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Different patterns of local field potentials from limbic DBS targets in patients with major depressive and obsessive compulsive disorder

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Abstract

The role of distinct limbic areas in emotion regulation has been largely inferred from neuroimaging studies. Recently, the opportunity for intracranial recordings from limbic areas has arisen in patients undergoing deep brain stimulation (DBS) for neuropsychiatric disorders including major depressive disorder (MDD) and obsessive compulsive disorder (OCD). Here we test the hypothesis that distinct temporal patterns of local field potential (LFP) activity in the human limbic system reflect disease state and symptom severity in MDD and OCD patients. To this end, we recorded LFPs via implanted DBS electrodes from the bed nucleus of stria terminalis (BNST area) in 12 patients (5 OCD, 7 MDD) and from the subgenual cingulate cortex in 7 MDD patients (CG25 area). We found a distinct pattern of oscillatory activity with significantly higher α-power in MDD compared with OCD in the BNST area (broad α-band 8–14 Hz; $P<0.01$) and a

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DISCLOSURE

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similar level of α-activity in the CG25 area as in the BNST area in MDD patients. The mean α-power correlated with severity of depressive symptoms as assessed by the Beck depression inventory in MDD ($n = 14$, $r = 0.55$, $P = 0.042$) but not with severity of obsessive compulsive symptoms in OCD. Here we show larger α-band activity in MDD patients compared with OCD recorded from intracranial DBS targets. Our results suggest that α-activity in the limbic system may be a signature of symptom severity in MDD and may serve as a potential state biomarker for closed loop DBS in MDD.

Keywords

alpha oscillations; deep brain stimulation; depressive disorder; local field potential; obsessive compulsive disorder

INTRODUCTION

Deep brain stimulation (DBS) has recently gained attention as a promising therapeutic approach in therapy-resistant psychiatric disorders and encouraging results have been obtained in patients with Tourette syndrome, major depressive disorder (MDD) and obsessive compulsive disorder (OCD).[1-4] Other psychiatric conditions, such as addiction, anorexia nervosa and schizophrenia, are also under clinical evaluation.[5-7] However, the mechanism of action of DBS is still not well understood. Target areas for DBS in psychiatry and neurology have been adopted from empirical data derived from neurosurgical lesion studies that reported beneficial clinical results rather than being driven by pathophysiological hypotheses.[8] The opportunity to record local field potentials (LFPs) from DBS electrodes during and shortly after DBS surgery, while DBS electrodes are still externalised, has contributed considerably to our understanding of the underlying pathophysiology of circuit disorders such as Parkinson's disease (PD), and of the physiology of the basal ganglia.[9-12] Studies from patients undergoing DBS for movement disorders have pointed to abnormal patterning of neuronal activity that differs between disease states.[13,14] DBS may suppress disruptive aberrant activity across different frequency bands such as increased β-band activity in PD,[15,16] thereby offering an explanation for how disparate clinical states may be effectively treated by DBS in the same target area.[13] Moreover, abnormal neuronal patterns may serve as biomarkers that are currently tested for optimised closed loop DBS in movement disorders.[17]

Our understanding of the oscillatory neuronal circuits subserving psychiatric disorders is growing;[18] however, little is known about the underlying nature of subcortical oscillatory neuronal activity in the structures targeted by DBS. Thus, the optimal target structures for psychiatric indications are less well defined, as evident in the current investigation of five target areas for DBS in MDD (nucleus accumbens, medial forebrain bundle, anterior subgenual cingulate cortex (CG25), anterior limb of internal capsule and the inferior thalamic peduncle)[3,4,19-22] and four areas for OCD (nucleus accumbens, ventral subthalamic nucleus, anterior limb of internal capsule and the inferior thalamic peduncle).[1,19,22-28] For MDD, two of these anatomical structures have been targeted more frequently than others: the CG25 and the anterior limb of the internal capsule with the bed nucleus of stria

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terminalis (BNST) in the trajectory (subsequently referred to as the BNST area). Clinical case series of DBS in treatment-resistant MDD have reported favorable results from chronic high-frequency stimulation of the CG25.[4,29,30] A series of positron emission tomography studies have established hypermetabolism in this area as a correlate of negative mood and depression. Furthermore, DBS-related remission of MDD symptoms has been associated with a reduction of cerebral blood flow in the target area and downstream limbic and cortical areas.[4,31] The BNST area is the second major DBS target area investigated in MDD following significant improvement of depression ratings in patients operated for OCD.[28,32] The BNST is one of the main output nuclei of the extended amygdala[33,34] and functionally related to sustained fear and anxiety as perceived in major depressive and anxiety disorders.[35] A recent animal study demonstrated that optogenetic photostimulation of efferent subcortical γ-aminobutyric acid-containing (GABAergic) and glutamatergic network projections from BNST in freely behaving mice differentially elicited anxiolytic and anxiogenic behavioural phenotypes supporting the role of the BNST in the regulation of emotional states.[36] Clinical studies are now examining the benefit of BNST area stimulation in both OCD and MDD.

