with respect to clinical outcomes, we analyzed the electrode lead localization on the basis of postoperative imaging. This analysis revealed, that the

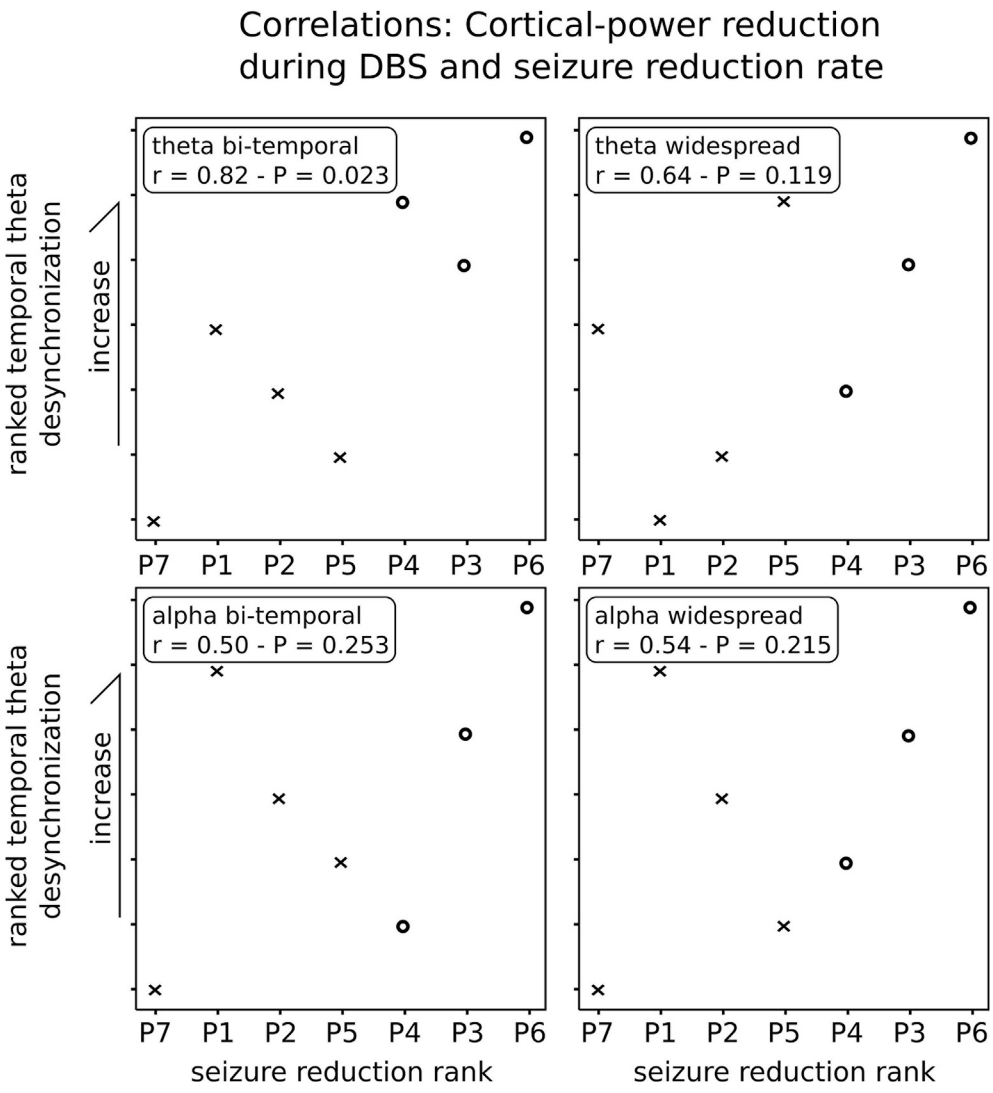

Fig. 3. Stimulation and seizure reduction. Spearman correlations were performed in order to compare seizure reduction with desynchronization of theta and alpha band activity in particular regions of interest (the seizure onset zones of the patient population; temporal lobe channels and multifocal/widespread). A significant correlation was found between seizure reduction and reduction of 4–6 Hz theta-band activity for the temporal lobe channels ($r = 0.82$; $p = 0.023$), whereas the three other correlations were not significant. Responders correspond to o's whereas non-responder correspond to x's.

active contact locations were not significantly different between responders and non-responders in our study. This underlines the necessity to identify physiological biomarkers for refined targeting during DBS surgery.

Along these lines, when investigating regions of interest of modulated oscillatory activity, it was found that ANT-DBS, when effective in reducing seizure counts, was linked to a reduction of cortical theta-band activity in the temporal lobe channels. Furthermore, the level of theta desynchronization was found to be correlated with seizure reduction. At both the group level and the single-subject level, cortical theta-activity was significantly reduced in all responders, and only in one non-responder. Notably, this non-responder showed a larger seizure reduction rate (25%) compared to the other non-responders in this study (8%, 5.5%, and −3.5%). Finally, time-domain analysis revealed that the stimulation-induced theta desynchronization effects were rapid, immediate, sustained for the entirety of the stimulation period, but reverted equally fast following stimulation cessation, which matches previous findings in subcortical brain areas (Stypulkowski et al., 2013; Yu et al., 2018).

