

ORIGINAL ARTICLE

Modulation of Beta-Band Activity in the Subgenual Anterior Cingulate Cortex during Emotional Empathy in Treatment-Resistant Depression

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Abstract

Deep brain stimulation (DBS) is a promising approach in treatment-resistant depression (TRD). TRD is associated with problems in interpersonal relationships, which might be linked to impaired empathy. Here, we investigate the influence of DBS in the subgenual anterior cingulate cortex (sgACC) on empathy in patients with TRD and explore the pattern of oscillatory sgACC activity during performance of the multifaceted empathy test. We recorded local field potential activity directly from sgACC via DBS electrodes in patients. Based on previous behavioral findings, we expected disrupted empathy networks. Patients showed increased empathic involvement ratings toward negative stimuli as compared with healthy subjects that were significantly reduced after 6 months of DBS. Stimulus-related oscillatory activity pattern revealed a broad desynchronization in the beta (14–35 Hz) band that was significantly larger during patients' reported emotional empathy for negative stimuli than when patients reported to have no empathy. Beta desynchronization for empathic involvement correlated with self-reported severity of depression. Our results indicate a "negativity bias" in patients that can be reduced by DBS. Moreover, direct recordings show activation of the sgACC area during emotional processing and propose that changes in beta-band oscillatory activity in the sgACC might index empathic involvement of negative emotion in TRD.

Key words: deep brain stimulation, empathy, local field potential recordings, sgACC, treatment-resistant depression

Introduction

Major depressive disorder (MDD) is a widespread and chronic disorder that evokes a massive socio-economic burden (WHO 2004). One-third of depressive patients are therapy-refractory, and new treatment options are currently investigated (McIntyre et al. 2014). The dorsolateral prefrontal cortex (DLPFC) and the

subgenual portion of the anterior cingulate cortex are thought to be part of a limbic-cortical-striatal-pallidal-thalamic network that is involved in emotion processing and MDD (Mayberg 2003; Savitz and Drevets 2009). There is increasing evidence that deep brain stimulation (DBS) of different target regions has therapeutic effects in patients with treatment-resistant depression (TRD) (Mayberg et al. 2005; Holtzheimer et al. 2012), including

the nucleus accumbens, medial forebrain bundle (MFB), anterior subgenual cingulate cortex (sgACC), anterior limb of internal capsule, the habenula, and the inferior thalamic peduncle (Mayberg et al. 2005; Greenberg et al. 2006; Bewernick et al. 2010; Sartorius et al. 2010; Holtzheimer et al. 2012; Jimenez et al. 2013; Schlaepfer et al. 2013). The most rapid antidepressive effect so far showed direct MFB stimulation that may act as an extension of relevant pathways to the prefrontal cortex within the neurocircuitry underlying depression (Sartorius et al. 2013). One of the most investigated targets for DBS in patients with TRD comprises the sgACC area (Mayberg et al. 2005). On the basis of a series of positron emission tomography studies, Mayberg and colleagues established hypermetabolism in the sgACC as a correlate of negative mood and depression. Moreover, chronic DBS-related remission of TRD symptoms was associated with a reduction of cerebral blood flow in the target area and downstream limbic and cortical sites (Mayberg et al. 1999; Dougherty et al. 2003; Seminowicz et al. 2004; Ressler and Mayberg 2007). However, the mechanism of action of DBS and its role in the pathophysiology of depression is still not completely understood. Moreover, there are only few studies investigating the potential reasons for the striking different treatment response between patients with TRD that undergo DBS (Riva-Posse et al. 2014).

Neural oscillations are a crucial mechanism for enabling coordinated activity during normal brain functioning (Buzsaki and Draguhn 2004; Buzsaki 2006). The opportunity to record local field potentials (LFPs) from DBS electrodes during and shortly after DBS surgery, while DBS electrodes are still externalized, has contributed considerably to our understanding of the underlying pathophysiology of circuit disorders such as Parkinson's disease (PD) (Lozano and Lipsman 2013). Of importance, it had been demonstrated that DBS is capable of suppressing disruptive pathological oscillatory activity in neurological disease like PD (Kühn et al. 2008; Eusebio et al. 2011), thereby offering an explanation for how DBS may act to improve clinical symptoms in movement disorder patients (Eusebio and Brown 2009). Our understanding of the oscillatory neuronal circuits subserving psychiatric disorders is evolving (Uhlhaas and Singer 2010); however, little is known about the underlying nature of oscillatory neuronal activity in the structures targeted by DBS in these disorders. A recent report of patterning of oscillatory neuronal population activity in the human bed nucleus of the stria terminalis and sgACC area in depression and obsessive-compulsive disorder showed that oscillations might represent a surrogate parameter for abnormal circuit activity in patients with mood disorders (Neumann et al. 2014). Increased α -network activity as an oscillatory hallmark of the depressive state at the cortical level has been demonstrated in noninvasive electrophysiological studies (Fingelkurts et al. 2007). Resting-state EEG showed that frontal theta cordance predicted antidepressant response to sgACC DBS (Broadway et al. 2012). Moreover, anterior electroencephalogram α -power asymmetry with increased left frontal α -power in depressed patients has been related to abnormal emotional processing (Aftanas et al. 2001). Although classically considered as being related to motor functions, the functional role of the beta-band oscillations is still under debate (Engel and Fries 2010). It has been suggested that beta-band (13–35 Hz) oscillations occurring during cognitive processes would decrease if a novel or unexpected event happened and would increase if tasks involving a top-down component were involved (Engel and Fries 2010). A still open question is the influence of cortical layer or target region in which LFP recordings are performed, and it seems possible that different cortical areas exhibit different modulation in the various frequency bands (Siegel et al. 2008). Interestingly, Lipsman and colleagues recorded in

human subcallosal ventro-medial prefrontal cortex (vmPFC) from deep brain electrodes implanted in subjects with TRD (Lipsman et al. 2014). While the patients engaged in an emotion tracking task that required the assignment of positive or negative affective value to ambiguous facial expressions, low beta-band (15–20 Hz) coherent activation was engaged in vmPFC. We therefore test the hypothesis that distinct temporal patterns of local field potential activity in the human fronto-limbic system reflect core features of depressive symptoms in MDD. MDD is a mood disorder with a complex pattern of interlinked emotional disturbances. Among them, a reduced reward perception and valuation as well as negativity bias (Watters and Williams 2011) “referring to selective attention to negative rather than positive information” constitute a stable feature. Further, depression is often accompanied by deficits in cognition, like declarative learning and memory which might be a consequence of impaired hippocampal neurogenesis (Sapolsky 2004). It is thus very likely that symptoms of patients with TRD result from an alteration of affective processing (Thoma et al. 2011). A consequence is social withdrawal, problems in social functioning, and avoidance behavior in depressive patients (Seidel et al. 2010). It is conceivable that impaired empathy might constitute 1 main mechanism conveying these biased cognitive and emotional processes. Empathy is a multidimensional construct (Singer 2006; Decety and Meyer 2008) including 2 components—a cognitive component: the capacity to infer others' mental states (“perspective taking”) (Blair 2005), and an affective component, relying on perspective taking and facilitating affective sharing of other people's emotional states (Singer 2006). The latter is associated with an activation of limbic structures such as the ACC, the nucleus accumbens (Schilbach et al. 2014), and the anterior insula (Singer 2006) as revealed by functional imaging (fMRI) studies. A recent fMRI study showed that altruistic decisions driven by empathy-based guilt probe residual sgACC hypersensitivity in MDD even after symptoms are fully remitted (Pulcu et al. 2014). Two lines of evidence suggest that empathy might be impaired in MDD: 1) impairments in domains of self-reported measures and objective tasks of empathy and disrupted interpersonal interactions have been observed both in acute and remitted patients with depression (Schreier et al. 2013), 2) the PFC, the ACC, the temporal cortex and the amygdalae show changes in depression (Clark et al. 2009) and have also been found as neural correlates of cognitive and affective empathy components (Singer and Lamm 2009).