The aims of our study were twofold. First, we sought distinct spatio-temporal patterns of synchronised neuronal network activity related to MDD and OCD in patients undergoing DBS of the same target, the BNST area. Second, we sought to determine whether any such phenotype-dependent neuronal activity was a local feature or also represented in other limbic structures. To this end, we also recorded from MDD patients undergoing surgery to the CG25. In all, we compared LFP activity recorded directly from DBS electrodes in 14 patients suffering from intractable MDD and five patients with OCD. We hypothesised that oscillatory patterning differs between disease states providing a neurophysiological signature of the disease that may reflect symptom severity. Our results provide evidence that the relative level of synchronised α-oscillations in limbic structures may distinguish MDD and OCD and that these oscillations correlate with the patients' self reported symptom severity as assessed by the Beck depression inventory (BDI) at the time of recording.

MATERIALS AND METHODS

Patients and surgery

Fourteen patients with treatment-resistant MDD (seven female; age: 50.4 ± 1.9 years, mean ± s.e.m., disease duration, 19.2 ± 2.6 years) who underwent bilateral implantation of DBS electrodes in the CG25 area (Berlin; seven patients) or BNST (Leuven; seven patients) and five patients with treatment-resistant OCD (Leuven; one female, age: 46 ± 5.5 years; disease duration, 31.6 ± 6 years) who underwent bilateral implantation of macroelectrodes in the BNST area as part of ongoing clinical trials were included in the study. The clinical details are summarised in Table 1. The clinical outcomes of stimulation and related effects are to be presented separately. For all patients informed consent was obtained before inclusion in the study, which was approved by the local ethics committees in accordance with the standards set by the Declaration of Helsinki. Preoperative assessments included the BDI, Hamilton depression inventory and, for patients suffering from OCD, the Yale-Brown Obsessive Compulsive Scale (YBOCS). At the time of the LFP recordings, the BDI was obtained again

in all patients (except for case 17). The macroelectrode used in Berlin was model 3387 (Medtronic Neurological Division, Minneapolis, MN, USA) and in Leuven models 3387, 3391 or 3887 (Medtronic Neurological Division) with four platinum–iridium cylindrical surfaces (1.27/1.27/1.3 mm^3 diameter and 1.5/3/3 mm^3 length for 3387/3391/3887) and centre to centre separations of 3/4/4 mm^3 (3387/3391/3887). Contacts 0 and 3 were the lowermost and uppermost contacts, respectively. Neurosurgical targeting procedures have been reported in detail in previous studies for both areas.[4,37] It is important to note that targeting of the BNST area was identical for OCD and MDD, and there was no systematic difference between OCD and MDD patients with respect to the electrodes used. Correct placement of the DBS electrodes was confirmed by post-operative imaging using computed tomography (Leuven) and magnetic resonance imaging (Berlin) in all patients (Figure 1; for examples of postoperative imaging in the BNST area see Nuttin et al[37]). However, the optimal region within the target area for CG25 DBS is still a matter of debate.[38-40] Moreover, owing to the size of the electrode not all contacts of a given electrode can be placed within the intended target area.[37] However, to avoid a selection bias, all three bipolar electrode pairs of each electrode were analysed.

Experiments and recordings

All patients were studied within 2–7 days after initial DBS surgery, while the DBS leads were externalised. There was no difference in timing of recordings between OCD (5 ± 0.5 days) and MDD (4.9 ± 0.9 days) patients in Leuven (average timing for Berlin was 2.7 ± 0.3 days). LFPs were obtained bipolarly from the adjacent contacts of the DBS macroelectrode (01, 12, 23), amplified (×50 000) and filtered at 1–250 Hz. For patients 1–7 (Berlin), a D360 amplifier was used (Digitimer, Hertfordshire, UK) and signals were recorded at a sampling rate of 1 kHz through a 1401 A-D converter (CED, Cambridge UK) onto a computer using Spike2 (CED) software. For patients 8–19 (Leuven), we used a portable amplifier (Biopotential Analyzer Diana, St Petersburg, Russia) with sampling frequency 1.5 kHz (except for MDD cases 9 and 10, which were recorded with an older version of the recording system and therefore sampled at 185 Hz). Overall, 42 CG25 and 72 BNST contact pairs were recorded from 38 electrodes in 19 patients. All patients completed rest recordings of at least 100 s duration (127 ± 1.5 s for CG25 and 137 ± 8.8 s for BNST, mean ± s.e.m.). During recordings, patients were seated comfortably in an armchair and asked to relax with eyes open, and not to speak.