Early studies have described epilepsy as a disorder of hypersynchonization, at least during periods of epileptiform activity (Penfield and Jasper, 1954). Ictogenic regions are expected to show increased correlated activity with other brain areas, which is interpreted as a form of hypersynchonization (Kramer and Cash, 2012). Recent evidence suggests abnormal connectivity and network topology, especially for the delta and theta bands, in patients with focal epilepsy (Horstmann et al., 2010; Wilke et al., 2010). Previous studies have shown that patients with various forms of epilepsy had increased cortical theta-band activity compared to healthy controls (Adebimpe et al., 2015; Miyauchi et al., 1991; Quraan et al., 2013). This was corroborated by our findings when comparing non-responders to healthy controls, but not when comparing responders to healthy controls. Moreover, a recent study in humans not only demonstrated ictal recruitment of the ANT in focal epilepsy, but also found that the emergence of the theta rhythm maximally discriminated the endogenous ictal state from other interictal states (Toth et al., 2019). In humans, high frequency stimulation of the ANT has been shown to reduce broadband (Yu et al., 2018) and theta-specific (Zumsteg et al., 2006) activity in the hippocampus/mesial temporal lobe, and has been suggested to work by desynchronizing epileptic networks. As such, when efficacious, the cycling stimulation protocol of ANT-DBS may work by periodically suppressing or resetting epileptic networks and limiting the buildup of hypersynchronous activity.

A transcranial magnetic stimulation study demonstrated that continuous ANT-DBS led to increased short-interval intracortical inhibition, suggesting that ANT-DBS might drive cortical inhibitory circuits (Molnar et al., 2006). Here, we not only found a potential pathophysiological role of cortical theta-band activity (albeit phenotype-specific, i.e. in temporal lobe epilepsy), but also found that desynchronization of temporal theta-band activity may be therapeutically relevant. To the best of our knowledge, this is the first study which has shown a physiological

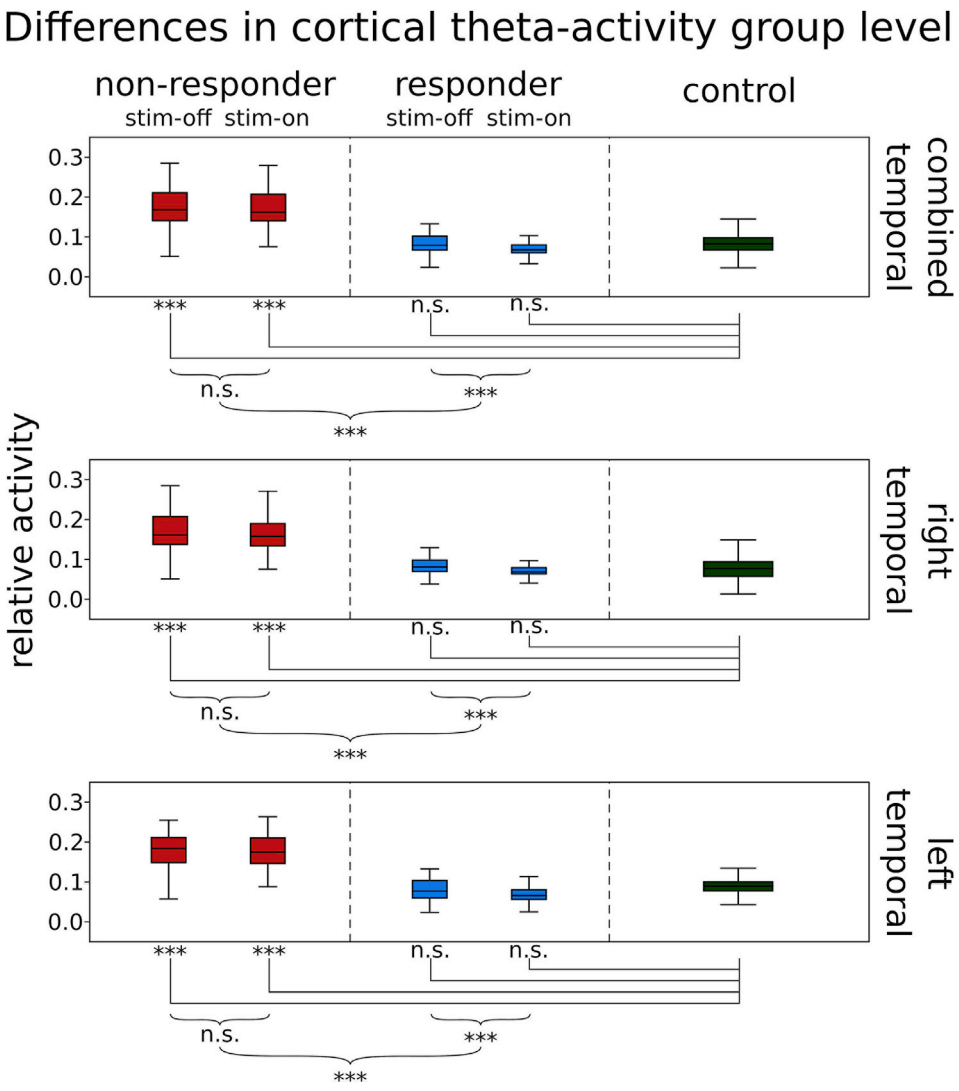

Fig. 4. Group level differences in temporal theta activity between non-responders, responders, and healthy control subjects. These evaluations revealed significantly greater levels of theta-band activity in non-responders (during stimulation ON and OFF) compared to both responders and healthy controls (i.e. temporal theta activity was greater for non-responders compared to responders and healthy controls). Temporal lobe channels theta activity did not differ between responders and healthy controls. Furthermore, the difference in temporal lobe channels theta band activity between stimulation ON and stimulation OFF was significant for responders, whereas this difference was not significant for non-responders. Notes: Each box portrays the lower and upper quartiles and median; whiskers end at 1.5-times the values of the interquartile range before/after the first/third quartile. ***($p < 0.001$).

correlative link between ANT-DBS induced changes of cortical activity and seizure reduction rates, while highlighting differences in ANT-DBS effects between responders and non-responders. These findings not only shed light on different nodes of pathological network activity, but also demonstrate the feasibility of non-invasively interrogating them in relation to the effectiveness of ANT-DBS.

