Journal of Psychiatric Research 58 (2014) 129–136

Contents lists available at ScienceDirect

Journal of Psychiatric Research

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

Abnormal deactivation of the inferior frontal gyrus during implicit emotion processing in youth with bipolar disorder: Attenuated by medication

Danella M. Hafeman [a, *], Genna Bebko [a], Michele A. Bertocci [a], Jay C. Fournier [a], Lisa Bonar [a], Susan B. Perlman [a], Michael Travis [a], Mary Kay Gill [a], Vaibhav A. Diwadkar [b], Jeffrey L. Sunshine [c], Scott K. Holland [d], Robert A. Kowatch [e], Boris Birmaher [a], David Axelson [f], Sarah M. Horwitz [g], L. Eugene Arnold [f], Mary A. Fristad [f], Thomas W. Frazier [h], Eric A. Youngstrom [i], Robert L. Findling [c, j], Wayne Drevets [k], Mary L. Phillips [a, l]

[a] Psychiatry, Western Psychiatric Institute and Clinic, University of Pittsburgh, USA
[b] Psychiatry and Behavioral Neuroscience, Wayne State University, USA
[c] University Hospitals Case Medical Center/Case Western Reserve University, USA
[d] Cincinnati Children's Hospital Medical Center, University of Cincinnati, USA
[e] The Research Institute at Nationwide Children's Hospital, USA
[f] Psychiatry, Ohio State University, USA
[g] Child Psychiatry, New York University School of Medicine, USA
[h] Cleveland Clinic, Center for Pediatric Behavioral Health, USA
[i] Psychology, University of North Carolina at Chapel Hill, USA
[j] Psychiatry, Johns Hopkins University, USA
[k] Janssen Pharmaceuticals Research & Development of Johnson & Johnson, USA
[l] Psychological Medicine, Cardiff University, UK

ARTICLE INFO

Article history:
Received 23 May 2014
Received in revised form
21 July 2014
Accepted 24 July 2014

Keywords:
Bipolar disorder
Functional MRI (fMRI)
Psychopharmacology
Neuroimaging
Emotion regulation

ABSTRACT

Previous neuroimaging studies of youth with bipolar disorder (BD) have identified abnormalities in emotion regulation circuitry. Using data from the Longitudinal Assessment of Manic Symptoms Cohort (a clinical sample recruited for behavioral and emotional dysregulation), we examined the impact of BD and medication on activation in these regions. Functional neuroimaging data were obtained from 15 youth with BD who currently were unmedicated with a mood stabilizer or antipsychotic (U-BD), 19 youth with medicated BD (M-BD), a non-bipolar clinical sample with high rates of disruptive behavioral disorders (non-BD, $n = 59$), and 29 healthy controls (HC) while they were shown task-irrelevant morphing emotional faces and shapes. Whole brain analysis was used to identify clusters that showed differential activation to emotion vs. shapes across group. To assess pair-wise comparisons and potential confounders, mean activation data were extracted only from clusters within regions previously implicated in emotion regulation (including amygdala and ventral prefrontal regions). A cluster in the right inferior frontal gyrus (IFG) showed group differences to emotion vs. shapes (159 voxels, corrected $p < .05$). Within this cluster, U-BD youth showed decreased activation relative to HC ($p = .007$) and non-BD ($p = .004$) youth. M-BD also showed decreased activation in this cluster relative to HC and non-BD youth, but these differences were attenuated. Results were specific to negative emotions, and not found with happy faces. IFG findings were not explained by other medications (e.g. stimulants) or diagnoses. Compared to both HC and a non-BD sample, U-BD is associated with abnormally decreased right IFG activation to negative emotions.

* Corresponding author. Western Psychiatric Institute and Clinic, 3811 O Hara St., Bellefield Towers, Room 518, Pittsburgh, PA 15213, USA. Tel.: +1 412 246 5820; fax: +1 412 246 5230.
E-mail address: hafemand@upmc.edu (D. M. Hafeman).

http://dx.doi.org/10.1016/j.jpsychires.2014.07.023
0022-3956/

1. Objectives of the study and background

Deficits in emotion regulation are central to the clinical diagnosis of bipolar disorder (BD). The underlying neurobiology of these deficits is hypothesized to involve abnormally increased activation of limbic regions coupled with decreased activation of regulatory prefrontal circuitry (Chen et al., 2011; Womer et al., 2009). Supporting this hypothesis, BD in youth has been associated with abnormalities in amygdala and prefrontal activation during emotion processing tasks. Specifically, several groups have found amygdala hyperactivation in youth with BD during emotional processing (Garrett et al., 2012; Kim et al., 2012; Pavuluri et al., 2007; Rich et al., 2006). Abnormalities have also been found in regions including ventrolateral prefrontal cortex (VLPFC), orbitofrontal cortex (OFC), and anterior cingulate cortex (ACC) during emotion processing, though the direction of these abnormalities differs according to task and study population (Brotman et al., 2013; Dickstein et al., 2007; Ladouceur et al., 2011; Pavuluri et al., 2009). Limited studies with multiple patient groups have shown findings to be specific to BD, and not simply a marker of psychopathology (Passarotti et al., 2010b; Thomas et al., 2012). While medications seem to have a normalizing effect (reducing differences between activation in youth with BD versus healthy controls), few studies compare medicated and non-medicated youth (Hafeman et al., 2012; Singh and Chang, 2012).

