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Functional Correlates of childhood maltreatment and symptom severity during affective theory of mind tasks in chronic depression

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ABSTRACT

Among multiple etiological factors of depressive disorders, childhood maltreatment (CM) gains increasing attention as it confers susceptibility for depression and predisposes to chronicity. CM assumedly inhibits social-cognitive development, entailing interactional problems as observed in chronic depression (CD), especially in affective theory of mind (ToM). However, the extent of CM among CD patients varies notably as does the severity of depressive symptoms. We tested whether the extent of CM or depressive symptoms correlates with affective ToM functions in CD patients. Regional brain activation measured by functional magnetic resonance imaging during an affective ToM task was tested for correlation with CM, assessed by the Childhood Trauma Questionnaire (CTQ), and symptom severity, assessed by the Montgomery-Åsberg Depression Rating Scale (MADRS), in 25 unmedicated CD patients (mean age 41.52, SD 11.13). Amygdala activation during affective ToM correlated positively with CTQ total scores, while (para)hippocampal response correlated negatively with MADRS scores. Our findings suggest that differential amygdala activation in affective ToM in CD is substantially modulated by previous CM and not by the pathophysiological equivalents of current depressive symptoms. This illustrates the amygdala's role in the mediation of CM effects. The negative correlation of differential (para)hippocampal activation and depressive symptom severity indicates reduced integration of interactional experiences during depressive states.

1. Introduction

The individual presentation and course of depressive disorders reflect multifactorial contributions (Beck and Alford, 2009). A chronic course of depression, which corresponds to the DSM-5 diagnosis of persistent depressive disorder (PDD) (American Psychiatric Association, 2013), is characterized by symptoms of a depressive mood most of the day for more days than not and persisting for at least 2 years (McCullough and Clark, in press). Chronic depression (CD) is additionally associated with multiple relapses and a heightened treatment resistance (Keller et al., 1992). As about 65% of chronically depressed patients report a history of childhood maltreatment (CM) (Wiersma et al., 2009) and up to 70% of all CD cases are manifested before the age of 21 years (Cassano et al., 1992), the impact of early life experiences such as experiencing abusive or neglectful parental behaviour is assumed a major contributing factor of CD (Teicher and Samson, 2013). CM increases the lifetime risk for depression (Chapman et al., 2004), accompanied by a strong dose-response relation between frequency of exposure and the extent of depressive

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symptoms (Hovens et al., 2010). Furthermore, CM increases the risk for chronicity and thus represents an independent determinant of a chronic course in depression (Klein and Santiago, 2003; Nanni et al., 2012; Wiersma et al., 2009). However, not all chronically depressed patients report CM and those who do show various extents of severity. Given that CM constitutes specific susceptibility for chronicity in depressive disorders, it should be possible to disentangle the persistent functional effect of CM that accounts for the chronicity, i.e., non-remission, from the functional correlate of current depressive symptoms. In healthy adults, long-term effects of CM are detectable in brain structures, functional activations and connectivity (Chaney et al., 2014; Heim et al., 2013; Jedd et al., 2015; Teicher et al., 2003; van Harmelen et al., 2010) and result in cognitive and behavioural deficits: CM facilitates the development of dysfunctional attitudes and negative cognitive schemas, accompanied by negative attention seeking and interpretation biases, which are commonly provoked in social interactions (Beck, 2008). The frequent activation of these negative schemas manifests the depressive mode, which is composed of automatic thoughts, cognitive distortions, dysfunctional beliefs and unfavourable information-processing, as well as maladaptive patterns of affective, behavioural and motivational approaches in social situations (Beck, 2008). Maintaining such dysfunctional cognitions and reactions constitutes survival factors like defensive strategies, mainly facilitated by escape and avoidance learning. By this, enduring neural consequences that reinforce destructive interactional behaviour and heighten the prevalence of a refractory cognitive-emotional dilemma are formed (Neudeck et al., 2012). Further, CM provokes a cognitive emotional derailment, impairing the appropriate development of social-cognitive functions (McCullough, 2003). The resulting interactional and emotional difficulties are subsequently transferred into adulthood and characterize chronically depressed patients (Heim et al., 2004; McCullough, 2003). Additionally, McCullough (2003) postulates that CM causes specific deficits in affective theory of mind (ToM) generation among chronically depressed patients, leaving them stuck in an egocentric perspective. This assumption is supported empirically by a recent study reporting a specific deterioration of affective ToM abilities in CD (Mattern et al., 2015). Affective ToM, also known as affective mentalizing, is a subdomain of ToM functions and can be defined as the ability to infer, represent and attribute mental states (emotions, moods) to other individuals (Frith and Frith, 2006). The emerging question is how CM impacts on affective ToM functions.