Spectral analysis

All data were downsampled (or interpolated for cases 9 and 10) to 1 kHz, visually inspected for artefacts and analysed using custom MATLAB code (The Mathworks, Natick, MA, USA) based on SPM8 for magnetoencephalography/electroencephalography (Wellcome Department of Cognitive Neurology, London, UK; www.fil.ion.ucl.ac.uk/spm/) and FieldTrip (Donders Center for Cognitive Neuroimaging, University Nijmegen, Nijmegen, the Netherlands; http://fieldtrip.fcdonders.nl/). All continuous rest recordings were divided into arbitrary epochs of 1.024 s (1024 samples) and transferred into the frequency domain using fast Fourier transform-based methods. This resulted in a frequency resolution of 0.98 Hz over 512 frequency bins. Power-spectra were normalised to the mean s.d. of 3–47 Hz and 53–97 Hz power and further expressed in arbitrary units (a.u.). The 0–3 and 47–53 Hz

ranges were omitted so as to avoid contamination by movement artefact and mains noise, respectively. Relative rather than absolute power was analysed to allow comparison across subjects, as absolute power is more likely to be dependent on proximity to the LFP source than relative power and to vary with minor changes in recording technique. As two patients were originally sampled at 185 Hz in accordance with the Nyquist theorem, we only further analysed frequency bins up to 90 Hz for all patients. For visualisation purposes power spectra were averaged over all three contact pairs of each electrode and subsequently averaged across each patient group. In order to define the focality of spectral activity, the contact pair with the highest band power in the frequency range of interest (8–14 Hz) was selected and power at the remaining contact pairs per electrode was expressed as percentage of maximum band power.

Statistical analysis

Averaged power spectra of MDD and OCD patients recorded from the BNST were compared using non-parametric Monte Carlo permutation tests for each frequency bin.[41] Therefore, the null hypothesis was tested that power spectra from both groups were interchangeable by comparing mean sample values from each frequency bin in MDD and OCD patients to 5000 replications of the test statistic generated by randomly exchanging elements between distributions from MDD and OCD spectra. This procedure is free from any assumptions about the distributions of power and differences in power and is robust against small sample size.[41] Multiple comparisons were corrected for all frequency bins by controlling the false discovery rate for an α-level of $\alpha = 0.05$.[42] To rule out undesired effects caused by differences in recording procedures, this direct comparison was only carried out between seven MDD patients (cases 8–14) and five OCD patients (cases 15–19) with LFPs recorded from the BNST target area using the same recording set-up. Only *P*-values that were smaller than the false discovery rate-corrected threshold of $P = 0.0074$ (for $\alpha = 0.05$) and that extended over at least three frequency bins were considered significant. After confirmation of significant α-power differences between MDD-BNST and OCD-BNST, spectral power averages were computed for the significant α-range (8–14 Hz) for all patients. All α-band averages were normally distributed as confirmed by one-sampled Kolmogorov–Smirnov tests. In a subsequent analysis, we compared only contact pairs with the highest α-band power for the MDD-BNST and OCD-BNST patients' group with a parametric independent *t*-test to rule out a possible localisation bias introduced by averaging of contact pairs. Furthermore, a potential systematic influence of medication was tested by subgroup analyses of OCD and MDD patients treated by benzodiaze- pine (5/5 OCD patients; patients 15–19; 5/14 MDD patients; patients 1,2,6,8 and 9) using non-parametric Wilcoxon's rank-sum test across groups (OCD versus MDD) and within-group analysis for atypical neuroleptics, tricyclic antidepressants and lithium for MDD (atypical neuroleptic medication: 5/14 MDD patients, patients 1,3,4,6 and 7; tricyclic antidepressant treatment: 4/14 MDD patients, patients 1,6,12 and 14; lithium 6/14 MDD patients, patients 2,3,4,11,12 and 14).

In a next step, α-band power averages for each electrode were submitted to a 3 × 2 × 2 mixed analysis of variance. Between-subject factors were patient group (MDD-CG25, MDD-BNST and OCD-BNST) and sex (male, female) and the within-subject factor was the

electrode's hemisphere to test for laterality effects. *Post hoc* significance levels were false discovery rate corrected for multiple comparisons. In order to evaluate frequency-specific effects, the analysis of variance was repeated for mean power in the β-frequency band (15–35 Hz). To test for an association of oscillatory power with psychiatric symptom severity, bivariate two-tailed Spearman's correlations were carried out for averaged α- and β-power values per patient and the individual perioperative BDI (MDD patients) and YBOCS (OCD patients).

