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Preliminary communication

Time course of recovery showing initial prefrontal cortex changes at 16 weeks, extending to subcortical changes by 3 years in pediatric bipolar disorder

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ABSTRACT

Objective: Activation changes at the interface of affective and cognitive systems are examined over a 3 year period in pediatric bipolar disorder (PBD).
Methods: Thirteen participants with PBD and 10 healthy controls (HC) matched on demographics and IQ were scanned at baseline, at 16 weeks, and after 3 years. All patients received pharmacotherapy based on a medication algorithm. A pediatric affective color matching paradigm was used to probe cognitive processing under emotional challenge.
Results: At baseline, in response to emotional vs. neutral words, patients with PBD showed greater activation than HC in the right dorsal lateral prefrontal cortex (DLPFC) and amygdala, ventral lateral prefrontal cortex (VLPFC), bilateral anterior cingulate cortex (ACC), and ventral striatum. Increased activation in DLPFC in the PBD group normalized by 16 weeks. By 3 years, normalization was observed in VLPFC, ACC, amygdala, and striatum.
Limitations: Small sample size renders the present findings preliminary.
Conclusions: Greater activation in fronto-striatal and fronto-limbic circuits were observed in unmedicated patients with PBD. Present findings suggest the possibility that DLPFC is most malleable to pharmacological intervention with systematic pharmacotherapy leading to immediate response, which extended to amygdalostriatal and ventral cortical regions at 3 years. The seminal observation from this study is the prolonged length of recovery time in the normalization of subcortical activity along with their interfacing cortical regions. Findings from this proof of concept study need to be replicated in a larger sample.

1. Introduction

Pediatric bipolar disorder (PBD) is an early onset variant of the bipolar diathesis (Birmaher et al., 2009; Geller et al., 2002; Pavuluri et al., 2005), and patients are often burdened with persistent neurocognitive deficits, despite achieving symptomatic recovery in mood (Pavuluri et al., 2009a). The cognitive deficits in the domains of attention, response inhibition and executive function correlate with poor academic performance (Pavuluri et al., 2005). Emerging findings highlight the impairment at the interface of cognitive and affective brain circuitry that is responsible for combined deficits in executive function and mood stability in PBD (Leibenluft et al., 2007; Passarotti et al., 2010a, 2010b; Rich et al., 2005). One important question, however, is whether the neural circuitry abnormalities in PBD normalize over time due to normative brain development or treatment. Longitudinal studies of neural circuitry abnormalities in PBD are critical as significant changes occur in the brain throughout childhood and adolescence (Casey et al., 2005) and thus, any examination of brain "normalization" in these patients should take into account normal developmental processes. Additionally, longitudinal studies have the potential in aiding with prognosis as well as estimating the utility of the treatment algorithms.

To date, few longitudinal studies of brain function have been conducted in patients with PBD. Gogtay et al. (2007) examined structural brain changes in 9 patients over time and found that adolescents with bipolar disorder exhibited an increase in gray

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matter density in the left temporal cortex and a decrease in gray matter density in the anterior cingulate cortex. In another study, Bitter et al. (2011) found that over 1 year, those with PBD did not exhibit the normative increase in amygdala volume seen in healthy controls (HC). Despite these earlier clues from structural neuroimaging studies, little is known about the *functional* neuroanatomical changes that occur over time in PBD.

Normative development in adolescence has illustrated increased top-down regulation with maturation of fronto-limbic activity (Casey and Jones, 2010; Somerville et al., 2010, 2011). Our recent studies have revealed that resting state limbic hyperconnectivity is associated with better cognitive and affective circuitry function (Wu et al., in press) and that increased amygdala engagement in affective circuitry was associated with response to short-term pharmacotherapy (Wegbreit et al., 2011). Untreated patients with PBD have demonstrated hyperactive amygdala, insufficiently regulated by VLPFC (Pavuluri et al., 2007, 2008, 2010). Furthermore, the DLPFC and striatum serve multiple functions including the cognitive modulation of emotion (Badgaiyan, 2010; Hare et al., 2008), attention (Saint-Cyr, 2003) and response inhibition (Padmanabhan et al., 2011). Untreated patients with PBD showed greater activity in the striatum during response inhibition, which normalized with 8 weeks of pharmacotherapy (Passarotti et al., 2011a; Pavuluri et al., 2011). It is not clear if the activity of these affective and cognitive fronto-limbic and fronto-striatal brain regions during the steep adolescent developmental curve will continue to improve, partially recover, or remain abnormal in PBD.

