Processing of emotional stimuli is reflected by modulations of beta band activity in the subgenual anterior cingulate cortex in patients with treatment resistant depression

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Abstract

Deep brain stimulation (DBS) of the subgenual anterior cingulate cortex (sgACC) has emerged as a new therapeutic option in patients with treatment resistant depression (TRD). At the same time, DBS offers a unique opportunity as an innovative research tool to study brain function in vivo. Indirect measures of brain function such as positron-emission-tomography imaging findings have revealed a hypermetabolism in the sgACC area in patients with TRD that normalizes in parallel with treatment response to DBS. We used direct intracranial recordings via implanted DBS electrodes to study the neuronal oscillatory activity in the sgACC area during a picture viewing task including emotional and neutral stimuli in eight patients with TRD who underwent DBS.

We found a stimulus-induced decrease in beta-band and increase in gamma-band activity, with a main effect of valence for event-related desynchronisation in the beta-frequency range (14–30 Hz). Unpleasant stimuli induced the strongest and most sustained beta-power decrease. The degree of beta-band modulation upon emotional stimuli correlated with the patients’ rating of stimulus valence. Our findings confirm the involvement of the sgACC area in emotional processing that was more enhanced for unpleasant stimuli. Moreover, stimulus evaluation may be encoded by modulations of beta-band activity.

Key words: emotional processing; local field potentials; subgenual cingulum; deep brain; stimulation; depression

Introduction

Major depressive disorder (MDD) is a multi-faceted heterogeneous syndrome that is the second leading cause of years lived with disability, according to a recent report on the global burden of disease (Murray and Lopez, 2013). The pathomechanism that leads to MDD is considered to be multifactorial in nature, including environmental and (epi)-genetic factors as well as a dysregulation of monoaminergic and other neurotransmitters (Krishnan and Nestler, 2008). Approximately one third of MDD patients remain unresponsive to conventional pharmaceutical or cognitive behavioral interventions, which then are classified as patients with treatment resistant depression (TRD) (Thase and Rush, 1997). Deep brain stimulation (DBS) offers a promising therapeutic option for this TRD subgroup (for review see Anderson et al., 2012). The subgenual anterior cingulate cortex (sgACC, including Brodmann area (BA) 25 and adjacent subgenual BA 24) was identified as a DBS target based on PET studies, which revealed a hyperactivity in the sgACC in TRD patients.
and in healthy subjects during transiently induced sadness (George et al., 1995; Mayberg et al., 1999). Moreover, a reduction of sgACC metabolic hyperactivity in MDD patients was associated with either successful cognitive behavioral and pharmacological treatment (Brody et al., 2001) or with a response to DBS in this area (Mayberg et al., 2005). The experience of positive feelings induced by listening to harmonic music is also reflected by an increase of sgACC metabolism (Brown et al., 2004), suggesting a more general involvement of this area in emotional processing. The sgACC is integrated in limbic fronto-striatal circuits and shares extensive bi-directional connections to other limbic structures, such as the amygdala, ventral striatum and the hypothalamus (Beckmann et al., 2009).

DBS provides a unique opportunity for direct recordings of neuronal activity from DBS target areas. This has so far mainly been explored in patients with movement disorders and has shed new light on the pathophysiology of Parkinson’s disease (PD) and other movement disorders by characterizing abnormal brain oscillatory network activity (Jenkinson and Brown, 2011) and its modulation by DBS (Brown and Eusebio, 2008; Kühn et al., 2008). Whereas there is a plethora of functional imaging studies exploring emotional processing in the anterior cingulate region, direct recordings of neuronal activity in this structure have only recently been adopted in MDD patients (Laxton et al., 2013; Lipsman et al., 2014; Neumann et al., 2014). First results using this approach revealed a different pattern of resting state neuronal activity in MDD and OCD patients, focusing on alpha band oscillatory activity as a potential state marker for depression (Neumann et al., 2014). Modulation of single unit activity recorded from the sgACC area during presentation of emotional stimuli was most consistent after negative emotional stimuli (Laxton et al., 2013). Lipsman et al. (2014) recorded local field potentials in two TRD patients during an affective choice paradigm, where subjects had to discern ambiguous (sad/happy) emotional facial expressions. They found an increased coherence in beta activity (15–20 Hz) before identification of sad faces. We followed a similar approach, taking advantage of invasive recordings of population activity reflecting synchronized neuronal activity in the sgACC area during presentation of emotional stimuli. To this end, we recorded local field potentials from the sgACC area in patients undergoing DBS for TRD during a passive emotion picture viewing task, and evaluated stimulus-induced modulation of oscillatory neuronal activity. Given the adherence to negative stimuli in depressive patients, we hypothesized that unpleasant stimuli will lead to the strongest and most sustained modulation of neuronal activity depending on the individual emotional experience elicited by the stimulus.