RESULTS

Power spectra

The relative power spectra averaged across all contact pairs, electrodes and subjects separately for each patient group and DBS area, revealed a distinct peak in the α-frequency range in MDD patients, irrespective of the DBS target area (Figures 2a and b). The α-power peak was not present in OCD patients. Individual examples of the spectrogram for each group are shown in Figure 3. Comparison of MDD and OCD power spectra for the BNST area revealed significantly higher power in MDD patients over a broad α-frequency band from 8 to 14 Hz ($P<0.01$; Figure 2b). Subsequent comparison of mean 8–14 Hz activity from the contact pairs with the highest relatively α-power in each electrode confirmed significantly higher α-power in MDD BNST (3.1 ± 0.4 a.u.) as compared with OCD BNST (1.4 ± 0.12 a.u.; independent samples *t*-test, $P<0.01$). This was also the case in a subgroup analysis of five MDD BNST patients that excluded cases 9 and 10, which were sampled at 185 Hz (2.6 ± 0.46 a.u.) and the five OCD BNST patients (1.4 ± 0.12 a.u.; Independent samples *t*-test, $P = 0.007$).

Analysis of variance of averaged α-power for each electrode confirmed significant main effects for the factor patient group (MDD-CG25 versus MDD-BNST versus OCD-BNST; F(2,13) = 9,008; $P = 0.004$, $\eta^2 = 0{,}581$; Figure 4a). No significant main effects were found for sex (F(1,13) = 0.1; $P = 0.76$, $\eta^2 = 0.008$) or hemisphere (F(1,13) = 0.119; $P = 0.736$, $\eta^2 = 0{,}09$), and none of the tested interactions were significant. *Post hoc t*-tests indicated significant higher α-power in the MDD-CG25 and MDD-BNST patient group compared with the OCD-BNST group ($P = 0.01$ and $P = 0.03$, respectively). Comparison of MDD-CG25 and MDD-BNST failed to show a significant difference ($P = 0.08$). The effect of patient group was frequency specific to the α-band; there were no significant main effects or interactions in a separate analysis of variance using mean β-power (15–35 Hz). Additional subgroup analysis of MDD and OCD patients treated with benzodiazepines confirmed the main result with significantly larger α-power in the MDD subgroup as compared with OCD (Wilcoxon's rank-sum test, $P<0.01$). Thus, the main result of larger α-power in MDD was irrespective of benzodiazepine treatment. Within the MDD group comparisons for atypical neuroleptics, tricyclic antidepressant therapy and lithium did not reveal significant differences (Wilcoxon's rank-sum test, $P = 0.6$, $P = 0.1$ and $P = 0.059$, respectively; see also Supplementary Figure). Interestingly, mean α-activity was lower in the subgroup treated with tricyclics and lithium, which would only mean that we may underestimate the α-activity in those MDD patients. Thus, medication is unlikely to explain the systematic α-power differences observed between OCD and MDD patients.

Alpha power maxima were arbitrarily distributed across contact pairs (MDD-CG25/MDD-BNST/OCD-BNST: contact pair 01: n = 5/4/3; contact pair 12: 6/3/2; contact pair 23: 3/7/4) with a mean drop of 15.0 ± 2.3% for MDD-CG25, 36.4 ± 4.0% for MDD-BNST and 30.3 ± 4.5% for OCD-BNST at the remaining contact pairs.

Correlation of oscillatory power and depressive symptoms

Relative α-power averaged across hemispheres correlated significantly with the self-reported disease severity as measured by the BDI at the time of LFP recordings in MDD patients (n = 14 MDD, Spearman's ρ = 0.55, P = 0.042; Figure 4b). The correlation remained significant when the two MDD patients sampled at 185 Hz were rejected (Spearman's ρ = 0.66; P = 0.026). No correlation was found for YBOCS in OCD patients. Beta band activity did not correlate with BDI or YBOCS (results not shown).

DISCUSSION

We have demonstrated that patterning of oscillatory neuronal population activity in the human BNST area can distinguish patients suffering from treatment-resistant depression and patients with medically intractable OCD. Furthermore, our results suggest a link between enhanced LFP broad α-activity (8–14 Hz) in the CG25 and BNST area in MDD and self-reported affective state. Although correlation does not prove causation, the demonstration of a significant correlation can be interpreted as support for the hypothesis that increased α-band activity may be a state marker for depressive symptoms in MDD. This raises the possibility that DBS may act by suppression of aberrant α-activity in MDD. Before we proceed with a more detailed discussion of our findings, we should bear in mind the potential limitations of our study.

