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Brief report

Effect of specific psychotherapy for chronic depression on neural Responses to emotional faces

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ABSTRACT

Background: Neurofunctional deficits in chronic depression (CD) have been understudied. Specifically there is no known published study of the effects of a specialized psychotherapy for CD (CBASP) on neurofunctional deficits.
Methods: Ten patients with a DSM-IV diagnosis of CD received a 12 week specialised psychotherapy (CBASP). Controls were healthy matched volunteers. All subjects participated in a prospective study with functional magnetic resonance imaging (fMRI) at baseline and after 12 weeks. During the fMRI scans, subjects performed an implicit and explicit emotional processing task while watching dynamic displays of neutral, positive (happy) and negative (fearful and sad) facial expressions. Effects of treatment were analyzed in a repeated measures design. The analysis was restricted to two anatomically defined regions of interest (ROI): the amygdala and the cingulum.
Results: 60% of patients responded to treatment. Patients with CD reported increased arousal to negative emotional expressions. They also showed an increase in left amygdala reactivity during implicit processing of emotional expressions following psychotherapy. We found no significant effect for the cingulum.
Limitations: The main limitation of our study is the small sample size. Due to the lack of a control group it is also unclear whether the demonstrated effect is specific to the psychotherapy used in this study.
Conclusions: For the first time our study demonstrates an effect of CBASP on neural processing of facial emotions in CD. It therefore adds to the growing evidence supporting this treatment.

1. Introduction

About a third of patients suffering from depression report a chronic course of their illness (Klein et al., 2000; Murphy and Byrne, 2012). Recently the different forms of chronic depression (CD) have been summarized in the DSM-5 as "persistent depressive disorder" (American Psychiatric Association, 2013). In spite of this fact, CD has long been under recognized and under treated. While a large number of functional neuroimaging studies exist in major depressive disorder there are, to our knowledge, no published studies that have specifically focused on changes of aberrant brain function in CD during the course of a specialized treatment. The Cognitive Behavioural Analysis System of Psychotherapy (CBASP) (McCullough, 2000) was specifically developed for the treatment of CD and has been shown to effectively reduce depressive symptoms (Keller et al., 2000; Kocsis et al., 2009b; Schramm et al., 2011; Swan et al., 2014).

On meta-analysis, depression has been associated with functional changes in anterior cingulate, dorsolateral, medial and inferior prefrontal cortex, the insula and the amygdala (Fitzgerald et al., 2008). These changes have been found to be reversible for the following successful treatment both with antidepressants (Fitzgerald et al., 2008; Hoflich et al., 2012) and with psychotherapy, mainly cognitive behavioural therapy (CBT) (DeRubeis et al., 2008). The amygdala has been said to play a central role in the pathophysiology of depression (Disner et al., 2011). Some but not all studies

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have found increased amygdala activity in depression (Fitzgerald et al., 2008). Psychotherapy has been found to normalize amygdala functioning (Fu et al., 2008) and this change has been hypothesized to be mediated through increased prefrontal control (DeRubeis et al., 2008). Psychotherapy (CBT) has also been shown to normalise activity in the dorsal and subgenual cingulate cortex (Fu et al., 2008; Fu et al., 2013; Goldapple et al., 2004; Kennedy et al., 2001; Kennedy et al., 2007).

The aim of the present study was to assess the effects of CBASP treatment on both the behavioural and neural correlates of CD. We hypothesized that amygdala activity would be increased at the beginning of treatment and normalize in the course of treatment. We also hypothesized to find decreased activity in dorsal cingulate that would normalize following treatment.

2. Methods

2.1. Subjects

Twelve Caucasian outpatients (7 female and 5 male) participated in the present study. 10 of these returned for the second MRI scan (drop-out rate of 16,7%). Therefore only the data of 10 patients will be presented here. All patients had a diagnosis of CD (assessed with the Structured Clinical Interview for DSM-IV - Wittchen et al., 1997). Diagnosis was made by two experienced clinicians (JPK and MC).

