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Successful group psychotherapy of depression in adolescents alters fronto-limbic resting-state connectivity

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A R T I C L E I N F O

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A B S T R A C T

Background: Current resting state imaging findings support suggestions that the neural signature of depression and therefore also its therapy should be conceptualized as a network disorder rather than a dysfunction of specific brain regions. In this study, we compared neural connectivity of adolescent patients with depression (PAT) and matched healthy controls (HC) and analysed pre-to-post changes of seed-based network connectivities in PAT after participation in a cognitive behavioral group psychotherapy (CBT).
Methods: 38 adolescents (30 female; 19 patients; 13–18 years) underwent an eyes-closed resting-state scan. PAT were scanned before (pre) and after (post) five sessions of CBT. Resting-state functional connectivity was analysed in a seed-based approach for right-sided amygdala and subgenual anterior cingulate cortex (sgACC). Symptom severity was assessed using the Beck Depression Inventory Revision (BDI-II).
Results: Prior to group CBT, between groups amygdala and sgACC connectivity with regions of the default mode network was stronger in the patients group relative to controls. Within the PAT group, a similar pattern significantly decreased after successful CBT.

Conversely, seed-based connectivity with affective regions and regions processing cognition and salient stimuli was stronger in HC relative to PAT before CBT. Within the PAT group, a similar pattern changed with CBT. Changes in connectivity correlated with the significant pre-to-post symptom improvement, and pre-treatment amygdala connectivity predicted treatment response in depressed adolescents.
Limitations: Sample size and missing long-term follow-up limit the interpretability.
Conclusions: Successful group psychotherapy of depression in adolescents involved connectivity changes in resting state networks to that of healthy controls.

1. Introduction

Affective disorders in youth are common, cause substantial functional impairment and have a high risk for relapses in adulthood. Mechanisms of effective therapy are still not well understood, also from a neurobiological perspective (Cox et al., 2014).

It can be assumed that depressive disorder is most likely more a result of failed network regulation than of a dysfunction of a specific single brain area (Mayberg, 2007). Some recent meta-analyses of imaging data have already suggested how depression could affect these networks (Kaiser et al., 2015), and how connectivity changes in these networks compared to healthy subjects contribute to the maintenance of this disorder in untreated patients. Current resting state imaging findings in depressive patients seem to consistently point towards relatively increased connectivities within the anterior default mode network (DMN), i.e. the medial prefrontal cortex, and the salience network, encompassing dorsal anterior cingulate cortex (dACC) and fronto-insular cortex. Connectivities within the cognitive control network, centering on the dorsolateral prefrontal cortex (dlPFC) were shown to be decreased in patients (Mulders et al., 2015). However,

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longitudinal resting state functional magnetic resonance imaging (rsfMRI) studies, particularly upon psychotherapy, are still very scarce. In one of the few examples, Crowther et al. (2015) investigated effects of Behavioral Activation Treatment for Depression with rsfMRI and could confirm previous findings of hyperconnectivity within the DMN and hypoconnectivity of brain regions of the salience network, particularly with the middle temporal gyrus. Also, effects of psychotherapy were predicted by connectivity with the temporal gyrus: the closer connectivity patterns in depressive patients aligned with those of controls the better were treatment outcomes.

In the present rsfMRI study we sought to assess effects of psychotherapy on network connectivities at rest in adolescent depression. In one of our previous studies (Straub et al., 2015) on reward-related brain activation, we found that task-related activation of particularly the amygdala and the subgenual ACC (sgACC) changed with therapy, and that these changes were correlated with clinical measures of treatment outcome and predicted treatment success. For the present study we made use of these results and used independently defined regions of interest of the amygdala and sgACC as seed regions.

In line with previous studies on resting state connectivites in depression (Greicius et al., 2007), we expected that particularly in pre-treatment depression the amygdala and sgACC as crucial parts of the affective and salience networks would be hyperconnected with brain regions of the DMN. Prefrontal cortico-limbic connectivities were expected to be decreased in line with previous findings in depressed adolescents (Pannekoek et al., 2014). As in Crowther et al. (2015) we expected these connectivities to change in relation with individual treatment responses and even to predict individual treatment outcome.

2. Methods

2.1. Participants and study procedures

We included 38 adolescents (30 females, age/years: M=16.56, SD=1.43). 19 were patients with major depressive disorder (PAT) according to DSM-IV and with a raw-sum score≥36 in the Children's Depression Rating Scale Revised (CDRS-R, Keller et al., 2012). Data from the same sample have already been reported elsewhere (Straub et al., 2015). Furthermore, we included 19 healthy control subjects (HC), which were matched to the depressed patients with respect to age, gender and IQ. Demographics, recruitment and exclusion criteria are reported in detail in the Supplemental materials. All participants and their parent(s)/legal guardian(s) provided written informed consent in accordance with the Declaration of Helsinki and the Institutional Review Board of the local University.

