Archival Report

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Effects of Psychotherapy on Neuronal Correlates of Reappraisal in Female Patients With Borderline Personality Disorder

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ABSTRACT

BACKGROUND: Emotion dysregulation is a fundamental aspect of borderline personality disorder (BPD). Accordingly, one major focus of dialectical behavior therapy (DBT) is to teach strategies to regulate emotional reactions. To date, little is known about the neural mechanisms linked to the amelioration of BPD symptoms after therapy. In the present study, we used functional magnetic resonance imaging to investigate neural correlates of explicit emotion regulation before and after DBT.

METHODS: Female BPD patients ($n = 32$) performed a reappraisal task before and after a 12-week inpatient DBT program and were compared with 24 healthy control participants. Based on the change in symptom severity, the BPD group was separated into responders and nonresponders and compared with a clinical control group of 16 BPD patients. Both control groups were scanned twice within 12 weeks.

RESULTS: After DBT, BPD patients showed decreased insula and anterior cingulate cortex activity during reappraisal. Anterior cingulate connectivity to medial and superior frontal gyrus, superior temporal gyrus, and inferior parietal cortices increased after DBT. Responders exhibited reduced activation in amygdala, anterior cingulate cortex, orbitofrontal, and dorsolateral prefrontal cortex together with increased connectivity within a limbic-prefrontal network during the reappraisal of negative stimuli after psychotherapy.

CONCLUSIONS: This study revealed reduced activity and increased connectivity in neural networks related to salience processing and emotion regulation after therapy. Attenuated limbic hyperarousal together with an elevated coupling between limbic and prefrontal and inferior parietal control regions in BPD patients after successful therapy may indicate more efficient emotion regulation during reappraisal of negative pictures.

Keywords: Anterior cingulate cortex, Borderline personality disorder, Dialectical behavior therapy, Emotion regulation, Functional magnetic resonance imaging, Reappraisal

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Emotion dysregulation is a fundamental characteristic of borderline personality disorder (BPD) (1), contributing to various severe symptoms, including self-injurious behavior, anger outbursts, and instable interpersonal relationships. BPD patients show instable, intense emotional reactions combined with deficient regulation capabilities (1). Neurobiologically, emotion dysregulation in BPD is reflected by dysfunctional brain activation patterns, including limbic structures, associated with emotional reactivity, and prefrontal brain regions, also associated with the regulation of negative emotions. A first meta-analysis of neuronal correlates of negative emotionality in BPD revealed greater insula and posterior cingulate cortex activation and lower dorsolateral prefrontal cortex (DLPFC) activation but did not confirm previous evidence of enhanced amygdala activity (2). However, a recent meta-analysis revealed increased amygdala-hippocampal and posterior cingulate cortex activation as well as decreased bilateral DLPFC responses to negative versus neutral stimuli in BPD patients compared with healthy participants (3). It further demonstrated that methodologic and sample characteristics such as medication might be responsible for the inconsistent findings regarding amygdala hyperreactivity; that is, limbic hyperactivity was only seen in medication-free patients (3).

One factor contributing to emotion dysregulation in BPD is the difficulty using reappraisal as a cognitive emotion regulation strategy (4,5). During reappraisal, in comparison to viewing of negative pictures, healthy individuals showed increased recruitment of brain regions implicated in cognitive control and attention deployment such as the DLPFC and anterior cingulate cortex (ACC), and regions implicated in response selection and inhibition, that is, the ventrolateral and orbitofrontal cortex (OFC) (6). When using reappraisal to regulate emotions, BPD patients as opposed to healthy individuals showed a reduced ability to downregulate the amygdala (7) and insula (5). Furthermore, these studies revealed an anomalous engagement of OFC and ACC in BPD patients during reappraisal (5,7). There is also evidence of reduced prefrontal-limbic connectivity in BPD (8), possibly resulting in a deficient regulation of limbic hyperarousal.

With its focus on teaching skills to regulate intense emotional reactions, dialectical behavior therapy (DBT) is the most widely used psychotherapy program for BPD (9). DBT skills training is effective in reducing BPD symptomatology (10). Identifying key neural circuits underlying treatment processes, including the differentiation of therapy responders and nonresponders, is therefore of high importance for evaluating and further improving treatment strategies for BPD patients. Despite the clear emphasis of DBT on emotion regulation techniques, including reappraisal (11), neural correlates of emotion regulation after DBT have hardly been examined. One study investigated DBT-based changes in emotional hyperreactivity and suggested attenuated amygdala activity as treatment effect (12). Additionally, a recent study investigating neuronal changes after transference-focused therapy pointed to increased dorsal prefrontal activity in a go/no-go paradigm after psychotherapy (13).