Studies in rats and non-human primates have shown that the ANT has numerous projections, among which also various structures of the limbic system, including the hippocampus (Shibata, 1993; Shibata and Kato, 1993; van Groen et al., 1999; van Groen and Wyss, 1990a, 1990b). The hippocampal formation projects via the subiculum and entorhinal cortex to the perirhinal cortex, and from there to temporal cortical areas (Amaral and Cowan, 1980; Wyss et al., 1979). As such, the responder-specific desynchronization of temporal theta-activity reported here may be the result of a propagated suppression of activity via this pathway. While both responders and non-responders would be expected to have structural/functional connectivity between the ANT and temporal lobe areas, the possible influence of the ANT on ictogenic networks may vary between patients with temporal- and extratemporal epilepsies. Or, it could be that the increased levels of theta hypersynchronization in non-responders as compared to responders were less amenable by ANT-DBS. However, it could also be that variability in lead placement may have differentially affected these networks between the responder and non-responder sub-groups.

4.1. Clinical implications

Converging evidence (Fisher et al., 2010; Hodaie et al., 2002; Kerrigan et al., 2004) supports the hypothesis (Middlebrooks et al., 2018; Osorio et al., 2007) that ANT-DBS may have a more efficacious response in patients with temporal lobe epilepsy, compared to patients with multifocal or extratemporal epilepsy. This was reflected in our findings as well as during the double-blinded phase of the SANTE study where significant effects were found for temporal lobe epilepsy patients only. Therefore, patients with temporal lobe epilepsy may be preferred candidates for ANT-DBS procedures. Furthermore, the presented study not only discerned a physiological hallmark of clinically effective stimulation (i.e. desynchronization of theta-band activity), but also found that cortical signatures differed between patients with temporal lobe epilepsy (responder) and patients with extratemporal or multifocal epilepsy (non-responder) in that the latter presented with greater theta synchronization at rest (and during stimulation). This finding may represent a potential predictor of responsiveness (i.e. a potential patient selection criterion). One might have expected that the theta activity of responders during the OFF condition would be different from controls, which was not the case. This might be related to the fact that we most likely recorded from lateral temporal and not mesial temporal structures with scalp EEG electrodes.

However, since the seizure onset zone (temporal vs. extratemporal/multifocal) and level of theta synchronization were coupled in this study,

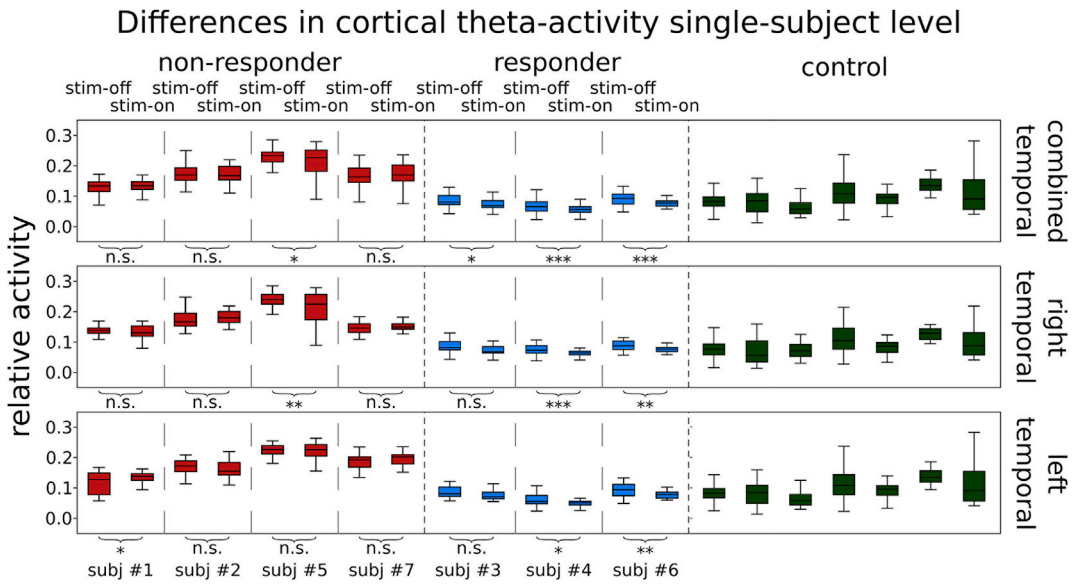

Fig. 5. Group level differences in temporal theta activity between non-responders, responders, and healthy controls. In line with the group results, the individual level results confirm the ANT-DBS modulation of theta-activity in responders. The ANT-DBS effect was somewhat weaker in subject #3 who presented with unilateral temporal lobe seizures, whereas subjects #4 and #6 presented with bi-temporal lobe seizures. Notably, the non-responder (subject #5) who showed an ANT-DBS effect as well had a relevantly higher seizure reduction (i.e., 25%) than the other non-responders. Notes: Each box portrays the lower and upper quartiles and median; whiskers end at 1.5-times the values of the interquartile range before/after the first/third quartile. ***($p < 0.001$).

further data are required to determine whether a predictive factor of ANT-DBS responsiveness may have been dependent upon (i) seizure onset zone/epilepsy type, (ii) the level of theta synchronization, or (iii) indeed a combination of these two phenomena.