Participants in the CBT group were assigned to groups of four to six patients who received weekly sessions (75–90 min) over five consecutive weeks, following the CBT programme ´Manualized Intervention to Cope with depressive symptoms, Help strengthen resources and Improve emotion regulation´(Sproeber et al., 2012; Straub et al., 2013).

Resting-state scans, lasting ten minutes each, were performed twice in patients, before and after a course of CBT, and once in HC. Upon each fMRI scan, depressive symptoms were assessed by means of the CDRS-R and the Beck Depression Inventory Revision (BDI-II) capturing symptoms during the past two weeks. FMRI scans and psychological assessments took place within ten days before the start and after the end of CBT.

2.2. Statistical analyses of clinical assessments

Within the CBT group a one-way repeated-measures ANOVA was run to assess pre-to-post-test differences with respect to the CDRS-R and BDI-II. Differences between PAT and HC before treatment were tested by means of the Wilcoxon's test signed rank test.

2.3. fMRI data acquisition and preprocessing

The ten-minute eyes-closed resting state scans were acquired on a 3.0 T Magnetom Allegra MR scanner (Siemens, Erlangen, Germany) equipped with a head coil. Preprocessing of the data was carried out by using Data Processing Assistant for Resting-State fMRI (DPARSF, Chao-Gan and Yu-Feng, 2010, http://www.restfmri.net). Detailed descriptions of fMRI data acquisition and preprocessing can be found in the supplements. Functional connectivity was calculated on the whole brain level for two independent regions of interest, the right amygdala and the sgACC. The right amygdala was defined as an anatomically shaped mask according to the wfu-pick atlas (http://fmri.wfubmc.edu/software/PickAtlas). Coordinates for the sgACC were taken from Sheline et al. (2010) and defined as spherical region of interest with a 7 mm radius around x/y/z=10/36/0.

2.4. Second level statistics

Second level statistics were carried out using SPM 8. Effects between the HC group and the patient group before treatment (pre-CBT) were assessed using two-sample t-tests on whole brain z-transformed connectivity maps for each seed. Differences between patients before and after treatment were tested using a paired t-test for each region of interest. Results are reported at a conservative significance threshold of $p < .005$, cluster threshold > 10 adjacent voxels analogous to Metzger et al. (2015).

To investigate whether changes in connectivity between the amygdala and sgACC indeed reflect changes in clinical symptom severity, a whole-brain regression analysis was calculated using the differences in whole-brain connectivity maps for the right amygdala/sgACC (pre-CBT vs. post-CBT) and the corresponding change in BDI-II (pre-CBT to post-CBT) as a regressor. Differences in whole brain connectivity maps pre-CBT vs. post-CBT were calculated using the ImCalc function provided by SPM 8.

To analyse, whether connectivity of the right amygdala and sgACC pre-CBT was suited to predict the change in BDI-II scores (pre-CBT to post-CBT) - and therefore treatment outcome – a whole-brain regression analysis was calculated using the whole-brain connectivity maps for the right amygdala (pre-CBT) and the corresponding change in BDI-II (pre-CBT to post-CBT).

3. Results

3.1. Clinical data

PAT and HC differed with respect to the mean pre-test CDRS-R (W_s=190, z=−5.28, $p < .001$) and BDI-II (W_s=194, z=−5.16, $p < .001$). Within PAT group analyses revealed significant pre-to-post reductions in the CDRS-R $F(1,18)$=13.93, p=.002 and BDI-II $F(1,18)$=10.94, p=.004.

3.2. Amygdala-seeded connectivity

Comparisons between PAT pre-CBT and HC revealed greater connectivity in HC between right amygdala and the left dlPFC as well as between amygdala and right anterior insula. Connectivity between right amygdala and right orbitofrontal cortex was decreased in HC compared to PAT pre-CBT.

Comparing pre- to post treatment measures in patients, we observed that connectivity between amygdala and precuneus/calcarine fissure was greater pre-CBT than post-CBT. Relative to pre-CBT, connectivities post-CBT significantly increased between the amygdala and left dlPFC, between amygdala and bilateral dACC, and between amygdala and left anterior insula. This pattern of changes very much resembled the situation when comparing HC and patients pre-CBT. All results of the whole-brain connectivity analysis are summarized in