Progress in Neuro-Psychopharmacology & Biological Psychiatry 56 (2015) 215–220

Contents lists available at ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

Changes in brain activation following psychotherapy for youth with mood dysregulation at familial risk for bipolar disorder

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ARTICLE INFO

Article history:
Received 1 August 2014
Received in revised form 28 August 2014
Accepted 23 September 2014
Available online 2 October 2014

Keywords:
Bipolar
FMRI
Pediatric
Prefrontal
Psychotherapy

ABSTRACT

Background: Psychotherapy for youth with mood dysregulation can help stabilize mood and improve functioning, but the neural mechanisms of this improvement are not known. In this study we investigated the changes in brain activation underlying improvement in mood symptoms.
Methods: Twenty-four subjects (ages 13–17) participated: 12 patients with clinically significant symptoms of depression and/or mania, and 12 healthy comparison subjects (HC) matched for age and sex. All subjects completed functional magnetic resonance imaging while viewing facial expressions. The patients then received up to 4 months of psychotherapy and were rescanned at end of treatment. Whole brain differences between patient and control groups were assessed with a voxel-wise analysis. Changes in activation from pre- to post-treatment within the patient group were tested for correlation with changes in mood symptoms.
Results: At baseline the patient group had hypoactivation in the dorsolateral prefrontal cortex (DLPFC) and hyperactivation in the posterior cingulate cortex compared to the HC group. Between pre- and post-treatment activation increased in the DLPFC and decreased in the amygdala. Increases in DLPFC activation were significantly correlated with improvement in mania symptoms.
Discussion: Enhancement of frontal executive control brain regions may underlie improvement in mood dysregulation in pediatric patients at familial risk for bipolar disorder.

1. Introduction

Retrospective studies in adults suggest that bipolar disorder (BD) begins in childhood in 15% to 28% of cases and adolescence in 50% to 66% of cases (Perlis et al., 2004). Especially vulnerable to developing BD are those youth who are experiencing symptoms of mood dysregulation and also have a parent with BD. Nearly half of these patients will develop a diagnosis of BD I or BD II during the 4–5 years following assessment (Axelson et al., 2011) therefore they are considered to be at high risk for BD (HRforBD). Regardless of whether they develop BD, youth in the HRforBD group have mood dysregulation symptoms that cause significant problems with functioning and a lower quality of life (Birmaher et al., 2009; Carlson et al., 2009; Luby and Navsaria, 2010). Therefore it is important that we implement treatments that stabilize mood and improve functioning for HRforBD youth. Furthermore by seeking to understand the mechanisms of successful mood stabilizing therapies we may be able to identify biomarkers that could lead to individualized therapies. Recently we reported that psychotherapeutic intervention helps stabilize symptoms of mood dysregulation in HRforBD (Miklowitz et al., 2011). For the current study we aim to identify the mechanisms of clinical improvement by examining pre- versus post-treatment changes in brain activation.

Treatments for BD or HRforBD may target the brain regions that have been reported to be abnormal in these populations. A substantial literature shows that functional brain abnormalities in pediatric BD include

Abbreviations: HRforBD, high risk for bipolar disorder; HC, healthy control; BD, bipolar disorder; FFT, family focused therapy; FMRI, functional magnetic resonance imaging; DLPFC, dorsolateral prefrontal cortex; VLPFC, ventrolateral prefrontal cortex; YMRS, young mania rating scale; CDRS, childrens depression rating scale; DSM, diagnostic and statistical manual; IQ, intelligence quotient; WASH-U-KSADS, Washington University in St. Louis Kiddie Schedule for Affective Disorders and Schizophrenia; WASI, Wechsler Abbreviated Scale of Intelligence; MINI, Mini international neuropsychiatric interview; KSADS-PL, Schedule for Affective Disorders and Schizophrenia for School-Age Children - Present and Lifetime; GE, General Electric; T, Tesla; TR, repetition time; TE, excitation time; TI, interval time; SPM5, statistical parametric mapping 5; Mm, millimeter; FWHM, full width at half maximum; FDR, false discovery rate.

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http://dx.doi.org/10.1016/j.pnpbp.2014.09.007
0278-5846/

hypoactivation of dorsolateral prefrontal cortex (DLPFC) and ventrolateral prefrontal cortex (VLPFC) and hyperactivation of amygdala (Brotman et al., 2013; Chang et al., 2008, 2009; Frazier et al., 2005; Garrett et al., 2012; Rich et al., 2008; Thomas et al., 2013). These brain regions also may be functioning abnormally in youth at risk for BD (Olsavsky et al., 2012).

Investigations of the neural mediators of pharmacological treatments do, in fact, implicate the same regions. For example, divalproex treatment of youth with mood dysregulation is associated with decreased dorsolateral prefrontal cortex (DLPFC) activation, which is correlated with decreased symptoms of depression (Chang et al., 2009). For youth with a diagnosis of BD, lamotrigine treatment is associated with increased activation in the VLPFC and reduced activation in the amygdala, both of which were correlated with improvement in YMRS scores (Passarotti et al., 2011). Similarly, our lab reported decreased amygdala activation in youth with BD who were treated with lamotrigine, although activation was correlated with decreased severity of depression rather than mania symptoms (Chang et al., 2008). In another report, amygdala activation did not change following treatment with risperidone or divalproex, but higher amygdala activation at pre-treatment predicted less improvement in symptoms of mania (Pavuluri et al., 2011).

