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Neural correlates of response inhibition in pediatric bipolar disorder and attention deficit hyperactivity disorder

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ABSTRACT

Impulsivity, inattention and poor behavioral inhibition are common deficits in pediatric bipolar disorder (PBD) and attention deficit hyperactivity disorder (ADHD). This study aimed to identify similarities and differences in the neural substrate of response inhibition deficits that are associated with these disorders. A functional magnetic resonance imaging (fMRI) study was conducted on 15 unmedicated PBD patients (Type I, manic/mixed), 11 unmedicated ADHD patients, and 15 healthy controls (HC) (mean age = 13.5 years; S.D. = 3.5). A response inhibition task examined the ability to inhibit a motor response to a target when a stop cue appeared shortly after. The PBD and ADHD groups did not differ on behavioral performance, although both groups were less accurate than the HC group. fMRI findings showed that for trials requiring response inhibition, the ADHD group, relative to the PBD and HC groups, demonstrated reduced activation in both ventrolateral (VLPFC) and dorsolateral (DLPFC) prefrontal cortex, and increased bilateral caudate activation compared with HC. The PBD group, relative to HC, showed decreased activation in the left VLPFC, at the junction of the inferior and middle frontal gyri, and in the right anterior cingulate cortex (ACC). Prefrontal dysfunction was observed in both the ADHD and PBD groups relative to HC, although it was more extensive and accompanied by subcortical overactivity in ADHD.

1. Introduction

Pediatric bipolar disorder (PBD) and attention deficit hyperactivity disorder (ADHD) have distinct as well as overlapping clinical symptoms. PBD is characterized by emotional dysregulation, elated mood, irritability, increased energy and disinhibition (Geller et al., 1998; Pavuluri et al., 2007; Pavuluri and Passarotti, 2008). ADHD is characterized by motor hyperactivity, inattention, impulsivity and poor behavioral control (American Psychiatric Association, 1994; Barkley, 1997).

Neuropsychological studies often report similar neurocognitive deficits in patients with ADHD and PBD. Patients with PBD have deficits in cognitive flexibility, sustained attention and verbal working memory, independent of illness status (Dickstein et al., 2005; Pavuluri et al., 2006). Similarly, ADHD patients exhibit deficits in executive functions, attention, vigilance, working memory, planning and response inhibition (Doyle et al., 2005; Rubia et al., 2001; Seidman et al., 2004). Moreover, recent studies also suggest that adolescents with ADHD may present more severe neurocognitive impairment than those with PBD, with or without a comorbid ADHD diagnosis (Rucklidge, 2006; Galanter and Leibenluft, 2008). Given overlapping clinical symptoms, neurocognitive impairment, and the high levels of comorbid ADHD in patients with PBD (Geller et al., 1998; Biederman et al., 2000), there is a need for improved understanding of the similar and distinct neural substrates of these two developmental disorders.

Studies of adolescents with ADHD (Casey et al., 1997; Rubia et al., 1999) implicate the dorsolateral prefrontal cortex (DLPFC), the ventrolateral prefrontal cortex (VLPFC), and the dorsal striatum as regions of dysfunction in this disorder. For instance, recent functional magnetic resonance imaging (fMRI) that examined selective attention using the Flanker Task (Vaidya et al., 1998) and response inhibition using a Go-NogoTask (Casey et al., 1997; Durston et al., 2003, 2006; Tamm et al., 2004) or a Stop-Signal Task (Plitzka et al., 2006; Rubia et al., 1999) in adolescents with ADHD found decreased activation in prefrontal regions such as the VLPFC, the anterior cingulate cortex (ACC), and the mesial prefrontal cortex, as well as the caudate (Rubia et al., 1999). In addition to dysfunction of ventral fronto-striatal circuits, Durston et al. (2003) also found increased recruitment of posterior temporal and parietal regions in children with ADHD as compared with age-matched healthy controls (HC) during a Go-Nogo task, which has been considered a compensatory phenomenon for prefrontal

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cortex (PFC) underactivity (Durston et al., 2003; Vaidya et al., 2005). Findings of functional fronto-striatal abnormalities are also in line with studies showing reduced tissue volumes in the DLPFC and caudate in pediatric populations with ADHD (Castellanos et al., 1994, 1996, 2002; Filipek et al., 1997; Seidman et al., 2006).

With regard to PBD, a recent study using the Stop-Signal Task (Leibenluft et al., 2007) found that during failed Stop trials children with PBD, regardless of comorbid ADHD or medication, showed decreased activation in the right VLPFC and bilateral striatum when compared with HC. Similarly, decreased VLPFC activation in children with PBD compared with HC was found by Pavuluri et al. (2008) during an emotional Stroop Task. In another study that employed a color-naming Stroop Task (Blumberg et al., 2003a), patients with PBD exhibited increased activation in putamen and thalamus compared with HC. Moreover, a growing number of studies are reporting dysfunction in rostral ACC, a region important for emotion regulation, in PBD (Pavuluri et al., 2006; Malhi et al., 2005; for a review, see Fountoulakis et al., 2008).

To delineate disorder-specific disturbances in functional brain systems that might account for behavioral control deficits (e.g., impulsivity, motor disinhibition) associated with both disorders, we contrasted brain activation in pediatric patients with PBD and with ADHD to that of HC using a Response Inhibition Task.

The main goal of the present study was to examine the neural underpinnings of motor inhibition as compared with motor response in patients with ADHD and PBD, rather than addressing the more specific case of response inhibition in the context of a pre-potent tendency to respond, as in a typical Stop-Signal Task (Logan et al., 1984), because we think it is important to first elucidate the basic circuits for motor inhibition versus motor execution in these patients. Therefore, the present experimental task examined the ability to execute a motor response to a target, or inhibit a motor response that is already on the way, when a stop cue appears shortly after the target. Our primary fMRI comparison was between blocks of trials requiring predominantly inhibition of a motor response already on the way, and blocks of trials that required predominantly a motor response.