We present data from a relatively small cohort of patients, in line with the sparseness of these experimental procedures in psychiatric patients. Moreover, intracranial recordings in human subjects suffer from the major limitation that electrode placement is not backed up by histological investigation and hence remains presumptive. This was further compounded by the use of different electrode models across patients that span a variable distance as have been used in our patients. Postoperative imaging was conducted in all our patients and was consistent with electrode placement in the selected target area. Another confound is the action of antidepressant medications, although these are not known to alter cortical α-electroencephalographic activity in MDD;[43,44] moreover, MDD as well as OCD patients received pharmacological treatment for their mood disorder. Moreover, subgroup analysis of patients selected by medication classes within and across patient groups did not indicate systematic drug effects. Variations in vigilance could also present a possible confound and this was not explicitly tested in our patients. Furthermore, our results cannot be compared with those of healthy controls, an inherent limitation of intracranial recordings in humans. One way to overcome this limitation is to compare neuronal activity within the same target structure from patients with different disease entities or define a consistent pattern of oscillatory activity along the network nodes of a circuit for a specific disorder. Here, we follow both approaches. First, we compare our results from MDD patients with recordings from patients suffering from OCD, two different psychiatric conditions, although depressive

symptoms may also occur in OCD. Second, we revealed a disease-specific neuronal pattern for MDD from two target areas of the limbic network, the CG25 and BNST area. As the observed difference in oscillatory activity between MDD and OCD does not allow us to define which neuronal pattern relates to an abnormal affective state, we therefore conducted correlative analyses for both, the OCD and MDD symptom severity scales with neurophysiological parameters. Significant results were only obtained for the BDI and not for the YBOCS. Correlations pointed to higher rating scores of depression with enhanced α-power and also suggest that the symptomatology underlying the differences in the MDD and OCD groups may relate to depression rather than OCD. Interestingly, BDI scores were also high in some of the OCD patients indicating concurrent depressive symptoms, but in the presence of lower α-power. This might suggest a different basis for depressive symptomatology in OCD.[45] Thus, a previous PET study has demonstrated that depressive episodes occurring in OCD may be partially mediated by different basal ganglia-thalamic loops compared with primary MDD patients.[46] Finally, correlations of α-power were performed with the self-rated BDI score in our patients. Future studies should also use patient-independent clinical scales such as the Hamilton depression inventory to assess depressive symptoms in MDD at the time of LFP recordings.

Notwithstanding the above-mentioned limitations, and in addition to the evidence that oscillatory activity differs between the two conditions, a significant correlation between perioperative BDI and α-band power suggests that synchronous α-activity is related to current mood state across limbic target structures in MDD patients. Thus, it could be speculated that the observed α-activity is part of a limbic oscillatory network that is overly active in MDD. In line with the observations of a DBS-induced suppression of pathological network activity in PD patients that is paralleled by clinical improvement in motor symptoms,[12,15,16,47-49] aberrant α-band activity in MDD may potentially be decreased by DBS of limbic targets. Although the focus on α-band activity in this study is driven by the primary statistical comparison of OCD and MDD, it is further backed up by non-invasive electrophysiological studies that establish increased α-network activity as an oscillatory hallmark of the depressive state at the cortical level.[50-56] Anterior electroencephalogram α-power asymmetry with increased left frontal α-power in depressed patients has been related to abnormal emotional processing.[57,58] However, this asymmetry index is an inconsistent finding[59] and we could not replicate hemispheric asymmetry in the subcortical BNST or CG25 areas. Modulation of cortical α-power occurs during passive viewing of emotional pictures.[60,61] Moreover, intracortical recordings from the human subthalamic nucleus show oscillatory α-band modulations during emotional processing that are linked to the depressive symptoms in PD patients.[62-64]

Increases of α-activity have been related to inhibition and suppression of task-irrelevant information and α-desynchronisation may reflect active processing and excitation.[65,66] Viewed in this light, increased α-activity would indicate reduced activity of the respective brain areas in our MDD patients, which is in contrast to the bilateral CG25 hypermetabolism reported in MDD patients using PET.[4] Nevertheless, other recent studies also point to enhanced α-band coherence and loss of selectivity in resting functional connectivity in the α-band, primarily between different cortical sites and the prefrontal cortex.[50,51] Our findings extend these observations to subcortical areas, suggesting that enhanced α-band power may

disturb normal processing of emotional information in MDD (although cortical electroencephalogram for coherence measures were not available in our patients owing to surgical dressings). Corroboration and extension of our results in animal studies is highly desirable, but electrophysiological recordings in validated animal models for depression have been unavailable up to now. In this regard, it is intriguing that long-term high-frequency stimulation in the wild-type rodent nucleus accumbens leads to a significant decrease in oscillatory α-band network activity, whereas cessation of stimulation triggers an activity rebound in the same frequency band,[67] although these findings should be replicated in animal models for depression to allow inferences about the mechanism of DBS in MDD.