### Material and Methods

#### Patients and surgery

In our study, we included eight patients (four women, mean age 48 ± 12.2 year) with the diagnosis of TRD (mean disease duration 25 ± 17.5 year) according to DSM-IV criteria, who were refractory to anti-depressive medication, cognitive behavioral therapy (CBT) and/or electro convulsive therapy (ECT). Patients were carefully evaluated by clinical psychiatrists not involved in the neurophysiological testing. Disease severity was assessed using appropriate neuropsychiatric scales such as the Beck Depression Inventory (BDI) and the Hamilton rating scale for depression (HAMD-24) (cf. Table 1). All patients provided written informed consent to participate in the study, which was approved by the local ethics committee in accordance with the declaration of Helsinki. The patients had enrolled in an open-label clinical trial examining the acute and chronic effects of subgenual DBS as a treatment option for TRD (Merkl et al., 2013). Quadripolar deep brain electrodes (Model 3387, Medtronic, Minneapolis, MN) were targeted at the subgenual anterior cingulate cortex. The intended target area for the tip of the electrode (contact 0) was individually adjusted for each patient using the method proposed by Hamani et al. (2009). Post-operative T2-weighted MRI scans were available for each patient (except case 7) and adjusted to the Montreal Neurological Institute (MNI) standard space, which allowed for probabilistic assessment of electrode location (Horn and Kühn, 2015). Correct placement of electrodes in the subgenual cingulate area was confirmed in all patients (see Supplementary Figure 1). Contacts extended across the subgenual cingulum including Brodmann area 25, as well as the subgenual part of area 24 and area 32; we refer to this electrode placement as the sgACC area.

### Table 1. Demographic and clinical data

| No | Age/sex | Disease duration | No. of ECT sessions | Suicide attempts | BDI* | HAMD-24* | FUP BDI** | FUP HAMD-24** | AD medication |
|----|---------|------------------|---------------------|-----------------|------|----------|-----------|--------------|---------------|
| 1  | 49/w    | 33               | >49                 | 2               | 35   | 37       | 32        | 22           | Lorazepam, amitriptyline, quetiapine, topiramate |
| 2  | 61/f    | 23               | 53                  | 0               | 22   | 23       | 1         | 9            | Lorazepam, clomipramine, fluvoxamine, lithium, gabapentin, mirtazapine |
| 3  | 48/f    | 16               | 81                  | 10              | 46   | 30       | 36        | 27           | Lithium, quetiapine, duloxetine |
| 4  | 60/f    | 20               | 32                  | 0               | 36   | 34       | 12        | 7            | Lithium, tranylcypromine, pregabalin, quetiapine |
| 5  | 36/m    | 16               | 0                   | 0               | 57   | 24       | 52        | 33           | No medication |
| 6  | 50/m    | 34               | 18                  | 0               | 41   | 32       | 37        | 29           | Zopiclone, quetiapine, trimipramine |
| 7  | 55/m    | 20               | 35                  | 0               | 43   | 31       | 31        | 21           | Pregabalin, agomelatine, quetiapine, levohyrozoine, Mirtazapin |
| 8  | 25/m    | 3                | 22                  | 0               | 30   | 28       | 37        | 33           | |

ECT, electroconvulsive therapy; BDI, Beck depression inventory; HAMD-24, Hamilton Depression Ratings Scale 24-item version.

*Assessed at the time of LP7 recordings.