The current study examined the effects of diagnosis and psychotropic medication on neural activation during an emotional processing task in a subset of the Longitudinal Assessment of Manic Symptoms (LAMS) cohort, behaviorally and emotionally dysregulated youth who have been followed longitudinally (Findling et al., 2010; Horwitz et al., 2010). Participants in the parent cohort study (n = 707) were recruited from 9 clinical settings at four sites (Pittsburgh, Cincinnati, Cleveland, and Columbus), preferentially selected based on an elevated score on a screen for deficits in behavior, emotion and energy regulation (Parent General Behavioral Inventory-10, PGBI-10) (Youngstrom et al., 2008). Follow-up is ongoing for over 80% of these participants, with biannual assessments of clinical symptoms, diagnoses and functional impairments. The aim of the LAMS study is to describe abnormalities in behavioral and emotional regulation and arousal over time, and ultimately to predict progression of functional impairment and disorder. As part of this aim, functional neuroimaging data were collected on a subset of youth at three sites (Pittsburgh, Cincinnati, and Cleveland) while engaging in a number of tasks, including implicit emotion processing.

Our analyses capitalized on several key attributes of this cohort. The sample was large enough to include a number of youth with BD who were currently not medicated with an antipsychotic, antidepressant or mood stabilizing drug, thus permitting comparisons between youth with unmedicated BD (U-BD), medicated bipolar youth (M-BD), and healthy controls (HC). Because recruitment was not based on diagnosis, LAMS included youth who did not meet criteria for BD (non-BD). This unique comparison group allowed us to assess the specificity of neuroimaging findings for BD, and to test whether such results could be explained by co-morbidity.

The current study tested the following hypotheses: (1) youth would activate the amygdala and prefrontal regions (as measured by BOLD signal) in response to emotional stimuli (vs. morphing shapes); (2) these activation patterns would differ across groups defined by diagnosis and medication status; and (3) differences would be most prominent in U-BD (versus HC), attenuated (but still present) in M-BD, and even less robust in non-BD. Specifically, we hypothesized that amygdala activation would be elevated in bipolar youth (U-BD > M-BD > non-BD $\geq$ HC), while prefrontal activation would show the opposite pattern (U-BD < M-BD < non-BD $\leq$ HC). We also assessed the degree that abnormalities differed across specific emotional stimuli, and the extent to which neuroimaging findings were related to mood state.

2. Materials and methods

2.1. Participants

A subset of the initial LAMS cohort (n = 123) was recruited to participate in the neuroimaging component of the LAMS follow-up study. Additionally, 32 age- and gender-matched HC were scanned for comparison. Informed consent was obtained from parents or guardians after the nature of the study had been fully explained, and youth provided written informed assent. Participants received monetary compensation and a framed structural brain image. This investigation was carried out in accordance with the latest version of the Declaration of Helsinki, and the study design was approved by the appropriate Institutional Review Boards.

Exclusion criteria included pregnancy, inability to participate in scan (claustrophobia, metal objects in the body), positive urine drug and/or salivary alcohol screen on scan day, alcohol/substance abuse in the past three months, severe systemic medical illness, neurological disorders, history of head trauma with loss of consciousness, IQ < 70 (Weschler, 1999), visual disturbance (<20/40 Snellen visual acuity), inability to complete questionnaires in English, history of physical/sexual abuse, or autistic spectrum disorders/developmental delays.

Data from 30 LAMS youth and three HC were excluded due to data loss and/or excessive head movement (>4 mm, as used in previous studies studies (Bebko et al., 2013)), yielding usable scans from 93 LAMS participants and 29 healthy controls. Compared to included youth, those excluded were younger (p = .03) and had lower IQs (p = .0001); they were more likely to have disruptive behavior disorders (DBD) (p = .03) and unmedicated ADHD (p = .004), but did not differ according to group (U-BD, M-BD, N-BD, and HC) (p = .15). (Table S1).

2.2. Assessment

Baseline assessments gathered demographic data including age, sex, IQ and parents' education. The Family History Screen (Weissman et al., 2000) tracked 15 psychiatric disorders in biological parents, and included two questions to assess for lifetime parental history of mania. Diagnoses were determined at baseline and every six months using the Schedule for Affective Disorders and Schizophrenia for School Age Children, Present and Life Version with WASH-U mood supplement (K-SADS-PL-W) (Kaufman et al., 1997). During these biannual assessments, parents also completed the PGBI-10M. The PGBI-10M score nearest the scanning session (within 6 months) was used. PGBI-10M scores were very stable over the year immediately preceding scan day (Bebko et al., 2013).

On scanning day, the youth and a parent/guardian completed the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children Mania Rating Scale (KMRS) (Axelson et al., 2003) and Depression Rating Scale (KDRS)(Kaufman et al., 1997), to assess for hypomanic/manic and depressive symptom severity, respectively. Interviewers determined summary scores based on all available information. Additional rating scales were administered, including the Screen for Childhood Anxiety Related Disorders (SCARED) and the Moods and Feelings Questionnaire (MFQ). Psychotropic medications taken within the past 24 h were also recorded.