Exclusion criteria were acute suicidality; any history of mania or hypomania, schizophrenia, dementia, epilepsy, severe head injury or stroke; current substance abuse, borderline personality disorder, benzodiazepine treatment; age of 60 years and older, and the usual MRI contraindications. All subjects had normal or corrected-to-normal vision. All but one patient were medication free. One was on a stable dose of venlafaxine for several months. There were no changes in medication during the course of treatment. The patients progress was monitored regularly with the Beck Depression Inventory (Beck and Steer, 1987; Hautzinger et al., 1995) and the Hamilton Depression Rating Scale (Hamilton, 1960; Hamilton, 1967).

Ten age, gender, and education-matched healthy Caucasian comparison subjects with no history of psychiatric disorders were recruited by advertisement. All comparison subjects underwent the same psychiatric assessment as the patients. The study was conducted in accordance with the Declaration of Helsinki. The ethics committee at the Charité Berlin approved the study. Prior to the study, informed written consent was obtained from all participants.

2.2. Treatment

Patients received 12 weeks of CBASP with a therapist certified in the procedure (JPK). The mean number of sessions was 15.8 ($\pm$3.6). Sessions followed a manual (McCullough, 2000) and lasted 50 min each. They were supervised to ensure that adherence criteria were followed (McCullough, 2000,pp. 285,) and the required level of competency was met.

2.3. Experimental Design

Neural functioning was probed using a facial emotion processing task with dynamic facial stimuli. The presentation of static and dynamic emotional face stimuli has been shown to reliably elicit amygdala responses (Patin and Hurlemann, 2011). In the present study we used dynamic instead of static stimuli to increase the ecological validity (van der Gaag et al., 2007). The stimulus material consisted of 40 different film clips from 10 professional actors (five male and five female) who displayed neutral, positive (happy) and negative (fearful and sad) dynamic facial expressions (van der Gaag et al., 2007). The study participants were instructed to identify the gender of the actor (implicit emotional processing) or the emotion displayed (explicit emotional processing). For further description of the experimental design please refer to the supplementary methods. Following the fMRI scan, all participants were asked to rate the arousal of the emotional faces. To this end, the forty film sequences were presented again in a randomized order outside the scanner. Valence and arousal ratings were made on a seven point Likert scale.

2.4. Data Acquisition

The scanning sessions consisted of fMRI scans of 30 min total duration at baseline and after 12 weeks in a 1.5 T Siemens Sonata Scanner. Volumes for the study consisted of 26 axial slices (TR 2500 ms; TE 40 ms; flip angle 90°; resolution $4 \times 4 \times 4$ mm) oriented along the AC–PC line. In addition, anatomical T1-weighted images were obtained for each subject, using a MPRAGE sequence (TR 12.24 ms; TE 3.56 ms; flip angle 23°; resolution $1 \times 1 \times 1$ mm).

2.5. Data processing and statistical processing

SPSS 12.0 (SPSS Inc.) was used for the analysis of clinical and behavioural data. FMRI data were preprocessed and analyzed using SPM8 software (Wellcome Trust Centre for Neuroimaging, London, UK; http://www.fil.ion.ucl.ac.uk/spm) implemented in Matlab 7 (The MathWorks Inc., Natick, MA, USA). For a description of the pre-processing steps please refer to the supplementary methods.

Following pre-processing, separate onset regressors for the implicit and explicit conditions modelling each facial expression (neutral, happy, fearful, sad) for each time point (pre-, post treatment) were modelled by a stick-function convolved with a hemodynamic response function. To increase the statistical power to detect treatment effects the individual facial expressions (neutral, happy, fearful, sad) were pooled. Importantly, previous studies with the same stimuli found no emotion-specific differences in amygdala responses, i.e. equally robust amygdala responses for emotional and neutral stimuli (Hurlemann et al., 2010; Onur et al., 2009; van der Gaag et al., 2007). The movement parameters were included as confounds and specific effects were assessed by comparing the regressors with the implicit baseline. Effects of treatment were analysed in a repeated measures design incorporating the within-subject factor time point (pre-, post-treatment) and the between-subject factor group (controls, patients). For the implicit and explicit condition separate analyses were computed.

Because of our a priori hypothesis analyses were restricted to the anatomically defined bilateral amygdala and the cingulum as regions of interest (ROI). For a description of the ROIs please refer to the supplementary methods. All results are reported at a threshold of $P < .05$ corrected for multiple comparisons based on family-wise error (FWE) for the amygdala ROI. Activations were mapped using the Talairach Demon (Lancaster et al., 1997; Lancaster et al., 2000).