**Follow up data 24 weeks after continuous sgACC DBS.
Paradigm
Patients participated in a passive emotional picture viewing task (Kühn et al., 2005) two days after electrode implantation. We selected neutral, pleasant and unpleasant stimuli from the International Affective Pictures System (IAPS) (Lang et al., 2008) and composed six similar sets of 30 stimuli, including 10 pictures of each valence. IAPS stimuli are provided with a gradual rating for the emotional dimensions of valence (1 = unpleasant – 5 = neutral – 9 = pleasant) and arousal (1 = calm – 9 = exciting). The mean valence was 5.0 ± 0.4 for neutral, 7.3 ± 0.5 for pleasant and 2.67 ± 0.5 for unpleasant stimuli. Arousal levels were matched for pleasant (5.3 ± 0.7) and unpleasant (5.4 ± 0.7) stimuli. Neutral pictures commonly have a lower arousal (3.4 ± 1.0 in our dataset). The order of the sets was randomly chosen for each patient. Stimuli were displayed on a 14” laptop screen for 1000 ms with a variable inter-stimulus interval ranging from 6 to 8 s, during which a black fixation cross was shown on a white background. The short stimulus duration of 1000 ms was based on previous studies (Oya et al., 2002; Kühn et al., 2005) to capture an immediate emotional reaction and reduce exploratory saccades, induction of intrusive thoughts and rumination, which may be more likely in depressed patients under longer stimulus presentation. The order of the stimuli was pseudo-randomized, i.e. the maximum number of iteration for the same valence category of a picture was four. An additional neutral picture (IAPS#2880) was added, which occurred randomly three times per set, upon which the patients were supposed to press a button to ensure constant attention during the paradigm. Patients sat in a comfortable chair and were instructed to have their gaze directed at the screen at all times and not to comment on the stimuli. A short break was granted between sets. Patients completed 4–5 sets. After the recordings, patients were asked to review each stimulus and rate it in terms of valence and arousal using a paper and pencil version of the Self-Assessment-Manikin (SAM; Bradley and Lang, 1994). Patients were instructed to rate their immediate emotional sensation in terms of valence (i.e. how strong they feel about the picture from unpleasant to pleasant) and arousal (i.e. how arousing they perceive the picture from calm to exciting). We explained to the patients that there were no right or wrong answers and that they should respond as honestly as they could (Lang et al., 2008).

Recordings and data preparation
LFP activity was recorded in all patients via the implanted depth electrodes from the sgACC area during the emotional picture viewing task. We chose bipolar derivations from adjacent contact pairs (i.e. contact 0–1, 1–2, 2–3) which were referenced through a common ground electrode. Thereby, we aimed to minimize signal contamination by volume conduction of nearby structures. Scalp EEG recordings were obviated by post-operative wounds, surgical dressings and time constraints. LFPs were sampled at 1 kHz (cases 1–3) or 5 kHz (cases 4–8) through an Analog-to-digital-converter (1401power mk-II, Cambridge Electronic Design, Cambridge, UK) at 50 000-fold amplification (Digitimer D360, Digitimer, Welfordshire, UK), filtered from 0.5 to 250 Hz and stored on a hard drive for offline analysis.

LFP traces were down-sampled to a common sampling rate of 1 kHz. Trials were visually inspected for artifacts due to mains noise or movements and eventually rejected, leaving a mean number of 42 trials (range 32–50) for each valence. One channel (left contacts 2–3) of patient#6 had to be discarded due to technical artifacts. All further steps were realized with MATLAB and customized code from the SPM8 toolbox for MEG/EEG. After conversion into the SPM8 data format, LFP traces were band pass filtered between 0.5 and 150 Hz. Trials were epoched from 2250 ms prior to 3250 ms after stimulus onset. Time frequency (TF) representations of these epochs were calculated as event-related spectral perturbations (ERSP) (Makeig et al., 2004) using a multi-taper Fast Fourier Transform (FFT) approach. The length of the FFT sliding window was 400 ms, shifted in 50 ms steps. Tapers were applied in a frequency-dependent manner employing a single taper for the range 2.5–30 Hz, two tapers from 32.5 to 42.5 Hz, and three tapers from 45 Hz and beyond. This resulted in a frequency resolution of 2.5 Hz from 2.5 to 25 Hz, followed by 1/10 of the frequency between 25 and 50 Hz and 5 Hz for the remaining frequencies to 100 Hz (Litvak et al., 2011). The power spectra were averaged across each valence category and corrected to a pre-stimulus baseline (-2000 to -250 ms) according to the additive model proposed by Grandchamp and Delorme (cf. supplemental material). Resulting TF values were quantified as z-scores (SD). The advantage of this approach lies with its robustness to outliers and noisy trials, which has been illustrated in a recent study (Grandchamp and Delorme, 2011).