Based on these findings, we hypothesized that in depressed individuals specific empathy features might be related to depression severity and that the ability to empathize with other people's emotional states might depend on the valence of these emotional states in terms of a “negativity bias.” Thus, the aim of the present study was to evaluate the role of the sgACC for empathic emotional processing using invasive recordings of neuronal activity via DBS electrodes in 9 patients with TRD during the presentation of an active empathy task. First, we sought to identify oscillatory response patterns during cognitive and emotional empathy and its association with clinical symptoms using the multifaceted empathy test (MET) (Dziobek et al. 2011), because the test uses real life interpersonal interactions demanding the patient's personal involvement. Second, we aimed to characterize the modulation of behavioral responses during chronic sgACC stimulation in patients with TRD.

Methods and Materials

Patients and Surgery

Nine patients with treatment-resistant major depressive disorder (TRD), diagnosed according to DSM-IV criteria by 2 senior

clinicians not involved in the protocol (4 women; age: 50.11 years, mean \pm 12.73 SD), who underwent bilateral implantation of macro-electrodes in the subcallosal cingulate cortex comprising the sgACC area as part of an ongoing clinical trial (NCT00531726) were included in the study. The clinical details of patients are summarized in Tables 1 and 2. Informed consent was obtained from the local ethics committee of the Charité University-Medicine in Berlin and the University of Cologne (Germany). Preoperative assessments included the Hamilton Depression Rating Scale (HAMD) 24-item version (Hamilton 1960) and the Beck Depression Inventory (BDI) (Hautzinger 1991) as well as a rigorous neurological and neuropsychological assessment as part of a routine preoperative work-up. BDI and HAMD-24 were obtained in all patients at the time of the LFP recordings and 6 months after chronic DBS as main outcome parameter. DBS was performed targeting the sgACC area as described previously (Mayberg et al. 2005; Hamani et al. 2009) using quadripolar DBS electrode (model 3387; Medtronic Neurological Division). Contact 0 and 3 were the lowermost and uppermost contacts, respectively. Correct placement of the DBS electrodes was confirmed by postoperative MR imaging in 7 of the patients and a fusion of postoperative computed tomography (CT) with preoperative MR scans in 2 patients (#6 and #8). Reconstruction of electrode contact placements was determined using the LEAD-DBS toolbox (Horn and Kühn 2015; <http://www.lead-dbs.org>) is shown in Figure 1.

Experimental Paradigm and Recordings

All patients were studied within a mean of 3.4 days (range 3–6 days) after initial DBS surgery, whereas the DBS leads were still externalized. Patients were taking their usual medication (Table 1); 2 patients took benzodiazepines, which were stopped in the evening before the day of LFP recordings.

To assess cognitive and emotional empathy, the MET (Dziobek et al. 2008) was administered, which has been shown a reliable and sensitive measure of empathy in previous studies involving healthy participants and those with psychiatric disorders (Hurlmann et al. 2010; Dziobek et al. 2011; Wingenfeld et al. 2014). Study participants were presented with a series of 80 photographs (with 40 negative and 40 positive stimuli) that were taken from the original MET (Dziobek et al. 2011) using customized experimental control software (Presentation, Neurobehavioral Systems, Inc., <http://www.neurobs.com/>). Patients had to respond to a block of stimuli testing either cognitive or emotional empathy. Eight blocks containing each 10 stimuli (negative valence or positive valence) were performed (for details, see Fig. 2). The emotional and cognitive empathy stimuli were used in different blocks of trials. The ratio of stimuli testing cognitive and emotional empathy was equal.

Recordings

Bipolar recordings were obtained from 3 adjacent DBS contact pairs (01, 12 and 23). Thereby, we aimed to minimize signal contamination by volume conduction of nearby structures. Scalp EEG recordings were obviated by postoperative wounds, surgical dressings, and time constraints. LFPs were filtered from 0.5 to 250 Hz and sampled at 1 kHz (cases 1–2) or 5 kHz (cases 3–9) through an AD converter (1401power mk-II, Cambridge Electronic Design) at 50 000-fold amplification (Digitimer D360, Digitimer, Wellesbourne) and stored on a hard drive for offline analysis. LFP traces were downsampled to a common sampling rate of 1 kHz. Trials containing artifacts due to noise or movements were rejected. One channel (left channel 0) of patient #9 had to be

discarded due to technical artifacts. Overall 54 contact pairs were recorded from 18 electrodes in 9 patients.

Time-Frequency Analysis and Statistical Analysis

All data were analyzed using custom MATLAB code (The Mathworks, R2013b) based on SPM8 for MEG/EEG (Wellcome Department of Cognitive Neurology; www.fil.ion.ucl.ac.uk/spm/) (Litvak, Mattout et al. 2011). To avoid a selection bias, all 3 bipolar electrode pairs of each electrode were analyzed. To assess event-related changes in LFP activity, responses were averaged across trials of the same condition and were calculated independently. Trials were divided into event-related epochs (times -3000 to 3000 ms centered at stimulus appearance) and transformed to the frequency domain using a multitaper fast Fourier Transform (FFT)-based approach. The length of the FFT sliding window was 400 ms, shifted in 50-ms steps. The time-frequency (TF) representations were then averaged for all trials per contact pair and baseline corrected to the standard deviation of the pre-stimulus baseline taken from -3000 to -1000 ms for each frequency band (Z-score) as described in the additive model by Grandchamp and Delorme (2011). Analysis of movement-related changes after button press was analyzed using event-related epochs (times -6000 to 3000) and baseline corrected to a pre-stimulus baseline from -6000 to -4000 ms with button press at time point 0. Therefore, baseline-corrected TF maps for each contact pair and each patient were converted to image files (NIFTI format, <http://nifti.nimh.nih.gov/nifti-1/>), which is a prerequisite for subsequent analysis with the SPM8 toolbox. The images were smoothed with a Gaussian Kernel of $4 \text{ Hz} \times 400 \text{ ms}$ full width at half maximum, to ensure conformance to the assumptions of random field theory (Kilner et al. 2005). Changes of oscillatory activity between 2 and 90 Hz were compared with the baseline for stimulus and button press-aligned TF representations separately using flexible factorial models with the smoothed images in SPM (Litvak, Jha et al. 2011). All cluster-level-based inference was Family-Wise Error (FWE) corrected for multiple comparisons at a threshold of $P < 0.01$. Contrasts were chosen to identify significant positive (ERS) or negative (ERD) deviations of oscillatory activity from the baseline period using SPM's F-statistics for the stimulus as well as the button press aligned data regardless of the task condition ("Grand Average statistic"). For the purpose of visualization, all time-frequency representations aligned to 1) stimulus presentation and 2) motor response were averaged across all patients, contact pairs, and conditions ("Grand Average visualization"). Standard frequency bands that were included in the main significant clusters were chosen for emotion-specific analysis on the basis of the results of the grand average TF maps. The averaged time \times frequency values (0.5–2.0 s peristimulus time; theta 4–8 Hz, alpha 9–13 Hz and beta 14–35 Hz) were subsequently subjected to repeated-measures (rm) ANOVAs, with 2 main factors empathy/performance (EMO EMP "more") and (COG EMP "correct") and valence (positive, negative) and between-subject factors electrode's hemisphere to test for laterality, and sex. Extracted power band changes over time are displayed as cumulative sums, that is, the power value at each time bin is the sum of power of all previous time bins. Thereby changes of power (either increase or decrease) in comparison with baseline activity are reflected by a deflection from a zero gradient (=horizontal line). To test for an association of task-dependent oscillatory power change with psychiatric symptom severity, bivariate two-tailed Spearman's rank (non-parametric) correlations were carried out for frequency-specific averaged power values per patient and the individual perioperative BDI and BDI difference (baseline during LFP recordings and BDI score after

