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Research report

Neural correlates of successful psychotherapy of depression in adolescents

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ABSTRACT

Background: While major effort has been put in investigating neural correlates of depression and its treatment in adults, less is known about the effects of psychotherapy in adolescents. Given the concordance of the ventral striatum, amygdala, hippocampus and the subgenual anterior cingulate cortex (sgACC) as correlates of depression and their involvement in reward processing, we used functional magnetic resonance imaging (fMRI) during performance of a monetary reward task in an intervention versus waitlist-control design to investigate the clinical and neural effects of cognitive behavioral group therapy (CBT-G).

Methods: 22 medication naïve adolescents with major depressive disorder were scanned before and after five sessions of CBT-G (PAT-I), or before and after five weeks of waiting (PAT-W). Changes in symptom scales were analyzed along with neural activation changes within the amygdala, hippocampus, sgACC and ventral striatum regions of interest (ROI).

Results: Psychometric assessments and ROI activation remained unchanged in PAT-W. In PAT-I, significant reduction in clinical symptoms accompanied significant changes in brain activation within the left amygdala, left hippocampus and bilateral sgACC. In line with previous findings in adults, pre-to-post-activation changes in the bilateral sgACC correlated with pre-to-post and pre-to-follow-up symptom improvement, and individual expressions of sgACC activation before treatment were related to pre-to-follow-up therapeutic success.

Limitations: Future studies should include larger sample sizes.

Conclusions: Successful group psychotherapy of depression in adolescents was related to signal changes in brain regions previously demonstrated to be reliably linked with successful, particularly pharmacological treatment in adults.

1. Introduction

Given the increased risk for the development of affective disorders in youth (Duggal et al., 2001), with a raising number of incidents (Ryan et al., 1992), and the risk for relapses in adulthood (Patton et al., 2014) effective therapies for depressed adolescents are needed (Jonsson et al., 2011). Understanding the neural correlates of adolescent depression may assist in better shaping of therapies to the special characteristics and needs of this particular group of patients. Furthermore, investigating the neural correlates of psychiatric disorders in adolescents offers the opportunity to research a disorder at an early stage, thus bypassing otherwise relevant effects of previous medication and/or by changes in neural processing due to a chronic course of the disorder like in studies with adults (Cullen, 2012).

Research on regional brain activity modulated by depression showed a particularly consistent pattern of involvement of the amygdala, hippocampus, subgenual anterior cingulate cortex (sgACC), and ventral striatum for both adults and adolescents (Arnone et al., 2012, Forbes et al., 2009, Fu et al., 2008, Godlewska et al., 2012, Goldapple et al., 2004, Gotlib et al., 2005, Hall et al., 2014, Kennedy et al., 2001, Mayberg et al., 2000, Sheline et al., 2001, Yang et al., 2010). In adults, pre-to-post-comparisons of the effect of antidepressant medication reliably showed a reduction of amygdala reactivity (Arnone et al., 2012, Godlewska et al., 2012, Sheline et al., 2001). Likewise, pharmacological pre-to-post-modulation of activations of the hippocampus and sgACC has been repeatedly reported, although the direction of activity changes was less consistent as compared to results for the amygdala (Kennedy

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et al., 2001, Mayberg et al., 2000). Some evidence supports similar effects for psychotherapeutic interventions in adults (Fu et al., 2008, Goldapple et al., 2004). For example, two previous studies have shown that pre-treatment activity in the sgACC was associated with subsequent psychotherapeutic treatment response in adults (Siegle et al., 2006, 2012), which is in line with the notion that the sgACC seems to be a key structure for emotional processing (Thomason et al., 2011).

Treatment effects in depressed adolescents are much less investigated. Some evidence supports consistency with studies in adults with modulation of activity levels in the sgACC and amygdala by antidepressant medication (Tao et al., 2012). However, effects of psychotherapy in adolescents with depression still await further empirical investigation. To probe the modulation of the activation of amygdala, hippocampus, sgACC and ventral striatum by a psychotherapeutic intervention in depressed adolescents, we used functional magnetic resonance imaging (fMRI) of a reward paradigm. Selection of this paradigm was mainly motivated by the empirical observation from previous studies (Forbes et al., 2009, Haber and Knutson, 2010) that these core regions discussed in the development and maintenance of depression were robustly challenged at the individual level. Another motivation to let reward related activation serve as a surrogate marker of neural responsiveness of these brain structures came from a recent discussion on reward processing as a candidate endophenotype of depression, as it may constitute a risk characteristic that is likely to be heritable, is predictive for the onset of depression (Forbes and Dahl, 2012) and has been proposed as a correlate of depressive symptoms (Russo and Nestler, 2013). In adolescent patients, an association between depression and a lowered behavioral activation system, that regulates approach and appetitive motivation with a specific relation to reward sensitivity, has recently be shown by Gruber et al. (2013), and dysfunctional reward processing appears to align with altered motivation to obtain rewards and reduced enjoyment of rewarding outcomes (Forbes and Dahl, 2005). This may explain why patients tend to overestimate failure and punishment, and tend to underestimate success and positive reinforcement (Elliott et al., 1997).