3. Results

For a full description of our sample please refer to Table 1. Briefly, there were no differences between the 10 patients and the 10 controls regarding age, gender distribution, education, IQ and handedness.

3.1. Clinical response

Six out of the 10 patients who completed the study (60%) showed a 50% decrease in HAMD, which is indicative of a clinical response. Four patients (40%) met criteria for full remission with a post-treatment HAMD below seven. For a detailed description of the clinical characteristics of patients and controls and the therapeutic response, please refer to Table 1.

3.2. Behavioral data

Only six of 10 patients were available for the second assessment of the behavioural data. The available data were analysed with a repeated-measures MANOVA with one within-subject factor (pre-, post-treatment) and one between-subject factor (patients, controls) and arousal scores as dependent variable. Here we observed a significant main effect of group ($F4,11=4.03$, $P=.03$). Post-hoc analysis using Bonferroni-corrected paired *t*-tests showed that there was a group difference only for the neutral faces. Here, patients reported a significantly higher arousal than controls ($t14=5.13$, $p=.04$) (Supplementary Table 1). We did not find a main effect of time ($P=.75$) or a group × time interaction ($P=.29$).

3.3. Functional results

For the explicit condition there were no significant main (timepoint, group) or interaction (time × group) effects in the bilateral amygdala ROI. Moreover, for the implicit condition there were no significant main effects (timepoint, group). However, we observed a significant group × timepoint interaction effect in the left amygdala (MNI coordinates $x=-30$, $y=-4$, $z=-14$, $F1,18=25.32$, $P<.05$, FWE-corrected). For further analysis individual parameter estimates for both timepoints were extracted from a 8 mm radius sphere centered at the coordinates of the group × timepoint interaction effect. Subsequently, the individual parameter estimates were subjected to a repeated measures ANOVA with the within-subject factor timepoint (pre-, post-treatment) and the between-subject factor group (patients, controls). This analysis revealed no significant main effects (timepoint, group; both $P>.28$); however, a significant timepoint × group interaction effect ($F1,18=7.23$, $P=.015$). Post-hoc analyses using Bonferroni-corrected paired t-tests showed that within the group of patients left amygdala activity significantly increased between the pre- and post-treatment sessions ($t9=1.70$, $p=.014$). In contrast there were no significant changes within the group of controls between the timepoints ($t9=-3.04$, $p=.122$) (Fig. 1). The results were essentially the same when the implicit and the explicit condition were analysed together. We did not find significant main (timepoint; group) or interaction (time × group) effects for the cingulum ROI.

Table 1
Sociodemographic and clinical characteristics of patients and controls (mean values, standard deviations).

	Patients ($N=10$)	Controls ($N=10$)
Age	38.2 (13.2)	39.2 (14.5)
Sex (female:male)	6:4	6:4
Education (yrs.)	16.6 (1,5)	16.6 (1.8)
Edinburgh handedness-score (Oldfield, 1971).	91.7 (7.6)	90.2 (12.9)
Verbal IQ (MWTB - Lehrl, 1995)	113 (8.2)	114 (8.2)
Fluid IQ (LPS-3 - Horn, 1983)	116 (12.6)	117 (8.5)
HAMD-17	16,6 (2.2)	2 (1.7)
BDI-II	29.1 (10.2)	5.4 (4.4)
Duration of current episode (wks)	109 (241.7)	n.a.
Number of depressive episodes	3.2 (1.3)	n.a.
Age of onset (< 21yrs: > 21yrs)	9:1	n.a.
Number of CBASP sessions	15.8 (3.6)	n.a.
HAMD-17 response rate	60% ($N=6$)	n.a.
HAMD-17 remission rate	40% ($N=4$)	n.a.

4. Discussion

In this small study, we were able to demonstrate increased arousal to neutral facial expressions in patients with CD and an effect of specialised psychotherapy for CD (CBASP) on left amygdala reactivity.

Contrary to our hypothesis we found no difference in amygdala reactivity between patients and healthy controls at the beginning of treatment and increased activity in patients following treatment. These results contrast with earlier findings of decreased amygdala activity following psychotherapy (Dichter et al., 2009; Fu et al., 2008) and pharmacotherapy (Fu et al., 2004). Increased amyydala reactivity in depression has been found in some but not all previous studies (for review: Fitzgerald et al., 2008). We also did not find a previously reported effect of psychotherapy (Dichter et al., 2009; Fu et al., 2008; Goldapple et al., 2004) on cingulate functioning. This may be a false negative finding that is due to the small sample size and the fact that the stimulus material was optimized to find a robust amygdala response.