Table 1 Clinical data and follow-up

No.	Age/sex	Disease duration (DD)	BDI ^a	BDI ^b	HAMD-24 ^b	DE	Suicide attempt	Age (DO)	ECT life time ^c	FUP BDI ^d	FUP BDI ^e	ATHF ^f	FUP HAMD-24 ^d	FUP HAMD-24 ^e	Medication ^g
1.	61/f	23	22	22	23	5	0	23	53	1	6	13	1	9	Lorazepam, clomipramine, fluvoxamine, lithium, gabapentine, and mirtazapine
2.	48/f	16	46	46	30	10	10	16	81	36	41	18	21	27	Lithium, quetiapine, and duloxetine
3.	60/f	20	36	36	34	10	0	20	32	12	17	14	16	7	Lithium, tranylcyprominepregabalin, and quetiapine
4.	36/m	16	57	57	24	5	0	16	0	52	52	17	31	33	No medication
5.	50/m	34	41	41	32	5	0	34	18	37	42	20	36	29	Zopiclone, quetiapine, and trimipramine
6.	55/m	20	43	43	31	4	0	35	35	31	n.a.	n.a.	29	21	Pregabalin, agomelatine, quetiapine, and levothyroxine
7.	25/m	3	30	30	28	3	0	20	22	37	33	20	26	33	Mirtazapin
8.	65/m	15	24	32	30	15	1	36	24	35	19	32	32	29	Lorazepam, zopiclone
9.	50/f	6	36 ^h	36 ^h	24	6	1	29	24	8 ^h	n.a.	n.a.	14	5	No medication

n.a., not assessed; BDI, Beck Depression Inventory; HAMD-24, Hamilton Depression Rating Scale 24-item version; sgACC, subgenual anterior cingulate cortex; f, female; m, male; DE, depressive episodes; ECT, electroconvulsive therapy.

^aAs assessed at the time of recording.

^bAs assessed at the preoperative baseline of the clinical study.

^cRight unilateral and bilateral; acute and maintenance ECT.

^dFollow-up (FUP) after 12 weeks (3 months).

^eFollow-up after 24 weeks (6 months).

^fHigher scores in the antidepressant treatment history form indicate higher resistance (Sackeim 2001).

^gMedication was held stable 6 weeks prior and 6 months after the operation; ^hBDI-2.

Table 2 Behavioral analysis: comparison of patients and healthy subjects

	Patients (n = 8)	Healthy subjects (n = 18)	P-value
Emotional empathy (RT) (in ms)	2523.28 (\pm 701.16)	2031.80 (\pm 247.38)	0.089
Emotional empathy (RT) for positive stimuli (in ms)	2390.31 (\pm 785.06)	2097.04 (\pm 250.47)	0.333
Emotional empathy (RT) for negative stimuli (in ms)	2656.26 (\pm 673.42)	1966.57 (\pm 232.91)	0.023 ^{ab}
Emotional empathy (more; negative stimuli) (BP)	15.12 (\pm 4.12)	10.27 (\pm 3.93)	0.015*
Emotional empathy (more; positive stimuli) (BP)	9.62 (\pm 8.15)	9.61 (\pm 3.63)	0.299
Emotional empathy (delta more vs. less negative) (BP)	10.37 (\pm 8.07)	0.76 (\pm 8.22)	0.015 ^{aa}
Emotional empathy (delta more vs. less positive) (BP)	-2.25 (\pm 15.28)	-0.53 (\pm 7.82)	0.773
Cognitive empathy (RT) overall (in ms)	2991.58 (\pm 757.45)	2181.58 (\pm 205.84)	0.001 ^{***c}
Cognitive empathy (RT) for positive stimuli (in ms)	3013.67 (\pm 837.93)	2135.13 (\pm 159.71)	0.021*
Cognitive empathy (RT) for negative stimuli (in ms)	2969.49 (\pm 725.38)	2235.20 (\pm 234.94)	0.024*
Cognitive empathy (correct; negative stimuli) (BP)	13.50 (\pm 2.26)	14.55 (\pm 3.56)	0.374
Cognitive empathy (correct; positive stimuli) (BP)	13.00 (\pm 3.02)	14.44 (\pm 2.68)	0.267

Note: Mean scores and standard deviations for emotional and cognitive empathy: Healthy subjects significantly differed from patients' rating, showing no negativity bias toward negative stimuli^a ($T = 2.806$; $df = 24$; $P = 0.015$; T-test for independent samples). Healthy individuals reported that they shared their empathic concern for both positive and negative stimuli. Patients and healthy subjects differed significantly in RT for emotional empathy for negative stimuli^b and for the cognitive empathy task over all valences^c.

RT, response times in milliseconds; BP, button press.

* $P < 0.05$, ** $P < 0.001$.