Psychotherapy may utilize some of the same mechanisms as pharmacological treatments. Very few studies have examined the effects of psychotherapy on brain activation in youth with BD or at HRforBD. One such study examined depressed youth with BD undergoing treatment with a variety of medications and psychotherapies and found that activation decreased in the occipital cortex and increased in the insula, cerebellum, and VLPFC, but these changes were not correlated with changes in depression (Diler et al., 2013). No studies so far have looked at the effects of psychotherapy on brain activation among youth with HRforBD. Based on the literature reviewed above, we hypothesized that changes in mood symptom severity following psychotherapy would be associated with changes in the DLPFC, VLPFC, and amygdala, suggesting that these regions may mediate improvement in mood symptoms.

2. Methods

2.1. Participants

The study was approved by the Stanford University and University of Colorado Institutional Review Boards and written consent or assent was obtained from all participants. Thirteen patients were recruited from among those participating in a larger treatment study that was described in a previous publication (Miklowitz et al., 2011). Criteria for inclusion were (1) age 9–17; (2) English-speaking; (3) at least one first-degree relative with BD I or BD II; (4) significant current mood symptoms, defined as a score of >11 on the Young Mania Rating Scale (YMRS) (Young et al., 1978), or a score of >29 on the Children's Depression Rating Scale — Revised (CDRS-R) (Mayes et al., 2010); and (5) no previous manic episode according to DSM-IV criteria. Exclusion criteria (for both controls and patients) included developmental disorders, neurological conditions or major medical illness, substance use disorder, IQ of less than 80, MRI contraindications (metal in the body), orthodontic braces, and current hospitalization. One patient was excluded for unusable MRI data due to excessive motion artifact, leaving 12 patients in the final sample.

Healthy control subjects were selected from a group of 29 participants enrolled in a concurrent study in our laboratory. These volunteers had been scanned on the same MRI scanner using identical protocols during the same time period. Baseline but not follow-up scans were available. We selected the control subjects to be individually matched by age, sex, and IQ to each subject in the treatment study. They were free from current or past DSM-IV psychiatric diagnoses, were not taking psychotropic medications, had both parents without any psychiatric diagnosis (determined by the MINI), and did not have a first- or second-degree relative with BD.

2.2. Clinical assessments

The YMRS and CDRS were administered by reliable trained raters, both before and after treatment, and used as the primary outcome measures for correlation with fMRI data. For both patients and healthy controls, diagnoses were assessed by reliable trained raters using the affective module of the Washington University in St. Louis Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS) (Geller et al., 1996, 2001) as well as all modules of the Schedule for Affective Disorders and Schizophrenia for School-Age Children — Present and Lifetime (K-SADS-PL) (Kaufman et al., 1997). Parental diagnosis of BD I or BD II was confirmed by the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998). DSM-IV diagnoses were ultimately determined by a board certified child psychiatrist or psychologist. For all participants, IQ was assessed with the Wechsler Abbreviated Scale of Intelligence (WASI) (Psychological-Corporation, 1999).

2.3. Psychotherapy

The psychotherapy treatment was either family focused therapy or a comparison treatment-as-usual administered for up to 16 weekly sessions as described in the previous publication (Miklowitz et al., 2011). Both of these treatments included psychoeducation and mood stabilization plus medication management as needed. The study recruited and treated patients from two sites: Stanford University (P.I. Kiki Chang) and the University of Colorado (P.I. David Miklowitz, currently at UCLA), but all patients were scanned at Stanford.

2.4. FMRI scan parameters

All scans were collected on a 3T GE Signa Excite (General Electric Co., Milwaukee, WI) scanner using a custom-built head coil and a spiral-in/out fMRI pulse sequence (Glover and Law, 2001). The following parameters were used: TR = 2000 ms, TE = 30 ms, flip angle = 80°; 30 axial slices, 4 mm thick, 0.5 mm skip, field of view = 22 cm, 64 × 64 matrix, in-plane spatial resolution = 3.44 mm. A high resolution structural image was also collected to help normalize the images to a standard template (fast spoiled gradient recalled (3D FSPGR) pulse sequence: TR/TE/TI = 5.9/1.5/300 ms, flip angle = 15°, field of view = 22 cm, 256 × 256 matrix, inplane resolution = 0.86 mm^2, slice thickness = 1.5 mm).

2.5. Facial expression task

Emotional facial expressions were presented in a block design including fearful faces from the McArthur ('NimStim') stimulus set (macbrain.org/resources.htm) and a 'scrambled' picture baseline condition that controlled for viewing a complex visual stimuli and motor responses. Four (non-repeated) blocks of each condition were shown, and each block contained 8 pictures. Each picture was shown for 3 s with no inter-stimulus interval. Subjects pressed button 1 for female and button 2 for male models, therefore this was an implicit emotion processing task. Subjects alternately pushed buttons 1 and 2 for the scrambled stimuli. Participants viewed stimuli by looking directly up into a mirror attached to the head coil, which reflected the projection screen mounted at the foot of the scanner. Stimuli were presented using ePrime software (www.pstnet.com), which also collected responses.

2.6. FMRI whole brain voxel-wise analysis

Functional data were processed and statistically analyzed using SPM5 (Wellcome Department of Imaging Neuroscience, London, UK). Images were spatially realigned, motion-corrected, and spatially normalized into MNI stereotactic space, and smoothed with a Gaussian filter (7 mm full width at half-maximum). The ArtRepair toolbox (http://cibsr.stanford.edu/tools/human-brain-project/artrepair-software.html)