Statistical analysis
Time-frequency maps were converted to image files (NIFTI format, http://nifti.nimh.nih.gov/nifti-1/), which is a prerequisite for the subsequent analysis with the SPM8 toolbox. The images were smoothed with a Gaussian Kernel of 4 Hz x 400 ms full width at half maximum (FWHM). Gaussian smoothing warrants conformity with the assumptions underlying the general linear model (GLM) analysis using SPM and can improve the spectro-temporal overlap across subjects and thus increase the signal-to-noise ratio. The smoothed images of all contact pairs were implemented in the design matrix of a flexible factorial GLM. Since resting state EEG studies have shown an ‘anterior asymmetry’ with a decrease of right frontal activity in subjects with a depressive trait (e.g. review by Davidson, 1998), we also explored potential hemispheric asymmetry in activation pattern in our patients including ‘hemisphere’ as a factor in the GLM. The GLM was tested with the within-subject factors VALENCE (three levels: pleasant, unpleasant and neutral) and HEMISPHERE (two levels: right, left). We included all images from all contact pairs into the design matrix in order to avoid a selection bias of electrode contacts due to arbitrary electrophysiological or anatomical properties. In effect, the results will show grand averages of TF modulations across all contacts. After estimation of the GLM, contrasts of interest were computed from the model’s parameter estimates, yielding statistical parametric maps (SPMs) of F- and t-statistics that reflect the contrast’s significance at each TF bin. 75 adjacent TF bins that exceeded a threshold of \( P < 0.001 \) (uncorrected) qualified as a significant cluster (i.e. cluster forming threshold).

We were interested in the overall change in spectral power within the whole TF space and contrasted all stimuli against a zero-mean baseline (reflecting a one sample t-test). This contrast was also calculated for each valence. Our main interest, however, lay in the differential response pattern between each valence. Therefore, we used a non-directional F-contrast to test for a main effect of valence, i.e. to identify the relevant time and frequency space which showed differential responses according to stimulus valence. In a second step, clusters as revealed by the aforementioned non-directional F-contrast were used as an inclusive mask (i.e. region of interest) to look for specific
differences between valence categories via paired t-tests (e.g. unpleasant vs neutral). All cluster based inference was Family-Wise Error (FWE) corrected for multiple comparisons at a threshold of $P < 0.001$ using Random Field Theory (RFT, Kilner et al., 2005), except for the masking F-contrast where the threshold was set to $P < 0.01$ FWE corrected. Extracted power band changes over time are displayed as cumulative sums, i.e. 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 to baseline activity are reflected by a deflection from a zero gradient (i.e. horizontal curve).

In order to explore possible relationships between clinical behavioral data and LFP data, we applied regression analyses with linear and quadratic models. The beta event-related de-synchronization (ERD) was included as the dependent variable and the ratings of stimulus valence and arousal were used as independent variables. We considered linear and non-linear (quadratic) models within the regression analysis because the rating scales for valence and arousal have a different structure: highest emotional valence ratings are at both ends of the scale, whereas increasing arousal levels follow a linear rating scale. To disentangle both emotional categories, we calculated partial correlations between beta ERD, valence and arousal levels.

Since the scale for valence rating has linear steps of increasing emotional valence starting from neutral (value $5$) to two different directions (pleasant $= 9$; unpleasant $= 1$), we decided to calculate the difference value from neutral valence (neutral value $= 5$) as an absolute value for emotional valence rating independent on the direction of emotional valence. Thus, adjusted valence ratings ranged from $0$ to $4$, with a larger value reflecting a higher emotional rating (either positive or negative) of the stimulus. This approach allowed us to include all stimuli. Neuronal activity was averaged across hemispheres and relevant time and frequency regions within the identified clusters to obtain discrete values for each patient.