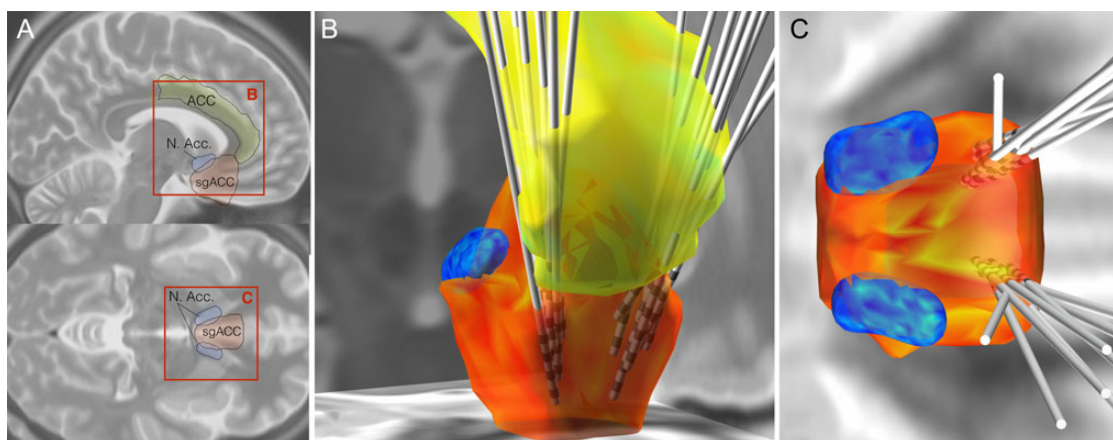


Figure 1. Three views of all electrode localizations in the MNI space. Anatomical regions from the Harvard-Oxford atlas are shown as isosurfaces of their probabilities: subgenual ACC (orange), nucleus accumbens (blue), and anterior cingulate cortex (yellow). Here, subgenual ACC is represented by the SCC region of the atlas but has been termed subgenual ACC to be consistent with the text. (A) Cuts through an MR template with field of views shown of Panels B and C marked in red, (B) three-dimensional reconstruction view from frontolateral right, (C) view from dorsal. Reconstruction of electrode contact placements: Images were first normalized into a standardized space defined by the Montreal Neurological Institute (MNI space) (Schonecker et al. 2009). In the 2 cases where CT imaging was performed after surgery, the CT and preoperative MR images were linearly coregistered, fused using the bioimage suite (<http://bioimagesuite.yale.edu>), and subsequently normalized using the same three-step normalization routine. Subsequently, on the normalized images, the centers of the hypointense (Weiler et al. 2013)/hyperdense (CT) electrode contact artifacts were manually localized in the form of 3D-coordinates in MNI space using in-house LEAD-DBS Toolbox (Horn and Kühn 2015; <http://www.lead-dbs.org>). The anatomical definition of the SCC was applied (Frazier et al. 2005) and visualized in line with the electrodes. Reconstruction of electrode contact placements is visualized (3D) for all electrodes, and the “International Consortium for Brain Mapping (ICBM) 2009b template” (Fonov et al. 2011) is shown in the background.

3–6 months). Only significant oscillatory activity of 500 and 2000 ms that occurred during the relevant task condition (emotional empathy for negative stimuli) was chosen for correlational analysis. Two cases (case #7 and case #9) had to be discarded from statistical LFP analyses due to a lack of sufficient trial numbers (condition EMO EMP, conditions with <8 response trials were discarded).

Behavioral analyses of the MET comprised analysis of the individual ratings for cognitive empathy (correct vs. wrong; negative vs. positive) and emotional empathy calculating a delta of more vs. less empathic involvement rating and negative vs. positive as well as a mean reaction time analysis of responses. Moreover,

we sought for a correlation between behavioral performance and depressive symptom severity (BDI) and its change with DBS. Analyses were done with non-parametric tests (Wilcoxon) as normal distribution (Kolmogorov–Smirnov Test) was not given. One patient (case #7) had to be discarded from behavioral analysis due to incorrect responding. As the task condition COG EMP represents a performance rating (“correct and incorrect”) and the task condition EMO EMP constitutes an appraisal rating (“more or less”), we calculated each condition separately. As we applied a modified version of the MET, we additionally investigated 18 healthy age- and sex-matched control subjects (mean age 47.33 ± 23.11 ; 9 women) using the same task to allow for correct interpretation



Figure 2. Schematic illustration of the experimental paradigm (MET). Top panel shows the emotional empathy (EMO EMP) condition: “How much are you feeling with this person?” vs. the cognitive empathy (COG EMP) condition: “What is this person feeling?” on the lower panel. Patients had to respond to either emotional empathy (EMO EMP) or cognitive empathy (COG EMP). The corresponding trials were preceded by the question “How much are you feeling with this person?” (EMO EMP) vs. “What is this person feeling?” (COG EMP). To assess EMO EMP, subjects were requested to select “less” or “more” when asked for their level of empathic sharing with the person depicted on a photo. Patients were instructed to press the button on the left or on the right, respectively. To assess COG EMP, subjects were required to infer the mental states of the individuals shown in the photographs by selecting 1 of 2 mental state descriptors. The introductory question lasted 4.5 s, followed by a fixation cross for 3.5 s. Each emotionally salient picture was presented for 4.5 s, and at the same time, a random response possibility was shown at the bottom of each picture. The same series of pictures were presented for the cognitive and emotional empathy conditions.

of the behavioral results in MDD patients. All data are given as mean and standard deviation if not stated otherwise.

Results

Behavioral Results

All patients attended to the paradigm with a 98% response rate across both tasks.

EMO EMP Task Condition

During LFP recordings (pre-DBS), patients showed significantly higher empathic involvement ratings with persons who depicted negative emotions than with persons who expressed positive emotions in the MET delta more-less_positive (-2.25 ± 15.28) vs. delta more-less_negative (10.37 ± 8.07 ; $T = 2.748$; $df = 7$; $P = 0.029$, see Table 2 and Fig. 3).

Comparing all negatively valenced empathic involvement ratings with respect to the selected response (i.e., more- vs. less-shared empathic involvement), a higher rating for more empathic sharing vs. less empathic sharing was revealed for negative stimuli ($T = 3.636$; $df = 7$; $P = 0.008$). Comparing all positively valenced empathic involvement ratings with respect to the selected response (i.e., more vs. less-shared empathic concern), no significant difference between more vs. less empathic sharing for positive stimuli was revealed ($T = -0.085$; $df = 7$; $P = 0.934$). No significant correlation between higher empathic sharing (delta more-less_positive vs. delta more-less_negative) for negative

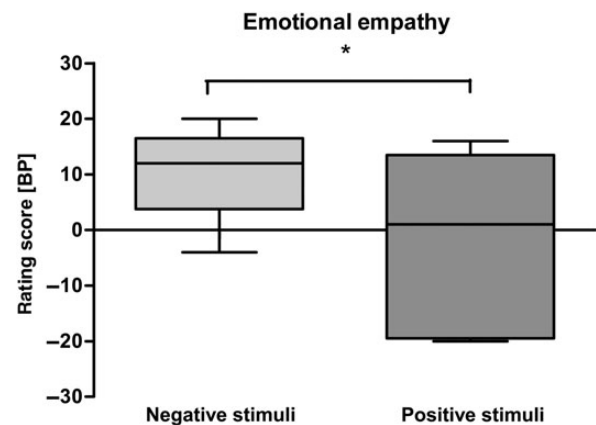


Figure 3. Behavioral results of the MET during LFP recordings: Paired t-test between Delta (Δ) more vs. less responses to negative stimuli and positive stimuli revealed a significant difference (Wilcoxon $t = 2.748$; $df = 7$; $P = 0.029$), suggesting a negativity bias in depressed patients. BP = button press.

stimuli (before DBS) and the BDI score (assessed during LFP recordings) was observed (Spearman Rho = -0.408 ; $P = 0.364$).