Moreover, the findings of this study may increase the efficiency of stimulation programming. Currently, an unambiguous definition of the most optimal stimulation has not been defined (Kulju et al., 2018; Lehtimäki et al., 2016; Möttönen et al., 2015). Evaluation of clinical efficacy is done over the course of several months and the use of a seizure diary. This time-consuming process limits the evaluation of a variety of stimulation paradigms, and generally only a few are actually evaluated in each patient. While other studies have demonstrated that ANT-DBS may be linked to reductions of subcortical (hippocampal) activity (Stypulkowski et al., 2013; Yu et al., 2018; Zumsteg et al., 2006), we have shown that efficacious stimulation was linked to suppression of cortical (temporal lobe channels) activity, which could be measured non-invasively. Thus, this physiological hallmark (i.e. ANT-DBS induced reductions of cortical theta-band activity) may be used as a potential candidate biomarker for selection of clinically effective stimulation parameters/contacts. As the theta suppressing effects were immediate, only few seconds may be required when evaluating candidate stimulation paradigms based on functional physiological read-outs (temporal lobe channels desynchronization), compared to months when using the established approach of using seizure diaries. Furthermore, considering that the next generation of DBS-leads may have increased numbers of stimulation contacts, development of a simple to use and quickly assessable physiological biomarkers for evaluating treatment response is important for optimizing clinical efficacy. For stimulation programming, we propose an assessment to initially scan the available contacts using the proposed candidate biomarker, and subsequent evaluation using the traditional long-term assessment of applying the seizure diary approach.

This candidate biomarker may not only represent a practical method of selecting optimal stimulation parameters/contacts for patients who have already been implanted, but may also serve as an intraoperative physiological hallmark for lead implantations. Currently, robust structural radiological methods to specifically delineate the ANT from other thalamic sub-structures have not been defined, nor have functional intraoperative physiological hallmarks (Liu et al., 2012; Stypulkowski et al., 2014; Van Hoesen, 1995). This may lead to misplaced electrode leads (Lehtimäki et al., 2018). While it is common to guide the implantation of the DBS-leads via imaging procedures only (Cukiert and Lehtimäki, 2017), we propose to investigate the theta-modulating effects of ANT-DBS as a potential biomarker for verification of the implantation site in order to improve lead positioning. This can be done intraoperatively through the use of scalp electrodes on the temporal lobe areas, and monitoring changes of cortical theta-activity during stimulation, which may be indicative of a clinically efficacious lead placement.

4.2. Limitations

We acknowledge that this study was limited by a low number of patients; however, phenotype-specific differences (i.e. temporal vs. extratemporal or multifocal seizure onset zones) in response rate were also reported in the blinded phase of the SANTE trial. Moreover, in the eyes-closed waking condition, the patients might fall asleep. Even though we took measures to avoid this and do not have any indication that this happened in our study, future work might consider investigating these patients in the eyes-open condition.

Due to the explorative nature of this study, we enforced strict steps to reduce the family-wise error rate. We initially investigated the effects of ANT-DBS in epilepsy patients without limiting our investigation to areas which have previously been identified as regions of interest or frequency bands of interest. This was done in order not to bias this study towards previously established findings, and to give room to the discovery of new effects. However, in order to limit the number of hypotheses (and thereby reduce the family-wise error rate), we reduced the number of frequency bands of interest in a step-wise manner. During the initial ANOVA analyses (which were corrected for multiple comparisons), the theta and the alpha bands were selected as frequency bands of interest due to significant main and interactions effects. The regions of interest were selected based on the seizure onset zones of the patient population. As only the temporal lobe channel areas in the theta-band correlated with seizure reduction, other regions and frequency bands of interest were discarded from further analyses in order to limit the number of hypotheses. Moreover, analyses were performed at the single-subject level in order to ensure consistency within sub-groups, and to ensure that no individual