We report the first evidence of disease-related oscillatory activity recorded directly from human limbic structures implicated in the pathophysiology of MDD. Our results suggest that locally generated α-oscillations in the human limbic system may relate to depressive symptoms and negative mood state in MDD. Pathological oscillatory patterns have been shown to be helpful in intraoperative target selection for DBS surgery in movement disorders[68] and are now being evaluated as a basis for feedback control in closed loop stimulation.[17,69] Our results suggest that increased α-band activity might be a candidate biomarker in MDD for adaptive DBS, although further studies investigating cortico-subcortical interactions of α-activity and emotional processing in the limbic system are needed to gain a comprehensive insight into the underlying oscillatory network and its role in depression.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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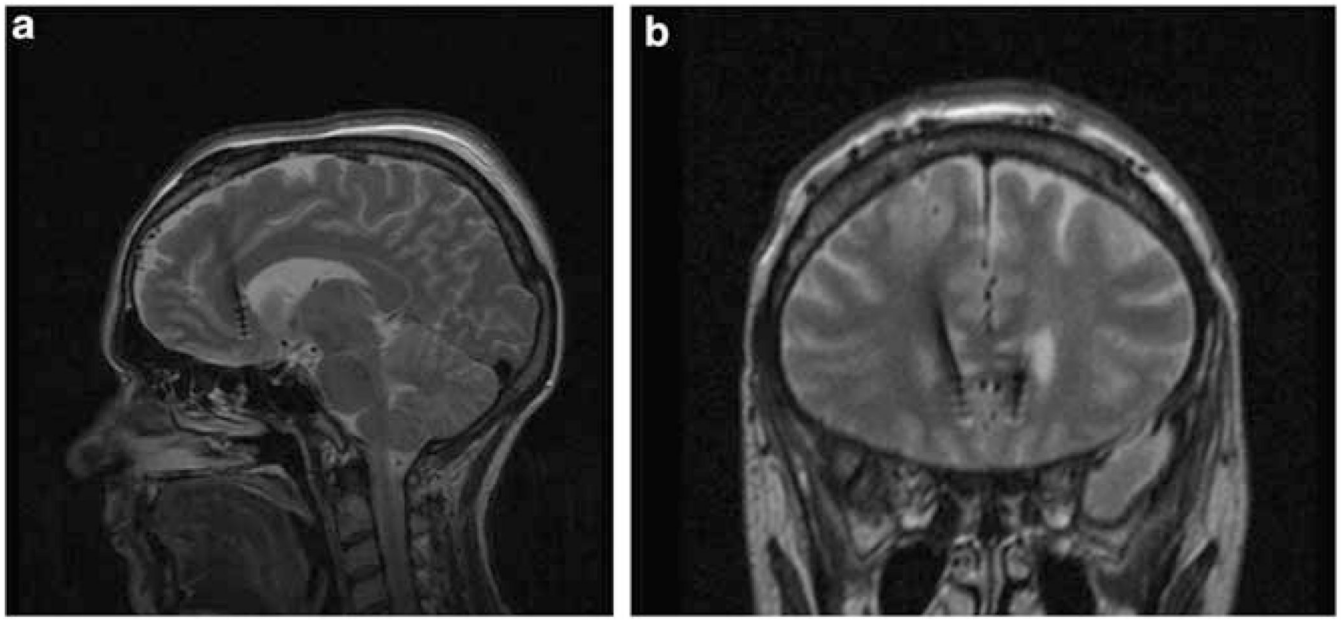

Figure 1.

Postoperative magnetic resonance imaging (MRI). Sagittal (**a**) and coronal (**b**) slice of a postoperative T2-weighted structural MRI with electrodes at CG25 target area (case 1).

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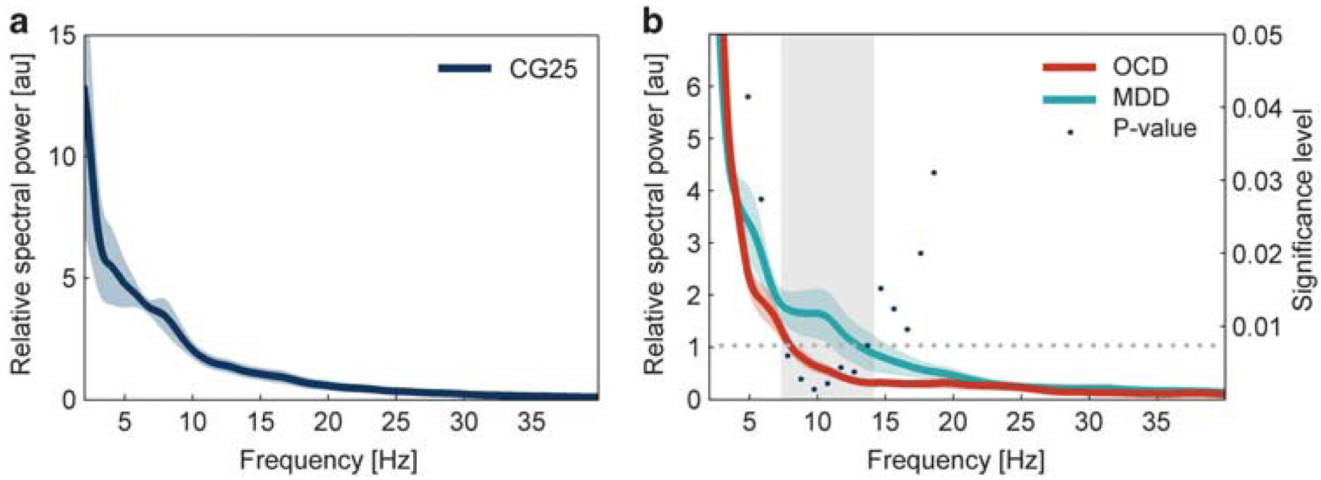

Figure 2.