COG EMP Task Condition

Overall patients yielded a total of 69.6% correct recognition responses in the COG EMP task during LFP recordings. No significant difference was revealed for correct emotion recognition

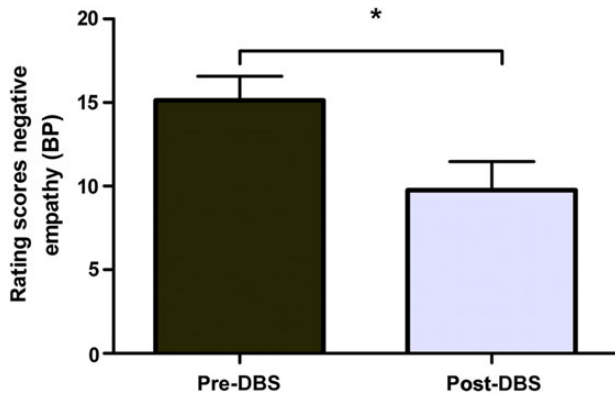


Figure 4. Follow-up after 6 months of the empathy task: T-test between empathic responses toward negative stimuli (Delta [Δ] more vs. less responses to negative stimuli) of pre-DBS and post-DBS (after chronic stimulation of 6 months) revealed a significant difference (Mann-Whitney $U = 8.50$; $P = 0.043$, non-parametric) between the 2 time points, suggesting a loss of negativity bias with DBS treatment.

performance between stimuli of positive (number of correct button presses: $n = 12.55 \pm 3.12$) and that of negative valence (13.44 ± 2.12 ; $T = -0.983$; $df = 8$; $P = 0.354$).

Follow-Up during Chronic DBS

EMO EMP Task Condition

Six months after chronic stimulation (post-DBS), patients showed no difference in empathic involvement ratings between persons who depicted negative emotions as compared with persons who expressed positive emotions in the MET (“delta_more_less_positive”: -4.0 ± 11.88 vs. “delta_more_less_negative”: 2.0 ± 6.53 ; $T = 1.567$; $df = 6$; $P = 0.168$). Consequently, we found significantly less empathic involvement ratings toward negative stimuli after chronic DBS (differences of pre-DBS vs. post-DBS, Mann-Whitney $U = 8.50$; $P = 0.043$) (Fig. 4), suggesting reduced negativity bias with DBS treatment. Interestingly, the change in empathic sharing with negative stimuli after DBS showed a tendency to correlate with the improvement in BDI with DBS (Spearman’s $Rho = 0.821$; $P = 0.089$, $n = 5$), suggesting that improvement in BDI with DBS is also associated with a reduction (normalization) of empathic sharing with negative stimuli.

EMO COG Task Condition

No change in emotion recognition was observed during DBS (difference between pre-DBS and post-DBS Mann-Whitney $U = 23.00$; $P = 0.946$).

Response Times (RTs) Results for EMO EMP and COG EMP in Patients

Button press response time averages over all conditions were 2743.11 ms (mean) \pm 687.72 ms (SD = standard deviation).

Response times EMO EMP: mean response times (RT) for all empathic involvement responses, regardless of valence, were 2526.69 ms (\pm 655.95 ms SD). Mean RT for positive stimuli in the EMO EMP task was 2390.31 ms (\pm 785.06 ms SD) and mean RT for negative stimuli was 2656.26 ms (\pm 673.42 ms SD). Analyses revealed no significant RT differences between positive and negative stimuli ($T = -1.808$; $P = 0.114$). No significant difference in RT for negative stimuli that induced more empathic involvement (2504.00 ms \pm 741.76 SD) compared with stimuli that induced less empathic involvement (2777.62 ms, \pm 1171.98 ms SD) was found ($T = 0.548$; $P = 0.593$).

Table 3 RT after chronic DBS (6 months)

Condition	Pre-DBS (ms)	Post-DBS (ms) (n = 6)	P-value
EMO EMP negative	2656.26	1892.47	0.006*
EMO EMP positive	2390.31	1962.17	0.038*
COG EMP positive	3013.67	2076.21	0.013*
COG EMP negative	2969.49	2254.26	0.009*

RT, response times in milliseconds; EMO EMP, emotional empathy; COG EMP, cognitive empathy.

* $P < 0.05$.

Response times COG EMP: Mean RT for all COG EMP stimuli regardless of valence was 2959.53 ms, \pm 719.50 ms SD, mean RT for recognition of positive stimuli was 3013.67 ms (\pm 786.43 ms SD), and that for recognition of negative stimuli 2969.49 ms (\pm 725.38 ms SD). There was no significant effect of valence for recognition speed ($P = 0.515$). Patients were faster responding to emotional empathy stimuli than that to cognitive empathy stimuli ($T = -3.112$; $df = 8$; $P = 0.014$).

Response times for both tasks for negative and positive stimuli, respectively, were significantly reduced after chronic DBS (see Table 3).

Results for Healthy Subjects

Emotional Empathy

In healthy subjects, no significant difference was revealed for empathic involvement ratings with persons who depicted negative emotions as compared with persons who expressed positive emotions (“delta_more_less_positive” vs. “delta_more_less_negative”; $T = -0.589$; $df = 17$; $P = 0.564$). Healthy subjects did not show a difference between more as compared with less empathic involvement ratings to negative ($P = 0.706$) and positive stimuli ($P = 0.794$) during the EMO EMP condition, they rather responded in a balanced manner.

Cognitive Empathy

Overall healthy subjects yielded a total of 72.5% correct recognition responses in the COG EMP task. Recognition speed during the COG EMP task did show a tendency for a difference between positive and negative stimuli (mean positive: 2135.13 ms, \pm 159.71 ms SD; mean negative: 2235.20 ms, \pm 234.94 ms SD; $T = -1.870$; $df = 17$, $P = 0.079$), suggesting faster responses to positive stimuli. Healthy subjects correctly recognized emotion expressions equally well for positive and negative stimuli ($T = -0.148$; $df = 17$; $P = 0.884$).

Comparison of Patients and Healthy Subjects

Most importantly, patients’ rating differed significantly from healthy subjects with patients feeling more involved with negative emotional stimuli ($T = 2.806$; $df = 24$; $P = 0.015$; T-test for independent samples). Patients had significantly slower RTs compared with healthy subjects for emotional empathy for negative stimuli ($P = 0.015$) and for the cognitive empathy task irrespective of valence condition (see values Table 2). Healthy subjects and patients did not differ in correct amount of positive ($P = 0.115$) and negative ($P = 0.400$) emotion recognition in the cognitive empathy task.

General Pattern of Stimulus-Related and Response-Related Changes in Oscillatory Activity

First, we explored the difference in the general oscillatory pattern related to emotional processing during stimulus presentation in