## Results

### Spectral analysis

The global contrast, including all stimuli vs baseline activity, showed three significant clusters (Figure 1, encircled clusters) in the low-frequency range (2–14 Hz, 100–1100 ms, $P_{\text{cluster}} < 0.001$ FWE), beta range (17–34 Hz, 300–2000 ms, $P_{\text{cluster}} < 0.001$ FWE) and gamma range (56–92 Hz, 100–1450 ms, $P_{\text{cluster}} < 0.001$ FWE). The valence specific contrasts (us baseline) showed a significant event-related beta band desynchronization (ERD) for emotional stimuli that was most pronounced for unpleasant stimuli, reflected by a large cluster spanning the beta range (14–30 Hz) that occurred from 500 to 2500 ms ($P_{\text{cluster}} < 0.001$ FWE, size $= 147$; Figure 2A). Furthermore, we found a concomitant increase in gamma power (76–90 Hz) from 100 to 1250 ms ($P_{\text{cluster}} < 0.001$ FWE, size $= 89$) for unpleasant stimuli. Pleasant stimuli induced a narrow ERD in the upper beta band (20–30 Hz), reflected by a significant cluster from 250 to 2000 ms after stimulus onset ($P_{\text{cluster}} < 0.001$ FWE, size $= 83$; Figure 2B); increases in lower gamma activity (60–60 Hz) did not reach significance. Neutral stimuli did not induce changes in the beta band but showed a large cluster of low frequency event-related synchronization (ERS) that occurred upon stimulus onset, and showed sustained increased activity extending up to 18 Hz throughout the trial period (0–3000 ms, $P_{\text{cluster}} < 0.001$ FWE, size $= 294$; Figure 2C). The time course of the beta band ERD is further illustrated by cumulative power changes (Figure 3A), which showed a prolonged beta ERD for unpleasant stimuli compared to neutral and pleasant stimuli.

The F-contrast represents the main effect of valence and identified one large significant cluster (size $= 364$ TB bins in the 2.5–30 Hz frequency range; Figure 4A). This cluster delineates the time and frequency region of interest. Within its boundaries, from approximately 750 ms after stimulus onset until 2500 ms, the subsequent post-hoc tests between each valence category were executed (see below). At the peak level, F-statistics for this cluster were maximal in the low frequency range (2.5–8 Hz) around 1500 ms ($F = 40.6$, $P < 0.001$ FWE corrected) after stimulus onset. In the beta band (14–30 Hz), the peak level was still highly significant at $P = 0.0003$, FWE corrected equivalent to an $F$-value of 17.31. We examined this cluster in more detail by performing post-hoc paired t-tests using T-contrasts between each valence category. Contrasting unpleasant with neutral stimuli, we found one significant cluster (1000–2500 ms, $P_{\text{cluster}} < 0.001$, FWE, size $= 269$; Figure 4B) including all frequencies from 2.5 Hz up to the beta range to 30 Hz. A smaller cluster was found for the contrast of pleasant vs neutral stimuli (1000–2500 ms, $P_{\text{cluster}} < 0.001$ FWE, size $= 187$; Figure 4C), with a main peak in the frequency range from 2.5 to 10 Hz range. There were no significant differences between pleasant and unpleasant stimuli at the cluster level. However, taking into account the obvious differences in the valence specific contrasts in the beta range (cf. Figure 2), we performed a repeated measures analysis of variance (rmANOVA) by averaging across the relevant frequency space and time (14–30 Hz, 750–2500 ms). Here we found a main effect of valence ($F = 6.3$, $P = 0.011$; Figure 3B), and post-hoc t-tests confirmed the significant difference between neutral ($0.09 \pm 0.129$ SEM) and unpleasant stimuli ($-0.40 \pm 0.12$, $P = 0.021$; Bonferroni corrected). We also found a stronger decrease for unpleasant than for pleasant stimuli ($-0.17 \pm 0.08$, $P = 0.041$). There was neither a main effect of hemisphere nor an interaction of valence and hemisphere.