We found these discrepancies to previous research in spite of the fact that the clinical response and remission rates of our study were similar to clinical outcomes with CBASP monotherapy in a much larger trial (Keller et al., 2000). The discrepancies can

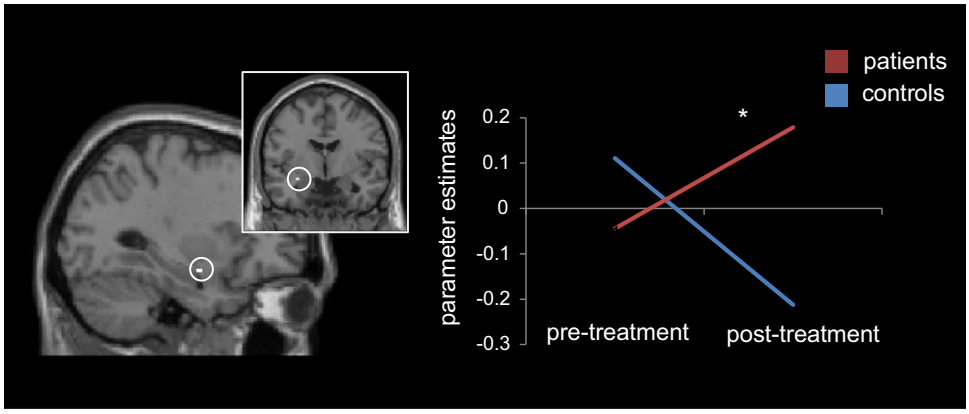

Fig. 1. Implicit emoitonal processing. Significant group × timepoint interaction effect in the left amygdala (MNI coordinates $x=-30$, $y=-4$, $z=-14$, $F1,18=25.32$, $P<.05$, FWE-corrected). Post-hoc analyses of the parameter estimates extracted from a sphere around this effect showed that only within the group of patients the activity significantly increased between the pre- and post-treatment fMRI sessions ($t9=1.70$, $p=.014$ for patients and $t9=-3.04$, $p=.122$ for controls).

therefore not be explained by unsuccessful therapy. We carefully speculate that the increased amygdala reactivity following therapy might be the consequence of patients improved ability to engage with their interpersonal environment following therapy. Engaging effectively with the interpersonal environment is the common goal of the different CBASP techniques (McCullough, 2000) and may temporarily increase rather than decrease affective reactions.

Our findings for arousal ratings are in line with earlier findings that processing deficits in depression can be specific to neutral faces (Gur et al., 1992; Leppanen et al., 2004). Here we only found a group effect however and failed to find an effect of therapy on arousal ratings. Increased arousal ratings with neutral faces can be interpreted in the context of our amygdala findings as the amygdala has been associated with processing of arousing stimuli (Brooks et al., 2012).

There are several limitations to consider in our study. The main limitation is the small sample size. We did not reach the target sample size of 25 participants in each group due to time constraints. Also the results may not generalize to the entire population of patients with CD, as the patients participated in the study because they specifically thought psychotherapeutic treatment. This preference may affect treatment effects (Kocsis et al., 2009a). Also, our effects cannot be reliably distinguished from effects of changes in illness severity or the supportive aspects of frequent contact with expert psychiatrists because there was no control group. Future studies should compare the neural effects of CBASP to those of another psychotherapy to study the specific effects of CBASP and include a follow-up as the effect of psychotherapy may unfold over time (Carroll et al., 1994; Gloaguen et al., 1998; Vittengl et al., 2007).

In conclusion we were able to demonstrate behavioural evidence of abnormalities in the processing of emotions in chronic depression. For the first time we also found neurofunctional evidence for the effect of CBASP. This study therefore adds to the growing literature elucidating the neural mechanisms underlying psychotherapy (DeRubeis et al., 2008).

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Conflict of interest

The lead author (JPK) is on the board of the CBASP Network (www.cbasp-network.org).

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.jad.2014.04.055.

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