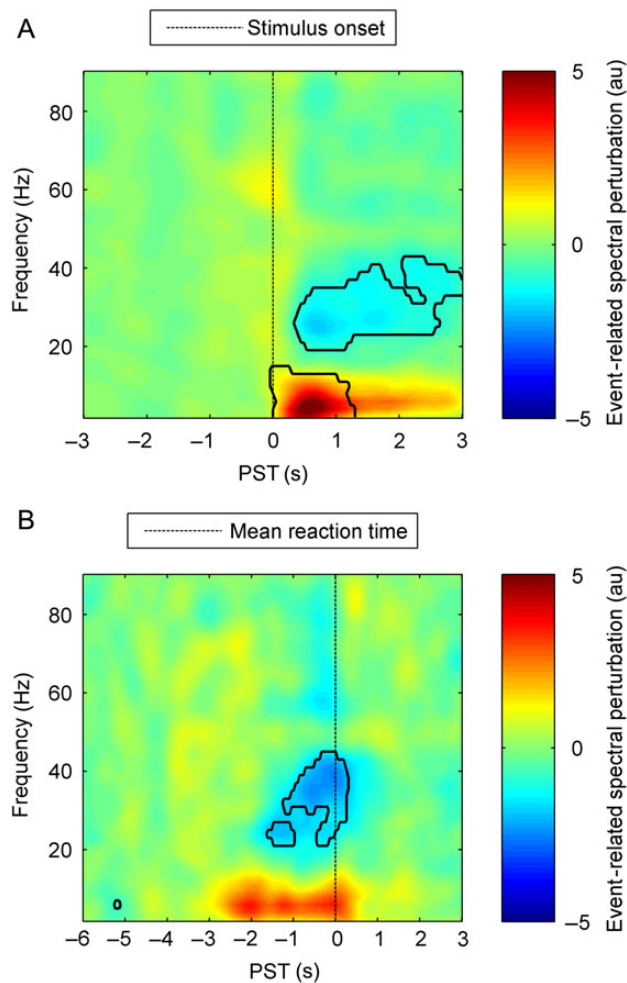


Figure 5. (A) Grand average for emotion-specific analysis: time frequency plot—grand average irrespective of empathy and valences. ERD and ERS depicted in the plot showing 2 significant clusters. Contour line comprises significant cluster-level of $P < 0.01$, FWE corrected, extent threshold 100 voxels. The grand average TF analysis across all conditions revealed an ERS in the theta (4–8 Hz) and alpha frequency range (9–13 Hz) that started from ~500 ms after stimulus onset and lasted up to ~1450 ms. At the cluster level, F-statistics for this cluster were maximal in the theta (4–8 Hz) range of ~500 ms. An ERD in the beta (14–35 Hz) band activity started ~500 ms after stimulus presentation and was ongoing for ~2500 ms. At cluster level, the most significant suprathreshold maximum in the beta (14–35 Hz) range was ~700 ms ($P < 0.01$; FWE corrected). Therefore, we examined these clusters in more detail by performing *rmANOVAs* and *post hoc* paired *t*-tests. Modulation in >35 Hz (gamma band) activity after stimulus onset did not reach significance. Dotted line represents stimulus onset. (B) Grand average for motor-specific analysis: Time-frequency plot for button press. Changes of oscillatory activity between 2 and 90 Hz were compared with the baseline for 7 sgACC patients. Averaged button press occurred after 2743.11 ms. Dotted line represents mean reaction time. Significant clusters are depicted. At the cluster level, F-statistics for the ERS cluster were maximal in the theta (4–8 Hz) range of ~500 ms ($P < 0.01$) and at ~700 ms ($P < 0.01$; FWE corrected) for the beta-band ERD. Contour line comprises significant cluster level of $P < 0.01$, FWE corrected, extent threshold 100 voxels. Event-related desynchronization (ERD) and ERS.

our patients compared with the second phase of the task, when patients had to give a motor response. To this end, a grand average was performed with all trials aligned to 1) the emotional stimuli irrespective of the emotional category (Fig. 5A) and 2) all trials aligned to the motor response/button press irrespective of task condition (Fig. 5B). We identified 2 large significant clusters of LFP changes in the grand average of emotion-specific stimuli:

an event-related synchronization (ERS) in the theta and alpha range that started from ~500 ms after stimulus onset and lasted up to ~1450 ms, and an event-related desynchronization (ERD) in the beta-band activity that started ~500 ms after stimulus presentation and was ongoing for ~2500 ms.

When trials were aligned to the button press, no significant changes in oscillatory activity occurred around the time of the motor response (Fig. 5B). In contrast, major changes in the LFP pattern occurred largely before the button press, that is, a synchronization occurred in the theta and alpha band that started at ~2700 ms before button press as well as a desynchronization in the beta band that started at ~1600 ms before button press and lasted until about the button press occurred suggesting that the LFP changes were related to emotional processing and not to the execution of the motor response that was required for the rating of the emotional stimulus. Modulation in >35 Hz (gamma band) activity after stimulus or movement onset did not reach significance.

Emotion-Specific Analysis

The 2 clusters that were revealed for emotional stimulus-related changes in oscillatory activity were subject to further analysis. Separate ANOVAs were performed for LFP changes related to emotional empathy and cognitive empathy in the beta frequency range using the time window from 500 to 2000 ms and in the theta and alpha range for the time window of 500–1500 ms. Analysis was restricted to the time window of up to 2000 ms after stimulus onset that yielded the major changes in LFP activity as revealed by the grand average and ensured to avoid any interference with the motor response that occurred on average at 2743 ± 688 ms.

Emotional Empathy

When evaluating the neuronal pattern with respect to the factor valence and empathy within the emotional empathy category, stimulus-related beta-band modulation revealed a significant interaction between factors valence and empathy ($F = 12.535$; $P = 0.009$), but no significant effect for the main factors empathy ($F = 0.194$; $P = 0.673$) and valence ($F = 1.410$; $P = 0.274$) nor sex ($P = 0.210$), nor laterality ($P = 0.199$) effect. Performing *post hoc* tests, the desynchronization in the beta band was significantly larger for emotional empathy (involvement) toward negative stimuli (mean ERD Z-score: -4.548) as compared with when patients did not share empathic concern with negative stimuli (mean ERD Z-score: 5.544 ; $T = -2.889$; $P = 0.018$; Bonferroni corrected; $n = 7$) (Fig. 6A). Further *post hoc* tests showed a trend for a larger beta ERD for reduced empathic concern to positive stimuli (mean ERD Z-score: -2.665) compared with the beta ERD for high empathic sharing for positive stimuli (mean ERD Z-score: 4.105 ; $T = 2.516$; $P = 0.066$, $n = 7$; Bonferroni corrected; Fig. 6A). The time course of the beta-band ERD is further illustrated by cumulative band power changes (Fig. 6B), which show a larger beta ERD for negative stimuli with more empathic involvement compared with less empathy and to positive stimuli.

Similar results were revealed when trials were balanced between response categories with a minimum of 8 stimuli per category (range 8–12; data not shown) to ensure that differences were not related to a variable signal-to-noise ratio due to more responses to negative perceived emotions. No significant LFP changes were observed in the theta and alpha range (data not shown).

Cognitive Empathy

When evaluating the neuronal pattern with respect to the factor performance and valence within the cognitive empathy category,