According to one of our studies, the core brain network for affective ToM generation consists of the dorsomedial prefrontal cortex (dmPFC), the bilateral posterior STS, the bilateral temporal poles, the left amygdala, the hippocampus and the left posterior cingulate gyrus (Schnell et al., 2011). The activation of amygdala and hippocampus is most likely associated with the simulation of affective states or cognitive reference to previous own emotional experiences, as it can be observed in the absence of direct emotional stimuli (Schnell et al., 2011). This function in autobiographic recall of emotional states corresponds to findings demonstrating that amygdalar and hippocampal functions are altered by CM (Dannlowski et al., 2013; Van Harmelen et al., 2013). However, it has been reported as well that function of the amygdala and hippocampus is affected by depressive syndromes (Abercrombie et al., 1998; Benson et al., 2014; Chaney et al., 2014; McKinnon et al., 2009; Opel et al., 2014; Sheline et al., 1999; Siegle et al., 2007).

As the differential functional contributions of CM and depression severity in CD patients is of great relevance for individual treatment, we tested the differential effects of these factors. We did not focus on regions that are associated with ToM in general, but on crucial regions for emotional perspective change in accordance to Schnell et al. (2011). Thus, we selected the amygdala and the hippocampus as target regions for our functional analyses as both areas share the reported functional involvement in affective mentalizing, depression and CM.

The main goal of our study was to disentangle the functional effects of adverse early life experiences on social-cognitive functioning in chronic depression from effects caused by current depressive symptoms. We examined if ToM network dysfunctions are more likely associated with CM or reflect a side effect of emotion dysregulation and cognitive disturbances due to current depression severity. Such knowledge about the long-term impact of CM in current states of depression should improve treatments by defining social-cognitive deficits as treatment targets in chronically depressed patients. The distinction between effects of CM and current depressive symptoms is important because for selecting an appropriate therapeutic intervention, especially antidepressant medication vs. specific psychotherapy. To investigate whether the activation of the amygdala and hippocampus during affective ToM generation is differentially influenced by CM and acute depression, we selected a group of chronically depressed patients for our study as they provide various combinations of CM and depressive symptom severity. This variance of CM and depression severity facilitates the examination of the functional effect of both factors during affective mentalizing in one group of patients (McCullough, 2003). Due to the findings concerning amygdalar and hippocampal activation during affective ToM generation and the reported impact of CM and depression, we hypothesized that CM and current depression severity would have distinguishable functional correlates during affective mentalizing, which could be detected in the activation of the amygdala and the hippocampus in a group of CD patients.

In addition, we aimed to probe the effects of CM on functional activation during affective social cognition, which is clearly distinguishable from a stimulus driven automatic response to highly overlearned emotional cues such as facial expressions (Dannlowski et al., 2013; Grant et al., 2011; Klein et al., 2014; Siegle et al., 2002; Van Harmelen et al., 2013), as it has been suggested that CM inhibits early development of social-cognitive functions.

2. Materials

2.1. Subjects

We analysed behavioural and functional data of 25 subjects with CD (16 female, mean age 41.52, SD 11.13) who had been free of psychotropic medication for at least 2 weeks. With regard to the reported conjunction between chronicity, multiple relapses and heightened treatment resistance in depression (Keller et al., 1992), we included subjects who met the DSM-IV (American Psychiatric Association, 2000) criteria for a current episode of chronic major depression (with the modification of at least 1 year of depressive symptoms) or recurrent major depressive episodes (≥ 3 episodes with the preceding episode no more than 2.5 years before the onset of the current episode), assessed by the Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID) (First et al., 2002). Our group was a subsample of a bicentric randomized clinical trial exploring the effects of psychotherapy (CBASP, Cognitive Behavioural Analysis System of Psychotherapy) versus medication with selective serotonin reuptake inhibitors (Schramm et al., 2015). For the clinical trial, 60 outpatients were recruited and observed over the course of 8 and 28 weeks, respectively. The main inclusion criterion was a score of at least 18 on the Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery and Åsberg, 1979), which was determined before the patients entered the study. Out of the 60 subjects, 34 participated in the additional functional magnetic resonance imaging (fMRI) trial involving two fMRI scan sessions – one before the beginning of the treatment, the second one 8 weeks later. Each fMRI examination comprised four functional paradigms, the ToM task reported in this article, a reward