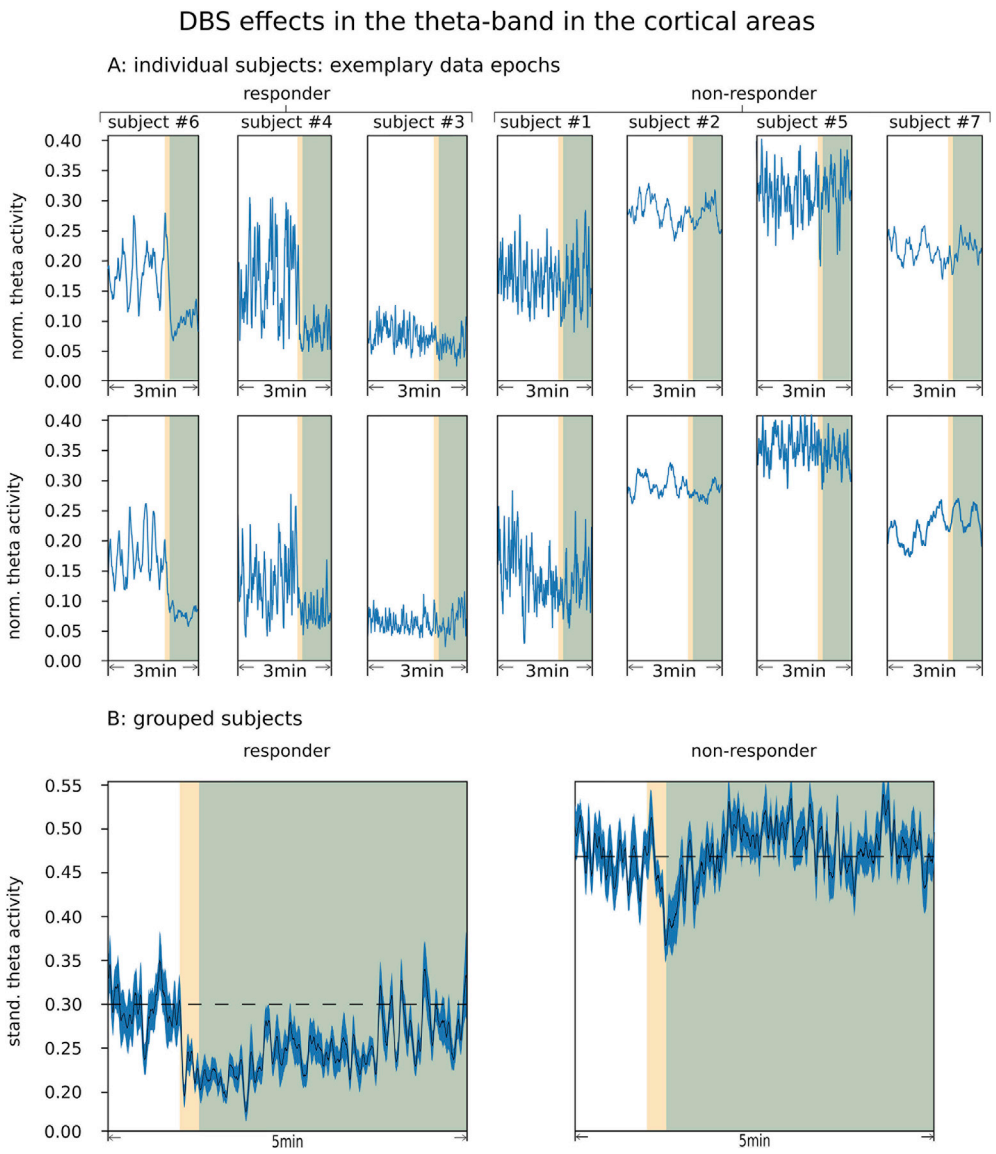

Fig. 6. Time-domain analysis of theta desynchronization effects. Individual epochs extracted from the time domain theta-band filtered signal (averaged for temporal lobe channels) of all patients are portrayed (A). Standardized group data averaged across all trials for all subjects confirms the effect that was observed in individual subjects (B). Variance is indicated by the blue shaded region. This figure demonstrates that stimulation activation coincided with rapid reduction in theta-power in responder. Non-responders did not show a sustained ANT-DBS related reduction in cortical theta-activity. Furthermore, responders had an overall lower level of theta activity. Note: Stimulation ramping is highlighted yellow, fully activated DBS is highlighted green.

patient disproportionately skewed the group results. While, to the best of our knowledge, this is the first study to assess cortical physiological hallmarks of ANT-DBS and clinical responsiveness, further studies regarding the stimulation-induced changes of neurophysiological activity are warranted in order to better understand the mechanisms of ANT-DBS, aid in patient selection, and optimize treatment success.

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Declaration of competing interest

None.

CRediT authorship contribution statement

Maximillian Scherer: Conceptualization, Investigation, Data curation, Formal analysis, Validation, Software, Writing - original draft, Writing - review & editing. **Luka Milosevic:** Conceptualization, Writing - original draft, Writing - review & editing, Project administration, Supervision. **Robert Guggenberger:** Data curation, Supervision, Writing - review & editing. **Volker Maus:** Investigation, Project administration, Writing - review & editing. **Georgios Naros:** Investigation, Writing - review & editing. **Florian Grimm:** Investigation, Writing - review & editing. **Iancu Bucurenciu:** Investigation, Writing - review & editing. **Bernhard J. Steinhoff:** Supervision, Writing - review & editing. **Yvonne G. Weber:** Investigation, Writing - review & editing. **Holger Lerche:** Supervision, Writing - review & editing. **Daniel Weiss:** Supervision, Writing - review & editing. **Sabine Rona:** Investigation, Project administration, Writing - review & editing. **Alireza Gharabaghi:** Conceptualization, Investigation, Supervision, Writing - original draft, Writing - review & editing, Project administration, Resources, Funding acquisition.

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Data and code will be shared upon reasonable request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuroimage.2020.116967.

References

Adebimpe, A., Aarabi, A., Bourel-Ponchel, E., Mahmoudzadeh, M., Wallois, F., 2015. EEG resting state analysis of cortical sources in patients with benign epilepsy with centrotemporal spikes. NeuroImage Clin. 9, 275–282. https://doi.org/10.1016/j.nicl.2015.08.014.