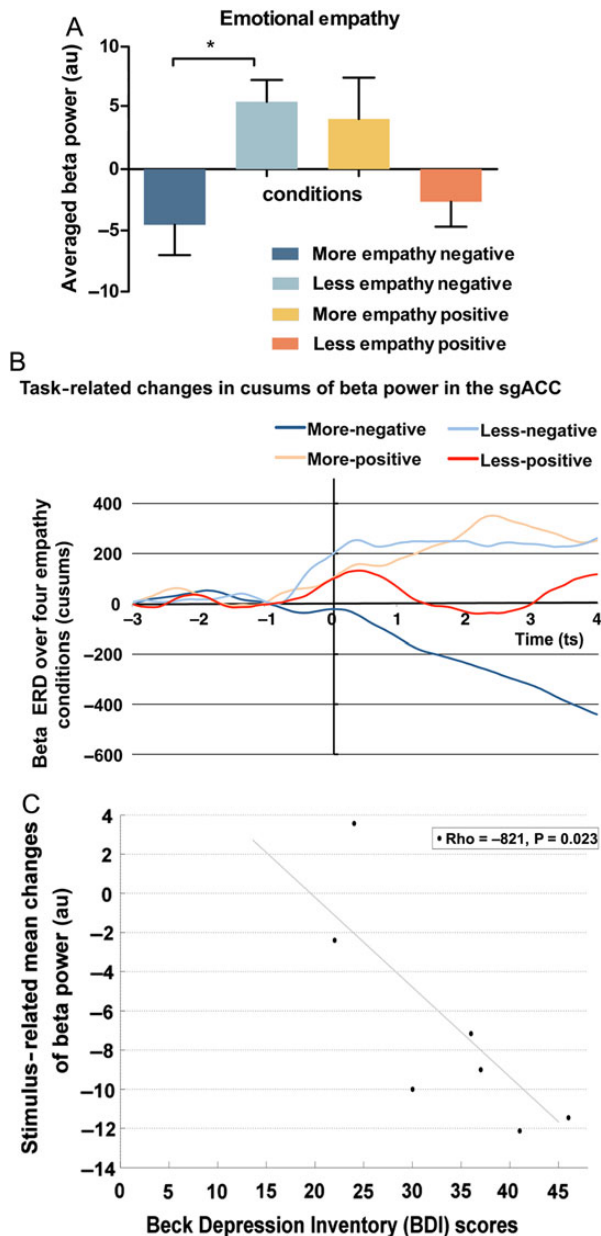


Figure 6. (A) Emotional empathy conditions and beta power: Averaged mean beta (14–35 Hz) band power for each of the 4 conditions (more and less empathic sharing for positive and negative stimuli) from the time window of 500–2000 ms during the task of emotional empathy. The desynchronization in the beta (14–35 Hz) band was significantly larger for emotional empathy (involvement) toward negative stimuli (mean ERD Z-score: -4.548) as compared with when patients did not share empathic concern with negative stimuli (mean ERD Z-score: 5.544 ; $T = -2.889$; $P = 0.018$; Bonferroni corrected; $n = 7$). (B) Plot of stimulus-related activity as a function of time in cusums: The time course of the beta-band ERD is further illustrated by cumulative band power changes. Task-related changes in cusums of beta power (14–35 Hz) in the subcallosal cingulate region (sgACC). Stimulus-related averaged beta power over the emotional empathy ratings in cusums for patients ($n = 7$) plotted as a function of time during more empathic ratings toward negative stimuli as compared with less empathic involvement ratings and more empathic ratings toward positive stimuli as compared with less empathic involvement ratings. Significant difference (rmANOVA) was found in the time window of 500–2000 ms. (C) Stimulus-related beta-band changes and the BDI scores. Correlation between stimulus-related beta (14–35 Hz) band changes during empathic sharing with negative stimuli and the BDI score at time of LFP recording (symptom burden). Spearman rank correlation for non-parametric data revealed a significant association between beta-band activity during enhanced empathic rating toward negative valenced stimuli and the BDI in ($n = 7$) (Spearman Rho: -0.821 ; $P = 0.023$).

stimulus-related spectral activity revealed a significant effect for a beta-band ERD for performance ($F = 5.562$; $P = 0.040$, $n = 7$) with larger beta ERD for correct responses (correct: mean ERD Z-score: -5.338 ± 8.088) as compared with wrong responses (5.672 ± 14.580). No significant effect for valence ($F = 2.236$; $P = 0.166$), no significant interaction between performance and valence ($F = 3.987$; $P = 0.074$, $n = 7$), and no effect for sex ($P = 0.821$) or laterality ($P = 0.750$) was found. No significant LFP changes were observed in the theta and alpha range (data not shown).

Clinical Data

Statistical analyses of 9 patients revealed a significant HAMD-24 and BDI score reduction after 6 months from baseline. We observed a $\sim 33.3\%$ response rate ($n = 9$ patients); meaning a score reduction of at least 50% in the HAMD-24 at 6 months compared with baseline measures. After 6 months of DBS, there was a significant reduction in the HAMD-24 mean score to 21.44 ± 11.43 SD ($Z = -2.199$; $P = 0.028$) and a significant reduction in the mean BDI score to 30.11 ± 15.03 SD ($Z = -1.956$; $P = 0.05$). The clinical outcome of stimulation of a smaller sample out of this sample (6 patients) is described in Merkl et al. (2013).

Correlation of Oscillatory Power and Depressive Symptoms

Further we sought for a correlation of severity of clinical symptoms of depression with the stimulus-related change in oscillatory activity. Since a significant valence-related modulation only occurred with beta-band activity, we limited our analysis to beta-band desynchronization (from 500 to 2000 ms after stimulus onset). The desynchronization in the beta band for the empathic sharing with negative stimuli during the emotional empathy task correlated with self-reported severity of depression as assessed by the BDI at the time of LFP recordings (Rho = -0.821 ; $P = 0.023$, $n = 7$) (Fig. 6C), that is, higher beta ERD was observed in those patients that had higher scores in the BDI. No correlation was found for BDI (Rho = -0.429 ; $P = 0.397$) with beta-band ERD to positive stimuli, neither for the ERD observed in the cognitive empathy task.

Discussion

In this study, we show for the first time a modulation of oscillatory activity pattern in the sgACC area with affective processing during an empathy task in patients with TRD and, second, revealed changes in behavioral responses during chronic DBS. The main finding of our study is a larger empathic sharing for negative stimuli before DBS that is associated with enhanced beta-band desynchronization in the sgACC area during empathic responses toward negative stimuli. Interestingly, the higher scores for the involvement with negative stimuli before treatment were significantly reduced after 6 months of chronic DBS, and patients rated the same stimuli equivalent to a healthy control group, pointing to a “negativity bias” before DBS. Moreover, the severity of depression correlated significantly with the degree of oscillatory beta-band suppression for negative stimuli with empathic involvement, suggesting that beta-band oscillatory activity may index the degree of individually perceived sharing of negative emotional state in our patients.

The subgenual portion of the anterior cingulate cortex (Mayberg 2003; Savitz and Drevets 2009) together with the DLPFC is thought to be part of a limbic cortical–striatal–pallidal–thalamic network that is involved in emotion processing (Uhlhaas and

Singer 2010; Anderson et al. 2012). We investigated 2 different empathy tasks, cognitive and emotional empathy to explore active emotional processing. Interestingly, our patients did not differ from controls in emotion recognition during the cognitive empathy task. In contrast, valence-related modulation of oscillatory activity pattern as well as changes in behavioral performance during chronic DBS occurred during the emotional empathy task pointing to enhanced processing of negative emotional stimuli. This larger empathic sharing for negative stimuli provides evidence for a negativity bias (Watters and Williams 2011) in our patients during execution of the emotional empathy tasks, which is in line with previous studies (Williams et al. 2009) and the general view on negativity bias in depression (Disner et al. 2011) showing enhanced attention specifically for stimuli depicting negative emotions (Wolkenstein et al. 2011). Empathizing with other people's emotional states requires intact emotion recognition ability and the capacity to maintain a self-other distinction (Decety and Meyer 2008). The latter process might rely on top-down mechanisms (i.e., prefrontal cortex and anterior cingulate), which establish down-regulation or enhancement of empathic response (Singer 2006). However, another argument for a bottom-up process is equally possible. Engel and Fries (2010) posit the hypothesis that beta-band frequency oscillations may support functional coupling of neurons over large distances and that one should observe a decrease of beta-band activity in paradigms where the behavioral response of the subject is largely determined by exogenous, bottom-up factors.