The current study utilized the pediatric color matching task that has previously yielded consistently reliable findings (Passarotti et al., 2010c; Pavuluri et al., 2008, 2010, 2011; Wegbreit et al., 2011) to probe the interface of affective VLPFC-amygdala circuitry and the cognitive DLPFC-striatal circuitry in PBD and HC. We followed participants over a 3-year developmental period when the patients received systematic pharmacotherapy for optimal recovery. Based on the leads from conventional fMRI (Mayanil et al., 2011; Pavuluri et al., 2011), patients are predicted to show normalization, relative to HC, in cortico-subcortical fMRI activity. Alternatively, PBD patients might show partial recovery among these circuits with residual impairment.

2. Methods

2.1. Participants

The sample consisted of 13 individuals with PBD (types I and II) and ten IQ and demographically matched HC (Table 1). All patients were unmedicated at baseline and received pharmacotherapy based on a standardized medication algorithm (Pavuluri et al., 2004). Participants were aged 10–18 years and were clinically assessed and scanned at baseline (13.4 ± 2.5 years), at 16 weeks (16 ± 14 weeks), and at 3 years follow-up (3.2 ± 1.1 years, Table 1). This study was approved by the institutional review board at the University of Illinois at Chicago. Verbal or written assent was obtained from all of the participants in addition to written consent from parents. Inclusion criteria for patients were a diagnosis of BD type I (mixed $N=2$, manic $N=6$) or type II ($N=5$) according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV; American Psychiatric Association, 1994), and a baseline score greater than 12 on the Young Mania Rating Scale (YMRS) (Young et al., 1978). Inclusion criteria for HC were no current and past DSM-IV diagnosis for axis I disorders or a family history of affective illness, and a score less than 12 on the YMRS at baseline. Exclusion criteria for both groups were substance abuse through urine toxicology screen; serious medical problems (e.g., epilepsy); IQ less than 70 as determined by the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999).

Table 1
Demographic and clinic characteristics of participants with PBD and HC.

Variables	HC ($n=10$) Mean (SD)	PBD ($n=13$) Mean (SD)	Analyses T (p)
Age (years) at baseline	13.61 (2.97)	13.25 (2.27)	0.33 (0.75)
IQ[a]	105.10 (14.39)	99.92 (17.17)	0.77 (0.45)
YMRS at baseline	2.40 (2.59)	25.62 (6.48)	10.65 (0.000)
YMRS at 16 weeks	0.78 (1.56)	9.36 (12.74)	2.00 (0.06)
YMRS at 3 years	2.60 (1.58)	8.54 (4.33)	4.11 (0.000)
CDRS-R at baseline	19.20 (1.48)	42.54 (18.19)	4.03 (0.001)
CDRS-R at 16 weeks	18.56 (1.01)	25.00 (7.20)	2.65 (0.02)
CDRS-R at 3 years	18.80 (1.14)	34.08 (12.09)	3.96 (0.001)
	N (%)	**N (%)**	**χ^2(P)**
Sex			
Male	7 (70)	9 (69)	0.002 (0.97)
Female	3 (30)	4 (31)	
Race			
White	6 (60)	9 (69)	0.21 (0.65)
Other	4 (40)	4 (31)	
Handedness			
Right	9 (90)	11 (85)	0.14 (0.70)
Left	1 (10)	2 (15)	
ADHD comorbid	0 (0)	6 (46)	

[a] IQ was measured using Wechsler Abbreviated Scale of Intelligence (WASI); PBD=pediatric bipolar disorder; HC=healthy controls; YMRS=Young Mania Rating Scale; CDRS-R=Child Depression Rating Scale-Revised.

2.2. Clinical assessment

Board-certified child psychiatrists completed the Washington University Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS) (Geller et al., 1998) supplemented by the episode characterization of bipolar disorder from the KSADS—present and lifetime version (Kaufman et al., 2000). Diagnostic interviews were completed by doctoral-level clinicians with established inter-rater reliability (Cohen's kappa=0.94). Information from the interview and all other clinical measures were reviewed to make a consensus clinical diagnosis. The primary clinical measures were the YMRS and the Child Depression Rating Scale-Revised (CDRS-R) (Poznanski et al., 1984).

2.3. Pharmacotherapy

All PBD patients were medication free or were washed out of medication at baseline. Medications used in the treatment paradigm are summarized in electronic supplemental Table S1. Psychostimulants were used in six of the 13 participants, and non-stimulants were used in 2 participants with PBD with comorbid ADHD, at the end of 3 years. The average number of medications received by each patient was 2.0 ± 1.1 at 16 weeks and 2.8 ± 1.5 at 3 years.

2.4. Pediatric Affective Color Matching Task

The primary task for the study was the Pediatric Affective Color Matching Task. As described previously (Pavuluri et al., 2008), this paradigm had the advantages of (1) assessing the impact of an emotional challenge on the cognitive control required to match the color; (2) presenting words briefly (200 ms) to limit prefrontal processing of affective valence and