Grand mean of normalised power spectra for the major depressive disorder (MDD)-CG25 (**a**) and MDD-bed nucleus of stria terminalis (BNST), and obsessive compulsive disorder (OCD)-BNST patient groups (**b**) plotted for the frequency range of 2–40 Hz. Shaded areas of power spectra indicate 95% confidence limits for each patient group and target area. Grey shaded area in panel **b** shows the significant difference between OCD-BNST (red line) and MDD-BNST (blue line) patient groups (8–14 Hz). The grey horizontal dotted line indicates the false discovery rate (FDR)-corrected significance threshold of $P = 0.0074$, blue dots indicate the *P*-value per frequency bin (only uncorrected *P*-values below $P = 0.05$ shown). Some of the individual power spectra in both BNST patient groups contained peaks in the β-frequency band (15–35 Hz; 37 out of 78 contact pairs), but β-band activity did not differ between patient groups. No peaks were present above 40 Hz. Power spectra in the figures are interpolated for the purpose of visualisation.

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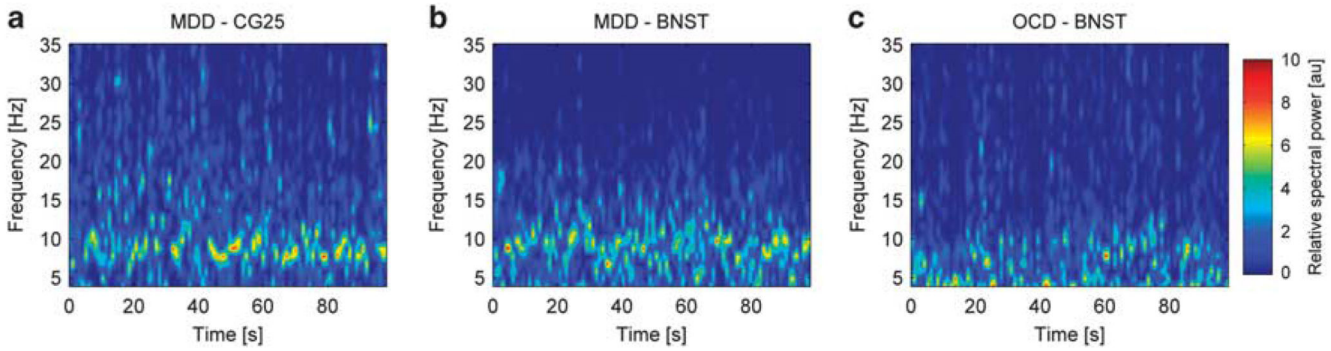

Figure 3.

Individual examples of relative power spectra for each group visualised over the recording time. Note the consistent α-power elevation in the major depressive disorder (MDD) patients (**a**), CG25, patient 7; (**b**), bed nucleus of stria terminalis (BNST), patient 10. In obsessive compulsive disorder (OCD) patients the α-power peak was smaller and less consistent over time (c), BNST, patient 17. Time–frequency representations in the figure were interpolated for the purpose of visualisation. Colour bar indicates relative spectral power (a.u.).