Fig. 1. Statistical parametric map (SPM) of the overall stimulus-induced responses relative to prestimulus baseline (-2000 to -250ms). T-values are color coded. Significant clusters formed by $>75$ adjacent T-values each exceeding $2.36$ (corresponding to a $P$-value $< 0.001$) are encircled with a solid black line. There are three (major) significant clusters (all $P_{\text{cluster}} < 0.001$, FWE). In the low-frequency range (2–14 Hz; smaller red cluster) an increase of spectral power (event-related synchronization, ERS) is visible at 100–1100 ms after stimulus onset. In the beta range (17–34 Hz) there is a sustained decrease of spectral power from 300 to 2000 ms after stimulus onset reflecting an event-related de-synchronization (ERD; blue cluster). In the higher frequency range there is a broad gamma ERD (56–92 Hz, larger red cluster) lasting from 100 to 1450 ms after stimulus onset. FWE, family-wise error corrected.
There was no significant change from baseline with emotionally salient stimuli in the lower frequency range (2–8 Hz, 750–2500 ms; all $P > 0.2$, uncorrected). Interestingly, we observed a significant 2–8 Hz power increase (0.89 ±0.18) in trials with neutral stimuli ($P < 0.001$).

Correlation with behavioral data

The ANOVA of the regression analysis was significant for a quadratic model ($F = 6.89$, $P = 0.005$), showing a U-shaped dependency between beta ERD and the rating of stimulus valence ($r = 0.63$, $P = 0.005$, Figure 5a). At both poles of the valence rating (unpleasant and pleasant) a strong beta ERD was observed, whereas for neutral ratings the beta ERD was diminished. There was no significant linear relationship between beta ERD and valence ratings. Calculating the regression analysis for arousal and beta ERD, we found a significant relationship for a linear model ($F = 13.1$, $r = -0.61$, $P = 0.002$, Figure 5b).

In order to further disentangle the inter-relationship of valence and arousal (Bradley et al., 2001), we carried out a partial correlation between beta ERD and valence and arousal, respectively, to assess the relationship of either rating with the beta ERD. We found a significant correlation between valence and beta ERD ($r = -0.5$, $P = 0.015$) when corrected for arousal. The correlation between arousal and beta ERD was no longer significant after correction for valence ($r = -0.35$, $P = 0.1$).

There was no correlation between beta ERD in response to the presented stimuli and the clinical scores. Gamma ERS did not correlate with stimulus valence/arousal or with clinical scores.

Discussion

The main finding of our study was a decrease in oscillatory beta activity that occurred during passive viewing of emotionally salient but not neutral pictures. The power decrease was more evident in unpleasant trials; a larger and more sustained suppression of beta activity in a broad frequency range from 14 to 30 Hz was observed, compared to pleasant stimuli that showed a smaller beta power decrease in the 20–30 Hz range. The modulation in oscillatory beta band activity correlated with the subjective rating of the emotional valence of the stimuli in our patients, but not with the severity of depressive symptoms.
The sgACC area, which is part of the ACC, comprises BA24 and BA25 (Drevets et al., 2008). The latter has been implicated as a key node in a limbic network that shows metabolic hyperactivity in TRD patients (Greicius et al., 2007; Sacher et al., 2012). In healthy subjects, induction of sadness led to the most robust activation of BA25 in the sgACC area, according to a meta-analysis of functional imaging studies of basic emotions (Vytal and Hamann, 2010). It was concluded that the sgACC area is critically involved in regulating negative affect and sgACC-area hyperactivity may be responsible for maintaining a depressed mood state in patients with TRD. Consequently, treatment response to sgACC-area DBS (Mayberg et al., 2005) or pharmacotherapy (Mayberg et al., 2000) is reflected by a decrease of local metabolic hyperactivity in the sgACC area in TRD. However, according to a large meta-analysis of imaging studies on brain representations of discrete emotions, activation of the sgACC area is not confined to negative emotions but has also been shown during induced happiness or passive emotion tasks (specifically BA24) (Vytal and Hamann, 2010). In line with previous imaging studies (Phan et al., 2002), stimuli of negative valence induced the most robust response in our patients, i.e. the strongest and most sustained decrease of beta band activity (BBA).