We hypothesized that both the PBD and ADHD groups would show impairment in response inhibition compared with the HC group. Moreover, we predicted that compared with findings in healthy controls, the PFC and the fronto-striatal stream would be more affected in ADHD (Casey et al., 1997; Bush et al., 1999; Rubia et al., 1999), whereas the PBD group would exhibit more localized dysfunction in regulatory regions such as the VLPFC and pregenual ACC (Pavuluri and Passarotti, 2008; Pavuluri et al., 2008).

2. Methods

2.1. Subjects

All participants were recruited from the Child Psychiatry Clinics at the University of Illinois at Chicago (UIC) and from the neighboring community. All groups were matched on age, sex, socioeconomic status (SES), race, handedness and IQ as estimated with the Wechsler Abbreviated Scale of Intelligence (WASI, 1999). Subject groups included 15 unmedicated patients with PBD (Type I, manic: $n=5$, and mixed: $n=5$; Type II, hypomanic: $n=5$) (8 F, 7 M; mean age: 13.2 ± 2.65; Young Mania Rating Scale score above 12), 11 unmedicated patients with ADHD (Type Combined) (5 F, 6 M; mean age: 13.09 ± 2.7), and 15 HC (8 F, 7 M; mean age: 14.13 ± 3.16). For children younger than age 15, an assent was obtained, and for children older than age 15, an informed consent was obtained, together with consent of at least one parent or legal guardian. The study was approved by the Institutional Review Board at UIC. The subject and a parent or legal guardian were interviewed using the Washington University Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS) (Geller et al., 1998) to determine the DSM-IV (DSM-IV, 1994) Axis I clinical diagnoses in the PBD and ADHD groups, and the absence of these and other psychiatric diagnoses in the HC group. A Parent ADHD Rating Scale IV-Revised (DuPaul et al., 1998) was also administered. Clinicians who were blind to diagnosis rated all subjects on the Young Mania Rating Scale (YMRS; Young et al., 1978) and the Child Depression Rating Scale-Revised (CDRS-R; Poznanski et al., 1984).

Inclusion criteria for PBD and ADHD subjects were: 10 to 18 years of age, a diagnosis of either bipolar disorder Type I with mania or hypomania or a diagnosis of ADHD, and consent to be scanned in a medication-free state for the study. Patients were studied if they were medication free, or when medication was withdrawn because the current regime was ineffective and a wash-out prior to new medication was warranted. Overall eight (58%) of the PBD patients [$n=6$ (38%) on mood stabilizers; $n=4$ (29%) on second generation antipsychotics (SGAs); $n=1$ (9%) on stimulants; for $n=4$ (24%) medication information n/a] and six (53%) of the ADHD patients [$n=5$ (48%) on stimulants; $n=1$ (12%) on SGAs; for $n=5$ (40%) medication information n/a] had received medication in the past. Close clinical supervision and monitoring was provided during drug-free periods, according to the approved IRB protocol. None of the patients were on fluoxetine or aripiprazole, which warrant a longer washout period. Medication was reduced gradually over a 3-week period, so that patients were drug-free for at least 7 days before testing.

Axis I diagnoses of bipolar disorder with mania or hypomania, and diagnosis of ADHD were based on DSM-IV criteria. ADHD comorbidity in patients with PBD was ruled out based on DSM-IV criteria. Other comorbid conditions in patients with PBD as assessed by the WASH-U-KSADS were as follows: generalized anxiety disorder: $n=2$; learning disability: $n=1$; social phobia: $n=1$. Individuals with ADHD diagnosis did not exhibit any of these comorbid conditions. Exclusion criteria for all subjects were: a history of head trauma with loss of consciousness for more than 10 min, neurological symptoms, speech or hearing difficulties, an IQ score of less than 70, a history of substance abuse, a history of mental illness other than PBD for the bipolar group and other than ADHD for the ADHD group, or a history of mental illness for HC participants, and any contraindications to MRI scans (i.e., metal implants, retractors, braces, pregnancy, and claustrophobia).

2.2. fMRI session and Response Inhibition Task

For the present block-design fMRI study subjects performed a Response Inhibition Task that examined the ability to inhibit the execution of a motor response to a target when a stop cue is presented shortly after the target. While we are currently conducting event-related studies, this was an initial pilot study for which we adopted a block design to benefit from the greater statistical power and signal stability that a block design offers relative to an event-related design, especially with clinical populations who have more variable neural activation. Moreover, by summating neural activation over a time period including several consecutive trials, the block design enabled us to look at sustained activation in prefrontal cortex, which could be both preparatory and in response to specific stimuli, to a greater extent than is readily possible with an event-related design. Prior to the fMRI scanning session all our subjects underwent training and were familiarized with the MRI scanning protocols using a mock scanner at the Center for Cognitive Medicine, UIC. The task lasted 5 min and 57 s, and consisted of six experimental blocks, three of which were Go blocks (G) and three of which were Stop blocks (S), and six resting blocks (F) of 10 s fixation each. In Go blocks (G) 70% of the trials required a motor response, and 30% of the trials required inhibition of a motor response. Conversely, in Stop blocks (S) 70% of the trials required to inhibit a motor response and 30% required inhibition of a motor response. Given that in Stop blocks most trials required response inhibition, there was not a prepotency of Go responses in these blocks. We constructed our trial blocks in this way because we wanted to examine behavioral control and active processes of response inhibition versus response execution per se, rather than inhibition processes in the context of pre-potent motor responses. Moreover, we