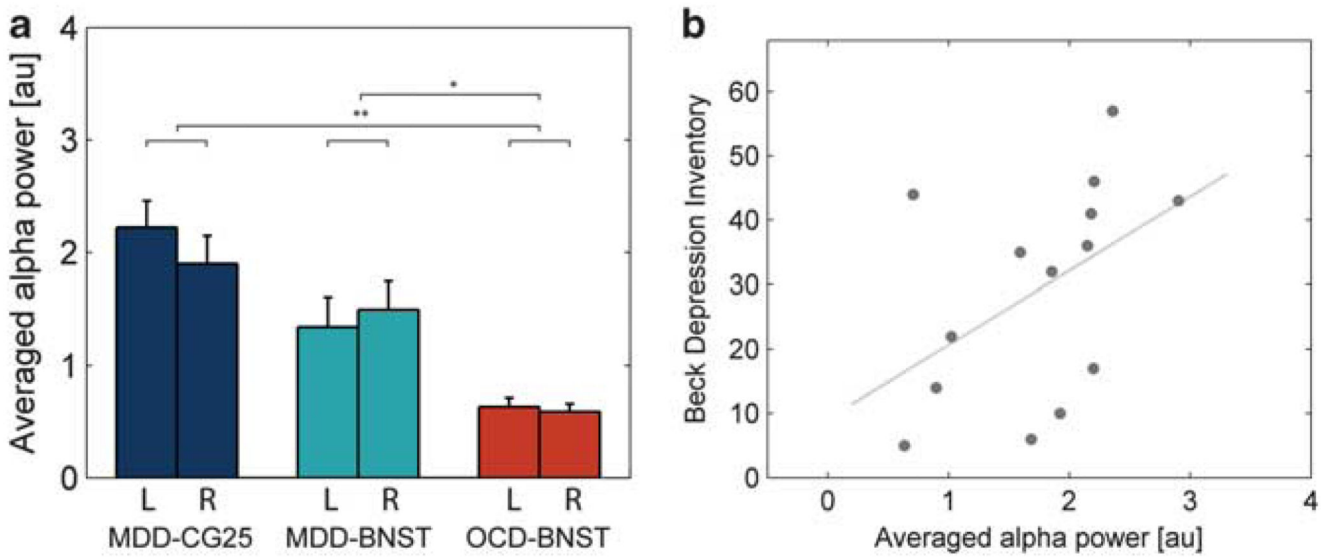

Figure 4.

Statistical analysis of averaged α-power (grand means shown in panel **a)** revealed significant differences between major depressive disorder (MDD) and obsessive compulsive disorder (OCD) groups (**P*<0.05; ***P* = 0.01), but no effect for laterality or sex. (**b**) Averaged α-power significantly correlated with the individual Beck depression inventory (BDI) for MDD patients (*n* = 14 MDD, Spearman's $\rho = 0.55$, *P* = 0.042).

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Table 1

Patients' clinical details

N	*Target*	*Diagnosis*	*Center*	*Age*	*Sex*	*Disease duration*	*BDI* [a]	*HAM-D* [b]	*YBOCS*[b]*/comorbid depression*	*Medication*
1	CG25	MDD	Berlin	49	F	33	35	22	NA	Loracepam, amitriptyline, quetiapine, topiramate
2	CG25	MDD	Berlin	61	F	23	22	23	NA	Loracepam, clomipramine, fluvoxamine, lithium, gabapentine, mirtazapine
3	CG25	MDD	Berlin	48	F	16	46	30	NA	Lithium, quetiapine, duloxetine
4	CG25	MDD	Berlin	60	F	20	36	34	NA	Lithium, tranylcypromine, pregabaline, quetiapine
5	CG25	MDD	Berlin	36	M	16	57	24	NA	No medication
6	CG25	MDD	Berlin	50	M	34	41	32	NA	Zopiclone, quetiapine, trimipramine
7	CG25	MDD	Berlin	55	M	20	37	21	NA	Pregabalin, agomelatine, quetiapine, levothyroxine
8	BNST	MDD	Leuven	58	M	34	10	21	NA	Reboxetine, zoplicone, clorazepat, allopurinol, trazodone
9	BNST	MDD	Leuven	42	F	25	32	27	NA	Lormetazepam, venlafaxine, lorazepam, promethiazine, trazodone, elthyrone
10	BNST	MDD	Leuven	51	F	5	17	27	NA	No medication
11	BNST	MDD	Leuven	55	M	11	14	21	NA	Venlafaxine RT, lithiumcarbonate
12	BNST	MDD	Leuven	45	M	9	44	23	NA	Clomipramine, trazodone, lithiumcarbonate
13	BNST	MDD	Leuven	46	M	9	6	26	NA	Duloxetine
14	BNST	MDD	Leuven	50	F	14	5	25	NA	Aripiprazole, clomipramine, lithiumcarbonate, trazodone, lormetazepam, simvastatine
15	BNST	OCD	Leuven	32	M	17	20	21	32/No	Clomipramine, quetiapine, fluvoxamine, clonazepam
16	BNST	OCD	Leuven	52	M	34	10	27	35/Yes	Prazepam
17	BNST	OCD	Leuven	60	M	52	NA	29	36/Yes	Buspirone, fluvoxamine, clonazepam
18	BNST	OCD	Leuven	51	F	33	35	14	37/Yes	Alprazolam
19	BNST	OCD	Leuven	34	M	22	10	20	37/No	Bisoprolol, melatonine, alprazolam

Abbreviations: BDI, Beck depression inventory; BNST, bed nucleus of stria terminali; F, female ; HAM-D, Hamilton depression inventory; M, male; MDD, major depressive disorder; NA, not available; OCD, obsessive compulsive disorder; YBOCS, Yale-Brown Obsessive Compulsive Scale.

[a] As assessed at the time of recording.

[b] As assessed at the preoperative baseline of the clinical study.