The enlarged beta ERD found in our patients during enhanced empathic sharing with negative stimuli might suggest that desynchronized beta-band activity reflects active processing of emotionally salient stimuli. Our findings are in line with evidence from neuroimaging showing that the sgACC is implicated in affective valuation (Lebreton et al. 2009). The sgACC is strongly connected to medial prefrontal and anterior midcingulate cortex (Johansen-Berg et al. 2008). Riva-Posse and colleagues reported in a recent probabilistic diffusion tensor tractography study from sgACC-DBS responders that (Riva-Posse et al. 2014) particularly determinant for predicting DBS clinical effectiveness was stimulation of projections to Brodmann (BA) 10. In detail, the authors showed connectivity of the sgACC to medial prefrontal cortex (mPFC) in responders to DBS as compared with non-responders, suggesting these areas within this neuronal circuit might play a crucial role in depression and in the social understanding of others (Li et al. 2014). The mPFC plays a key role in the social understanding of others, and the subregions of the mPFC contribute differently to this function according to their roles in different subsystems of the default-mode network (Li et al. 2014). Especially, the anterior mPFC and its connections with posterior and anterior cingulate cortex contribute mostly to making self-other distinctions that might be impaired in patients with TRD leading to enhanced empathizing with negative stimuli in the empathy task.

Interestingly, single-unit responses in the recording site of the right subgenual cingulate cortex in patients with intractable epilepsy (Kawasaki et al. 2005) to emotional stimuli showed more response selectivity to negative rather than positive valences. In this vein, another recent study in humans showed single neuron activity in the subcallosal cortex (SCC; referred here as Brodmann's areas [BA] 24, 25, 32, 10, 11, and 12) in intractable depression. It was modulated by emotion-category-specific responsiveness rather than arousal or valence alone, and the majority of the responses in this area were selective toward negative images (Laxton et al. 2013). In macaques, local microstimulation of the pregenual cingulate cortex has led to increased negative decision-making

(Amemori and Graybiel 2012). A possible explanation for our results could be that the patients, while unimpaired in their ability to correctly recognize the displayed emotion, failed to maintain a dissociation between their own emotional state and other people's mood. It could be speculated that the preferred pictures with which patients empathized are associated with the retrieval of personal memories (Wolkenstein et al. 2011). Patients may imagine how they would react in a negative context, and they might do this by imagining a negative reaction to a similar situation that was experienced in the past (Dagleish and Werner-Seidler 2014). In this context, the observed effect of beta-band suppression during less empathic sharing for positive stimuli could have been to the fact that positive expression could initially evoke negative emotions in depressed patients. An association between the beta-band oscillatory responses and emotional stimuli has been reported in various studies, for example with multisensory emotion perception and during the presentation of faces with painful emotional expressions (Jessen and Kotz 2011; Senkowski et al. 2011; Jabbi et al. 2014). Interestingly, a recent combined fMRI and MEG study on emotionally salient stimuli found event-related changes in early MEG beta-band (14–30 Hz) oscillatory activity (0–400 ms) in sensorimotor cortex, which was accompanied by a fronto-limbic extension after 400–1000 ms (Jabbi et al. 2014). In our patients, the desynchronization in the beta band for empathic involvement to negative stimuli correlated with self-reported severity of depression as assessed by the BDI, indicating an increased disposition toward more empathic sharing with negative stimuli, which appears to be related to clinical depression. This is in line with the literature suggesting that the symptoms of patients with depression result from an alteration of affective processing. Depressed individuals show a marked sensitivity to emotionally negative situations which induce a negative bias (Williams et al. 2009). The beta ERD might index the individual involvement toward negative emotion in our patients rather than a state biomarker for depression per se. Accordingly, there was no correlation of beta ERD during cognitive empathy and severity of clinical symptoms, which might hint at sgACC area activation being more related to the feeling of emotion rather than emotion recognition. This is in line with previous PET studies, which showed significant sgACC activation during negative emotion induction (Mayberg 2003). In the same vein, work on functional magnetic resonance studies and emotional processing in MDD suggests sgACC hyperactivity to negative stimuli, a positive correlation with depression severity and only few studies show that for positive stimuli (Jaworska et al. 2014).

The observed negativity bias in our patients subsided after 6 months of chronic DBS and correlated with clinical outcome, suggesting a benefit from therapy. Processing speed improved for both tasks after 6 months, suggesting an increased patients' willingness to engage in the task. Another explanation could be increased impulsivity. There is increased impulsivity described after Nucleus subthalamicus (STN) DBS in PD; however, this is related to inhibitory deficits commonly considered in relation to impulse control disorders associated with treatment with dopaminergic medication or the specific role of the STN (Jahanshahi et al. 2014). A positive association between depression and negative empathic sharing might be explained by an attentional focus on the self rather than on others (Mor and Winquist 2002). That is, depressed individuals may report high levels of empathic sharing in response to the problems of others because their affective responses are primarily driven by how they would react if others' problems were their own (Lamm et al. 2007).

Healthy subjects and patients did not differ in correct amount of positive and negative emotion recognition in the cognitive empathy task. This is in line with previous studies on theory of mind

and cognitive empathy in depressed patients in comparison with healthy subjects (Wilbertz et al. 2010; Wolkenstein et al. 2011). Few studies analyzed reaction time differences between patients and healthy subjects (Schreiter et al. 2013), and results are heterogeneous but a possible explanation of RT differences could be attentional effects.

Several limitations have to be discussed for our study. Intracranial recordings in human subjects are influenced by the major limitation that electrode placement is not backed up by histological investigation and therefore remains presumptive. However, postoperative imaging in all our patients was consistent with electrode placement in the target area and, by avoiding any assumptions in contact-pair selection, we further limited the effects of variance in electrode placement. The sample size is small and further limited by the inconsistent availability of depression scores, so that our results should be considered exploratory and subject to validation in larger TRD DBS cohorts. Our results cannot be compared with those of healthy controls, which is an inherent limitation of intracranial LFP recordings in humans. Moreover, we cannot exclude that the antidepressant medications of our patients have an effect on the observed LFP changes, which can only be explored in future studies using chronic LFP recordings after successful DBS that will allow reduction in antidepressant medication or by comparison of response pattern across patient cohorts with different diseases. Further, we did not show a differential neuronal modulation for negative and positive stimuli suggesting that the sgACC area is also involved in positive valenced emotional processing as has been shown by our group using a passive emotion viewing task. Finally, in our previous studies in patients with Parkinson's disease, we found prominent modulation of alpha but not beta-band activity with emotional stimuli (Kühn et al. 2005; Huebl et al. 2014), which is possibly due to the different subcortical area and disease entity. Beta desynchronization over motor areas has been related to motor preparation and motor processing (Buzsaki 2006). Here, it is important to note that we explored a limbic area in our patients and our analysis confirmed that beta-band modulation was not related to the motor response.

Taken together the results provide evidence for emotion-related oscillatory activity recorded directly from human fronto-limbic structures implicated in the pathophysiology of MDD. Our results propose that beta oscillations in the sgACC area relate to negative emotion sharing in our patients that was improved with chronic DBS. Further studies investigating oscillatory response pattern using different emotion task and target areas in the fronto-limbic system are required to gain a full insight into the underlying oscillatory network and its role in depression.

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Notes

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