Given DBT's strong focus on emotion regulation strategies and the previous evidence of impaired reappraisal in BPD patients, we investigated therapy-related changes in brain activity using a reappraisal paradigm. We assessed BPD patients undergoing DBT before and after treatment and compared their neural activity during reappraisal with a group of healthy participants. For investigating changes in neuronal activity associated with treatment response, we separated the DBT group into responders and nonresponders and compared them with a control group of BPD patients completing their usual, non-DBT treatment. We hypothesized that particularly responders would show a downregulation of brain regions associated with limbic hyperarousal (i.e., amygdala and insula), a differential engagement of cognitive control regions underlying aberrant reappraisal (i.e., OFC and ACC), and an elevated limbic-prefrontal network connectivity during reappraisal of negative pictures.

METHODS AND MATERIALS

Participants

Participants were 48 women with a diagnosis of current BPD ($n = 32$ in the DBT group; $n = 16$ in the BPD control group recruited to control for time effects) and 24 healthy women (trial flow diagram in Supplemental Figure S1). The study was part of a larger project on neural correlates of emotion regulation in BPD after DBT conducted from January 2011 to April 2014, with resulting publications based on the same participants (Niedtfeld I, Dr. sc. hum., *et al.*, unpublished data, 2016) (14).

General exclusion criteria were severe medical or neurologic illness, head injury, any psychotic or bipolar (type I) disorder, current severe depressive episode, and substance dependence within the past 12 months. Healthy participants hat no current or past psychiatric diagnoses. All patients met BPD DSM-IV criteria and had no prior DBT experience. They had either no medication (45.8%) or constant medication (54.2%) during the study period. See the Supplement for details.

DBT patients were recruited from specialized inpatient treatment facilities at Heidelberg University (Department of General Psychiatry, $n = 15$; Department of Psychosomatic Medicine and Psychotherapy, Central Institute of Mental Health, $n = 17$). They received a standard 12-week DBT inpatient treatment program (9,15), including weekly, manualized skills training groups, which focused on the improvement of emotion regulation capabilities (details in Supplement). Skill groups were parallelized with respect to topics and time across the study sites. Therapists were experienced Ph.D., M.D., or M.Sc. clinicians with regular supervision including that of a certified DBT supervisor.

The healthy and the BPD control groups were recruited through advertisements. The latter also had no DBT intervention during the study period but other unspecific interventions (details in Supplement).

BPD patient groups and healthy participants did not differ in age nor education (all $p \geq .441$). Treatment response was determined using the well-established reliable change index (RCI; cut-off: ≥1.96) (16) based on symptom reduction measured by Zanarini Rating Scale for Borderline Personality Disorder (ZAN-BPD) (17). The RCI of ZAN-BPD before and after change was calculated for each case, categorizing DBT patients into responders or nonresponders, that is, those who scored more or less than the RCI cutoff of 1.96. This resulted in 17 responders and 15 nonresponders. Responders did not differ from nonresponders and from the BPD control group patients in age, education, number of Axis I diagnoses, and medication status ($p \geq .191$). Tables 1 and 2 summarize demographic data and baseline clinical characteristics (see Supplement for patient flow/comorbid disorders).

Ethics Committees of the Medical Faculties Mannheim and Heidelberg approved the study. The study was conducted according to the Declaration of Helsinki. After thorough explanation of the study, participants provided written informed consent and were paid for participation.

Measures

Before the experiment, qualified and trained diagnosticians assessed BPD diagnosis [International Disorder Examination for DSM-IV (18)] and Axis I disorders (Structured Clinical Interview for DSM-IV). BPD symptom severity was assessed with the ZAN-BPD (17) at baseline (t1; for the DBT group: first week of inpatient treatment) and after 11 weeks (t2; for the DBT group: during the 12th week of treatment). For further sample characterization, the ZAN-BPD subscale Affect measuring the severity of affective dysregulation, the Borderline Symptom List (BSL) measuring BPD symptoms (19), and the Beck Depression Inventory (BDI) measuring depressiveness were used. Further, participants reported their skills use and perceived effectiveness within the past 3 days (details in Supplement).

Reappraisal Paradigm

At each session, participants performed a reappraisal task during the presentation of negative and neutral pictures (5). They were asked to either reappraise their emotion by imagining that the situation was not real or that they were a detached observer (reappraisal condition) or to view the pictures attentively without trying to alter their affective reaction (maintain condition). For paradigm details see Supplement.