Amaral, D.G., Cowan, W.M., 1980. Subcortical afferents to the hippocampal formation in the monkey. J. Comp. Neurol. 189, 573–591. https://doi.org/10.1002/cne.901890402.

Child, N.D., Benarroch, E.E., 2013. Anterior nucleus of the thalamus: functional organization and clinical implications. Neurology 81, 1869–1876. https://doi.org/10.1212/01.wnl.0000436078.95856.56.

Cukiert, A., Lehtimäki, K., 2017. Deep brain stimulation targeting in refractory epilepsy. Epilepsia 58, 80–84. https://doi.org/10.1111/epi.13686.

Fisher, R., Salanova, V., Witt, T., Worth, R., Henry, T., Gross, R., Oommen, K., Osorio, I., Nazzaro, J., Labar, D., Kaplitt, M., Sperling, M., Sandok, E., Neal, J., Handforth, A., Stern, J., DeSalles, A., Chung, S., Shetter, A., Bergen, D., Bakay, R., Henderson, J., French, J., Baltuch, G., Rosenfeld, W., Youkilis, A., Marks, W., Garcia, P., Barbaro, N., Fountain, N., Bazil, C., Goodman, R., McKhann, G., Babu Krishnamurthy, K., Papavassiliou, S., Epstein, C., Pollard, J., Tonder, L., Grebin, J., Coffey, R., Graves, N., the SANTE Study Group, 2010. Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy: deep Brain Stimulation of Anterior Thalamus for Epilepsy. Epilepsia 51, 899–908. https://doi.org/10.1111/j.1528-1167.2010.02536.x.

Fisher, R.S., Velasco, A.L., 2014. Electrical brain stimulation for epilepsy. Nat. Rev. Neurol. 10, 261–270. https://doi.org/10.1038/nrneurol.2014.59.

Halpern, C.H., Samadani, U., Litt, B., Jaggi, J.L., Baltuch, G.H., 2008. Deep brain stimulation for epilepsy. Neurotherapeutics 5, 59–67. https://doi.org/10.1016/j.nurt.2007.10.065.

Hamani, C., Ewerton, F.I.S., Bonilha, S.M., Ballester, G., Mello, L.E.A.M., Lozano, A.M., 2004. Bilateral anterior thalamic nucleus lesions and high-frequency stimulation are protective against pilocarpine-induced seizures and status epilepticus. Neurosurgery 54, 191–197. https://doi.org/10.1227/01.NEU.0000097552.31763.AE.

Hodaie, M., Wennberg, R.A., Dostrovsky, J.O., Lozano, A.M., 2002. Chronic anterior thalamus stimulation for intractable epilepsy. Epilepsia 43, 603–608. https://doi.org/10.1046/j.1528-1157.2002.26001.x.

Horstmann, M.-T., Bialonski, S., Noennig, N., Mai, H., Prusseit, J., Wellmer, J., Hinrichs, H., Lehnertz, K., 2010. State dependent properties of epileptic brain networks: comparative graph–theoretical analyses of simultaneously recorded EEG and MEG. Clin. Neurophysiol. 121, 172–185. https://doi.org/10.1016/j.clinph.2009.10.013.

Kerrigan, J.F., Litt, B., Fisher, R.S., Cranstoun, S., French, J.A., Blum, D.E., Dichter, M., Shetter, A., Baltuch, G., Jaggi, J., Krone, S., Brodie, M., Rise, M., Graves, N., 2004. Electrical stimulation of the anterior nucleus of the thalamus for the treatment of intractable epilepsy. Epilepsia 45, 346–354. https://doi.org/10.1111/j.0013-9580.2004.01304.x.

Kramer, M.A., Cash, S.S., 2012. Epilepsy as a disorder of cortical network organization. Neurosci. Rev. J. Bringing Neurobiol. Neurol. Psychiatry 18, 360–372. https://doi.org/10.1177/1073858411422754.

Kulju, T., Haapasalo, J., Lehtimäki, K., Rainesalo, S., Peltola, J., 2018. Similarities between the responses to ANT-DBS and prior VNS in refractory epilepsy. Brain Behav. 8, e00983 https://doi.org/10.1002/brb3.983.

Kwan, P., Brodie, M.J., 2000. Early identification of refractory epilepsy. N. Engl. J. Med. 342, 314–319. https://doi.org/10.1056/NEJM200002033420503.

Lane, M.A., Kahlenberg, C.A., Li, Z., Kulandaival, K., Secore, K.L., Thadani, V.M., Bujarski, K.A., Kobylarz, E.J., Roberts, D.W., Tosteson, T.D., Jobst, B.C., 2017. The implantation effect: delay in seizure occurrence with implantation of intracranial electrodes. Acta Neurol. Scand. 135, 115–121. https://doi.org/10.1111/ane.12662.

Laxpati, N.G., Kasoff, W.S., Gross, R.E., 2014. Deep brain stimulation for the treatment of epilepsy: circuits, targets, and trials. Neurotherapeutics 11, 508–526. https://doi.org/10.1007/s13311-014-0279-9.

Lehtimäki, K., Gielen, F., Abouihia, A., Beth, G., Brionne, T.C., Coenen, V.A., Gonçalves Ferreira, A., Boon, P., Elger, C., Taylor, R.S., Ryvlin, P., Gil-Nagel, A., 2018. The surgical approach to the anterior nucleus of thalamus in patients with refractory epilepsy: experience from the international multicenter registry (MORE). Neurosurgery 84, 141–150. https://doi.org/10.1093/neuros/nyy023.