Given previous results from intervention studies in adults with depression (Fu et al., 2008, Goldapple et al., 2004) we expected that positive psychotherapeutic treatment effects would be accompanied by significant activity changes in the amygdala, hippocampus, sgACC and ventral striatum in depressed adolescents. Furthermore, we hypothesized that pre-treatment neural activity in the sgACC would correlate with individual symptom improvement (Siegle et al., 2006). Signal and symptom changes of patients receiving therapeutic treatment were furthermore expected to differ from patients in a waiting group.

2. Methods

2.1. Participants

22 medication naïve adolescents (17 females; five males), between 13 and 18 years of age ($M=16.47$, $SD=1.36$), diagnosed with major depressive disorder according to DSM-IV and with a raw sumscore ≥ 36 (Plener et al., 2012) in the Children's Depression Rating Scale Revised (CDRS-R) (Keller et al., 2012) were included into the study. All participants were outpatients of the Department of Child and Adolescent Psychiatry and Psychotherapy of the local university. Exclusion criteria were a current or previous diagnosis of bipolar disorder, schizophrenia or substance abuse, IQ < 80, major somatic or neurological disorders and general contradictions to MRI scanning such as braces, metallic implants, or pregnancy. All participants and their caregivers provided written informed consents and the study was approved by the Institutional Review Board of Ulm University.

2.2. Procedures

Each subject received a psychological assessment upon inclusion to the study to evaluate psychiatric status and intelligence. Eligible patients were assigned to a group receiving psychotherapeutic intervention PAT-I ($N=10$) or a waiting group PAT-W ($N=12$). Functional MR imaging was performed before and after five weeks of intervention that comprised weekly sessions of a cognitive behavioral group therapy (CBT-G), and before and after five weeks of waiting, comprising appointments with a psychiatrist/psychologist one to three times within three months for approximately 30 min. The MICHI intervention and appointments with psychiatrist/psychologist, were comparable irrespective of waiting or of not waiting before. Five weeks after the end of the intervention, a booster therapy session was applied to patients of PAT-I. The first scan and psychometric assessment of depression (pre-waiting/pre-intervention) took place within 10 days before waiting or intervention. Post-waiting and post-intervention MR scans as well as psychometric assessment of depression took place within 10 days after completion of the five weeks periods. After the booster session another psychometric assessment of depression (follow-up-intervention), but no further fMRI imaging took place (see Fig. 1).

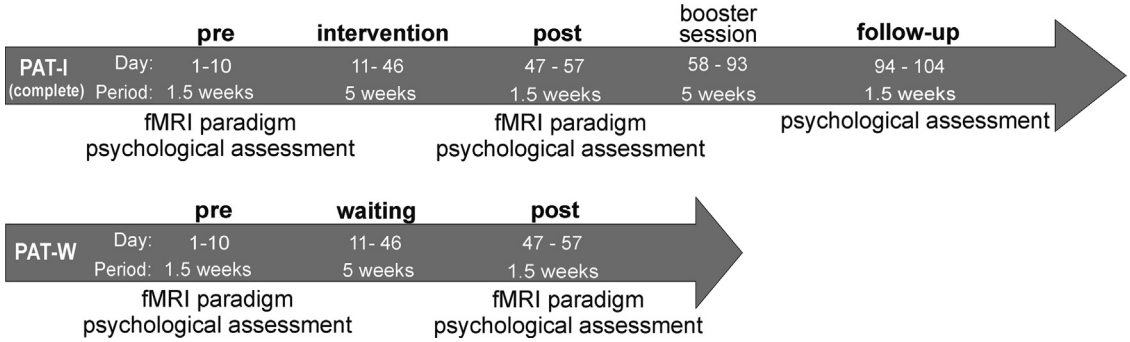

Fig. 1. Study design. PAT-W = depressed patients of the waiting group ($N=12$); PAT-I = depressed patients that participated in MICHI (Manualized Intervention to Cope with depressive symptoms, Help strengthen resources and Improve emotion regulation, $N=10$); PAT-I complete ($N=18$) encompasses all patients of PAT-I and eight patients of PAT-W that received psychotherapeutic intervention after their waiting period for ethical reasons. Psychological assessment included CDRS-R (Children's Depression Rating Scale Revised) and BDI-II (Beck Depression Inventory Revision).