To date, most knowledge of BBA has been gathered from studies on sensorimotor and—to a lesser degree—on cognitive or emotional processing. In scalp EEG studies, Pfurtscheller and colleagues found a decrease of BBA (termed event-related desynchronization, ERD) over cortical motor areas during finger movements, followed by an increase of BBA (i.e. event-related synchronization, ERS) upon movement offset (Pfurtscheller and Lopes da Silva, 1999), suggesting that the ERD reflects an activated cortical area (Neuper et al., 2006). More recently, Engel and Fries (2010) have proposed a more general hypothesis that sustained BBA in motor and frontal areas relates to the maintenance of the current state (i.e. the current cognitive or motor set or ‘status quo’), whereas changes of the current state, such as perception of externally delivered salient stimuli, induce a decrease of BBA and a concomitant local increase in gamma power is often found. Accordingly, beta oscillations play an important role in facilitating multimodal interaction between distant cortical areas (Senkowski et al., 2007; Varela et al., 2001), thus enabling stimulus integration and response preparation. A recent study illustrated this integrative aspect of beta oscillations during multimodal processing, combining visual stimuli of emotional and neutral faces with painful tactile stimuli (Senkowski et al., 2011). They found a more pronounced suppression of BBA in the sensorimotor cortex for painful stimuli, which were accompanied by emotional faces compared to neutral faces or compared to painful stimuli alone. In their seminal

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**Fig. 4.** (A) Statistical parametric map (SPM) of the non-directional F-contrast which tested for a main effect of valence (ANOVA), i.e. the relevant time and frequency space which showed differential responses according to stimulus valence. F-values are color coded and displayed above the threshold of the significance level (P < 0.01, FWE). The F-contrast shows one large significant cluster (2.5–30 Hz, 750–2500 ms, 364 bins) which served as a region of interest in time and frequency space for the post-hoc T-contrasts. (B) SPM of the post-hoc T-contrast between unpleasant and neutral stimuli. T-values are color coded and displayed above the threshold of the significance level (P < 0.001, FWE). One large cluster (269 bins) is evident from 1000 to 2500 ms including frequencies from 2.5 to 30 Hz. (C) A smaller cluster was found when contrasting spectral power changes of pleasant and neutral stimuli (1000–2500 ms, 2.5–30 Hz, 187 bins). FWE, family-wise error corrected.

**Fig. 5.** Scatter plot of the subjective rating (x-axis) of the stimulus valence (A) and stimulus arousal (B) and beta band activity (BBA, 14–30 Hz, 1000–2500 ms, y-axis) in response to stimuli (pleasant – light blue, unpleasant – light red, neutral – gray). Changes in BBA are quantified as z-scores. The regression analysis revealed a significant quadratic relationship (r = 0.69, P = 0.005) for valence (A) and a linear relationship (r = 13.1, P = 0.002) for arousal (B). The stronger the decrease in BBA (i.e. desynchronization) the more intense was the rating of stimulus valence following a U-shaped distribution (A). Similarly the stronger the decrease in BBA the more intense was the arousal rating (B) (r = 0.61, P = 0.002).
review on cortical oscillation patterns, Donner and Siegel (2011) corroborate this integrative aspect of beta oscillations.

Our findings of a decreased BBA in response to emotional stimuli are compatible with the interpretation of an activated cortical area, or more generally representing a multimodal integrative process related to later stages of emotional processing. After appraisal of an emotional stimulus, which occurs in an earlier time window during the first hundreds of microseconds (Kawasaki et al., 2001), later processing includes the generation of affective states, somato-motor responses and conscious emotional feelings (cf. review by Phillips et al., 2003). Based on patterns of connectivity and imaging studies, Bush and colleagues described an affective-cognitive gradient along the ventro-dorsal axis of the ACC (2000). The sgACC area, which is part of the affective ACC division, belongs to a network with numerous connections to subcortical and cortical regions essential for emotional processing such as the amygdala, nucleus accumbens, hypothalamus and the orbitofrontal cortex (Johansen-Berg et al., 2008). Among other functions mentioned above, the sgACC area is activated during detection of salient internal or external emotional triggers, as well as during generation and regulation of affective states (Devinsky et al., 1995; Bush et al., 2000; Seeley et al., 2007). The former may be mediated by a decrease of BBA, as shown in our study, representing conscious stimulus elaboration and the generation of emotional feelings.