Lehtimäki, K., Möttönen, T., Järventausta, K., Katisko, J., Tähtinen, T., Haapasalo, J., Niskakangas, T., Kiekara, T., Öhman, J., Peltola, J., 2016. Outcome based definition of the anterior thalamic deep brain stimulation target in refractory epilepsy. Brain Stimulat. 9, 268–275. https://doi.org/10.1016/j.brs.2015.09.014.

Lim, S.-N., Lee, S.-T., Tsai, Y.-T., Chen, I.-A., Tu, P.-H., Chen, J.-L., Chang, H.-W., Su, Y.-C., Wu, T., 2007. Electrical stimulation of the anterior nucleus of the thalamus for intractable epilepsy: a long-term follow-up study. Epilepsia 48, 342–347. https://doi.org/10.1111/j.1528-1167.2006.00898.x.

Liu, H.G., Yang, A.C., Meng, D.W., Chen, N., Zhang, J.G., 2012. Stimulation of the anterior nucleus of the thalamus induces changes in amino acids in the hippocampi of epileptic rats. Brain Res. 1477, 37–44. https://doi.org/10.1016/j.brainres.2012.08.007.

Löscher, W., Klitgaard, H., Twyman, R.E., Schmidt, D., 2013. New avenues for anti-epileptic drug discovery and development. Nat. Rev. Drug Discov. 12, 757.

Middlebrooks, E.H., Grewal, S.S., Stead, M., Lundstrom, B.N., Worrell, G.A., Gompel, J.J.V., 2018. Differences in functional connectivity profiles as a predictor of response to anterior thalamic nucleus deep brain stimulation for epilepsy: a hypothesis for the mechanism of action and a potential biomarker for outcomes. Neurosurg. Focus FOC 45, E7.

Mirski, M.A., Rossell, L.A., Terry, J.B., Fisher, R.S., 1997. Anticonvulsant effect of anterior thalamic high frequency electrical stimulation in the rat. Epilepsy Res. 28, 89–100. https://doi.org/10.1016/S0920-1211(97)00034-X.

Miyauchi, T., Endo, K., Yamaguchi, T., Hagimoto, H., 1991. Computerized analysis of EEG background activity in epileptic patients. Epilepsia 32, 870–881. https://doi.org/10.1111/j.1528-1157.1991.tb05544.x.

Molnar, G.F., Sailer, A., Gunraj, C.A., Cunic, D.I., Wennberg, R.A., Lozano, A.M., Chen, R., 2006. Changes in motor cortex excitability with stimulation of anterior thalamus in epilepsy. Neurology 66, 566–571. https://doi.org/10.1212/01.wnl.0000198254.08581.6b.

Möttönen, T., Katisko, J., Haapasalo, J., Tähtinen, T., Kiekara, T., Kähärä, V., Peltola, J., Öhman, J., Lehtimäki, K., 2015. Defining the anterior nucleus of the thalamus (ANT) as a deep brain stimulation target in refractory epilepsy: delineation using 3 T MRI and intraoperative microelectrode recording. NeuroImage Clin. 7, 823–829. https://doi.org/10.1016/j.nicl.2015.03.001.

Osorio, I., Overman, J., Giftakis, J., Wilkinson, S.B., 2007. High frequency thalamic stimulation for inoperable mesial temporal epilepsy. Epilepsia 48, 1561–1571. https://doi.org/10.1111/j.1528-1167.2007.01044.x.

Penfield, W., Jasper, H., 1954. Epilepsy and the Functional Anatomy of the Human Brain, Epilepsy and the Functional Anatomy of the Human Brain. Little, Brown & Co., Oxford, England.

Quraan, M.A., McCormick, C., Cohn, M., Valiante, T.A., McAndrews, M.P., 2013. Altered resting state brain dynamics in temporal lobe epilepsy can Be observed in spectral power, functional connectivity and graph theory metrics. PloS One 8, e68609. https://doi.org/10.1371/journal.pone.0068609.

Salanova, V., Witt, T., Worth, R., Henry, T.R., Gross, R.E., Nazzaro, J.M., Labar, D., Sperling, M.R., Sharan, A., Sandok, E., Handforth, A., Stern, J.M., Chung, S., Henderson, J.M., French, J., Baltuch, G., Rosenfeld, W.E., Garcia, P., Barbaro, N.M., Fountain, N.B., Elias, W.J., Goodman, R.R., Pollard, J.R., Tröster, A.I., Irwin, C.P., Lambrecht, K., Graves, N., Fisher, R., 2015. Long-term efficacy and safety of thalamic stimulation for drug-resistant partial epilepsy. Neurology 84, 1017–1025. https://doi.org/10.1212/WNL.0000000000001334.

Shi, L., Yang, A.C., Li, J.J., Meng, D.W., Jiang, B., Zhang, J.G., 2015. Favorable modulation in neurotransmitters: effects of chronic anterior thalamic nuclei stimulation observed in epileptic monkeys. Exp. Neurol. 265, 94–101. https://doi.org/10.1016/j.expneurol.2015.01.003.

Shibata, H., 1993. Direct projections from the anterior thalamic nuclei to the retrohippocampal region in the rat. J. Comp. Neurol. 337, 431–445. https://doi.org/10.1002/cne.903370307.