The possible relationship between modulation of BBA in the sgACC area and stimulus evaluation is further illustrated by the significant correlation between stimulus valence and BBA. The time window of the relatively late (750–2500 ms) and sustained BBA modulation in our study is similar to the time window reported in previous M/EEG studies on emotional processing (Kemp et al., 2002; Popov et al., 2012), and has been hypothesized as expression of ongoing conscious elaboration and semantic integration, possibly by triggering recall of stimulus congruent content of semantic memory. The higher sensitivity of the sgACC for negative stimuli may also be interpreted as a correlate of a negativity bias, which is discussed as a disease-inherent feature in patients with MDD (Gotlib et al., 2004). From the same point of view, one could argue that the reduced modulation in response to pleasant stimuli reflects a deficit of processing positive information. This may resemble the clinical symptom of anhedonia, which is a common feature in depressed patients. However, we did not find a correlation with disease severity (as measured by the BDI and HAMD) and modulation of BBA. Instead, we found support that BBA may index the degree of emotional valence of stimuli. The larger BBA with unpleasant stimuli is in line with recent observations from multi-unit activity recordings in the sgACC area in patients with TRD (Laxton et al., 2013).

We speculate that the sgACC area is involved in conscious stimulus elaboration rather than in direct orchestration of a visceromotor arousal reaction, in which case we would have expected an early neuronal response that correlates with stimulus arousal (as shown for gamma synchronization in the subthalamic nucleus in Parkinson’s disease patients; Huebl et al., 2014). Interestingly, in a different cohort of TRD subjects who underwent DBS of the bed nucleus of the stria terminalis (BNST)—an output nucleus of the extended amygdala—this very correlation between gamma band activity and stimulus arousal has been found (Neumann et al., unpublished data). Likewise, in patients with intractable epilepsy intracranial recordings of oscillatory activity in the amygdala revealed the strongest gamma band activity for stimuli with negative valence and high arousal (Oya et al., 2002). It is noteworthy that in our study, the only significant gamma ERS also occurred after presentation of unpleasant stimuli.

In our previous studies on emotional processing using intracranial recordings in PD patients, we found modulations of alpha band activity during emotional processing whereas no valence-specific changes occurred in the beta band (Kühn et al., 2005; Huebl et al., 2014). The different origin (subthalamic nucleus in PD; sgACC area in TRD) of the recorded activity may explain the observed differences in frequency band power changes between these studies. Importantly, excessively increased BBA is a pathophysiological hallmark of PD, which may preclude or substantially limit physiological modulation of BBA (Jenkinson and Brown, 2011).

We are aware of several limitations of our study. First, our study was performed in patients with severe and treatment resistant types of MDD in whom all prior therapies have failed. Therefore, the results can only be interpreted with caution with respect to physiological sgACC function. Nonetheless, the response pattern with predominant reactivity upon unpleasant stimuli fits well with the existing literature of emotional processing in patients with TRD. Second, emotionally evocative stimuli capture more attention than neutral stimuli. Therefore, we cannot distinguish whether the differences in the magnitude and direction of BBA modulations are due to emotional stimulus elaboration or are a mere byproduct of increased allocation of attention. However, previous studies that examined parameters of attention implicated gamma-band activity (GBA) in an earlier time window as a correlate for attentional demands (e.g. Jensen et al., 2007). Third, patients were on different types of anti-depressive, neuroleptic and/or sedative medication, which may potentially bias the results. However, we did not find any significant interaction between spectral power changes and type of medication when we included medication as a factor in the rmANOVAs.

In summary, our data extends current knowledge on the functional role of the sgACC area in patients with TRD through direct recordings of neuronal activity. Our findings suggest that beta oscillations may index the conscious processing of emotional stimuli, which was most pronounced for unpleasant stimuli in TRD. DBS of the sgACC area may influence stimulus perception by interfering with emotion-induced beta band activity.

Supplementary data
Supplementary data are available at SCAN online.

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