Shibata, H., Kato, A., 1993. Topographic relationship between anteromedial thalamic nucleus neurons and their cortical terminal fields in the rat. Neurosci. Res. 17, 63–69. https://doi.org/10.1016/0168-0102(93)90030-T.

Sitnikov, A.R., Grigoryan, Y.A., Mishnyakova, L.P., 2018. Bilateral stereotactic lesions and chronic stimulation of the anterior thalamic nuclei for treatment of pharmacoresistant epilepsy. Surg. Neurol. Int. 9 https://doi.org/10.4103/sni.sni_25_18.

Son, B., Shon, Y.M., Kim, S., Choi, J., Kim, J., 2016. Relationship between postoperative EEG driving response and lead location in deep brain stimulation of the anterior nucleus of the thalamus for refractory epilepsy. Stereotact. Funct. Neurosurg. 94, 336–341. https://doi.org/10.1159/000449012.

Stypulkowski, P.H., Stanslaski, S.R., Denison, T.J., Giftakis, J.E., 2013. Chronic evaluation of a clinical system for deep brain stimulation and recording of neural network activity. Stereotact. Funct. Neurosurg. 91, 220–232. https://doi.org/10.1159/000345493.

Stypulkowski, P.H., Stanslaski, S.R., Jensen, R.M., Denison, T.J., Giftakis, J.E., 2014. Brain stimulation for epilepsy – local and remote modulation of network excitability. Brain Stimulat. 7, 350–358. https://doi.org/10.1016/j.brs.2014.02.002.

Sweeney-Reed, C.M., Lee, H., Rampp, S., Zaehle, T., Buentjen, L., Voges, J., Holtkamp, M., Hinrichs, H., Heinze, H.-J., Schmitt, F.C., 2016. Thalamic interictal epileptiform discharges in deep brain stimulated epilepsy patients. J. Neurol. 263, 2120–2126. https://doi.org/10.1007/s00415-016-8246-5.

Takebayashi, S., Hashizume, K., Tanaka, T., Hodozuka, A., 2007. The effect of electrical stimulation and lesioning of the anterior thalamic nucleus on kainic acid–induced focal cortical seizure status in rats. Epilepsia 48, 348–358. https://doi.org/10.1111/j.1528-1167.2006.00948.x.

Téllez-Zenteno, J.F., Hernández-Ronquillo, L., 2012. A review of the epidemiology of temporal lobe epilepsy. Epilepsy Res. Treat. https://doi.org/10.1155/2012/630853, 2012.

Toth, E., Chaitanya, G., Pizarro, D., Kumar, S.S., Ilyas, A., Romeo, A., Riley, K., Vlachos, I., David, O., Balasubramanian, K., Pati, S., 2019. Ictal Recruitment of Anterior Nucleus of Thalamus in Human Focal Epilepsy. bioRxiv, 788422. https://doi.org/10.1101/788422.

Vajda, F.J.E., Eadie, M.J., 2014. The clinical pharmacology of traditional antiepileptic drugs. Epileptic Disord. 16, 395–408. https://doi.org/10.1684/epd.2014.0704.

van Groen, T., Kadish, I., Wyss, J.M., 1999. Efferent connections of the anteromedial nucleus of the thalamus of the rat. Brain Res. Rev. 30, 1–26. https://doi.org/10.1016/S0165-0173(99)00006-5.

van Groen, T., Wyss, J.M., 1990a. The connections of presubiculum and parasubiculum in the rat. Brain Res. 518, 227–243. https://doi.org/10.1016/0006-8993(90)90976-I.

van Groen, T., Wyss, J.M., 1990b. The postsubicular cortex in the rat: characterization of the fourth region of the subicular cortex and its connections. Brain Res. 529, 165–177. https://doi.org/10.1016/0006-8993(90)90824-U.

Van Hoesen, G.W., 1995. Anatomy of the medial temporal lobe. In: Magn. Reson. Imaging, Workshop on Magnetic Resonance Techniques and Epilepsy Research, 13, pp. 1047–1055. https://doi.org/10.1016/0730-725X(95)02012-I.

Wilke, C., van Drongelen, W., Kohrman, M., He, B., 2010. Neocortical seizure foci localization by means of a directed transfer function method. Epilepsia 51, 564–572. https://doi.org/10.1111/j.1528-1167.2009.02329.x.

Wyckhuys, T., Geerts, P.J., Raedt, R., Vonck, K., Wadman, W., Boon, P., 2009. Deep brain stimulation for epilepsy: knowledge gained from experimental animal models. Acta Neurol. Belg. 109, 63–80.

Wyss, J.M., Swanson, L.W., Cowan, W.M., 1979. A study of subcortical afferents to the hippocampal formation in the rat. Neuroscience 4, 463–476. https://doi.org/10.1016/0306-4522(79)90124-6.

Yu, T., Wang, X., Li, Y., Zhang, G., Worrell, G., Chauvel, P., Ni, D., Qiao, L., Liu, C., Li, L., Ren, L., Wang, Y., 2018. High-frequency stimulation of anterior nucleus of thalamus desynchronizes epileptic network in humans. Brain 141, 2631–2643. https://doi.org/10.1093/brain/awy187.

Zumsteg, D., Lozano, A.M., Wennberg, R.A., 2006. Mesial temporal inhibition in a patient with deep brain stimulation of the anterior thalamus for epilepsy. Epilepsia 47, 1958–1962. https://doi.org/10.1111/j.1528-1167.2006.00824.x.