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Research paper

Relationship of executive functioning deficits to N-acetyl aspartate (NAA) and gamma-aminobutyric acid (GABA) in youth with bipolar disorder

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ABSTRACT

Background: Although cognitive deficits in bipolar disorder (BD) have been repeatedly observed, our understanding of these impairments at a mechanistic level remains limited. Few studies that investigated cognitive impairments in bipolar illness have examined the association with brain biochemistry. This pilot study utilized proton magnetic resonance spectroscopy (^{1}H-MRS) to evaluate the relationship between neurocognitive performance and brain metabolites in youth with BD.

Methods: Thirty participants, twenty depressed BD participants and ten healthy comparison participants, ages 13–21, completed mood and executive function measures. ^{1}H-MRS data were also acquired from the anterior cingulate cortex (ACC) using two-dimensional (2D) J-resolved ^{1}H-MRS sequence. Proton metabolites including N-acetyl aspartate (NAA) and gamma-aminobutyric acid (GABA) were quantified for both groups.

Results: Participants with BD performed significantly lower on executive functioning measures than comparison participants. There were significant positive correlations between Wisconsin Card Sorting Test (WCST) performance and NAA ($p < .001$) and GABA ($p < .01$) in the ACC in bipolar youth, such that as WCST performance increased, both NAA and GABA levels increased.

Limitations: Small sample size and lack of control for medications.

Conclusions: These findings build on previous observations of biochemical alterations associated with BD and indicate that executive functioning deficits in bipolar youth are correlated with NAA and GABA. These results suggest that cognitive deficits occur early in the course of illness and may reflect risk factors associated with altered neurochemistry. Further investigation of the relationship between brain metabolites and cognition in BD may lead to important information for developing novel, targeted interventions.

1. Introduction

Neurocognitive deficits in adult bipolar disorder (BD) have been well documented; however, it has been debated whether deficits may be attributed to structural changes during neurodevelopment, medication use, or genetic factors (Henin et al., 2007; Tsitsipa and Fountoulakis, 2015; Wilke et al., 2004). While there are a growing number of studies that examine cognitive impairments in adults with BD, there are limited studies examining cognitive changes in youth with BD and very few exploring the neurobiology and mechanisms underlying these neurocognitive deficits. Further evaluation may lead to a better understanding of the onset and trajectory of neuropsychological deficits and opportunities for intervention.

Recent studies have suggested that neurocognitive dysfunction may be a prodromal marker for BD that exists prior to the expression of mood symptoms and may remain constant throughout the course of illness (Reichenberg et al., 2009). Moreover, neuropsychological deficits are relatively stable and exist independent of mood states (Robinson et al., 2016; Szmulewicz et al., 2015). A number of studies have provided evidence that cognitive deficits occur in healthy relatives of BD patients, and first-episode BD (Bora et al., 2009; Torres et al., 2010). Evidence from a meta-analysis of longitudinal studies suggests that cognitive performance for 14 variables did not change in adults with BD over approximately 4.5 years (Samame et al., 2014). Furthermore, cross-sectional studies have shown that BD adults with longer illness duration do not experience more severe deficits (Strejilevich

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et al., 2015). However, adult BD has shown to be associated with an increased risk of developing dementia (Wu et al., 2013). These findings are consistent with the perspective that cognitive performance may be independent of mood symptoms and medication.

Since the onset of BD occurs during childhood in up to 65% of cases, (American Psychiatric Association, 2013) the examination of neurocognitive functioning in BD may be most informative during development in youth. Significant deficits in processing speed, verbal/visual-spatial memory, working memory, and social cognition have been consistently reported across studies in pediatric BD (Frías et al., 2014). Meta-analyses have identified moderate neurocognitive deficits (Cohen's *d* effect size = .5–.8) for youth with BD in areas of attention, verbal memory, processing speed, and executive function (Joseph et al., 2008; Nieto and Castellanos, 2011). These cognitive impairments can impact social and academic performance for youth with BD (Bearden et al., 2010). Neuropsychological deficits are known to exist in all mood states and can contribute to negative long-term outcomes such as academic failure and unemployment (Bearden et al., 2010).

Neuroimaging studies have provided insight into structural, functional, and chemical differences for youth with BD (Keener and Phillips, 2007; Kondo et al., 2014; Terry et al., 2009). Abnormalities in frontal lobe morphology have been associated with cognitive deficits in bipolar youth. Specifically, a smaller anterior cingulate cortex (ACC) has been reported in manic and euthymic adolescents with BD (Wilke et al., 2004). The ACC plays an important role in cognition and emotion due to its connections with the limbic system and prefrontal cortex. Thus, the ACC has been shown to regulate emotions and mediate attention and executive functioning (Stevens et al., 2011). Zimmerman et al. (2006) also found that the relationship between ACC subregion volumes and executive functioning performance differed for bipolar and healthy comparison (HC) adult patients, despite comparable ACC volumes. Due to the interaction between lower performance on the Wisconsin Card Sorting Test (WCST) and subregion volumes, the researchers suggested participants with BD utilize different brain regions to perform those executive functions. Taken together, these studies demonstrate a role for the ACC in mediating neurocognitive deficits in BD.

Proton magnetic resonance spectroscopy (^{1}H-MRS) is a non-invasive scanning technique used to measure in vivo brain biochemistry. Using these techniques, researchers have found that brain metabolite concentrations in the ACC have shown to be altered in BD. Specifically, abnormal levels of N-acetyl aspartate (NAA), glutamate/glutamine (Glx), creatine/phosphocreatine (Cr-PCr), gamma-aminobutyric acid (GABA), and myoinositol have been observed in the frontal lobe in youth with early-onset BD (Frazier et al., 2005). NAA is considered a marker for neuronal and mitochondrial integrity; Glx is plays a role in neurotransmission, synapse formation, dendrite pruning, cell migration, differential, and death; GABA is an inhibitory central nervous system neurotransmitter, and myoinositol indicates glial disease (Agarwal and Renshaw, 2012; Stork and Renshaw, 2005). Given the reported changes in metabolite concentrations in BD, it is possible that alterations in neuronal integrity, neurotransmission, and inhibition in the ACC may contribute to compromised cognition in BD. Thus, application of ^{1}H-MRS techniques to examine irregularities in biochemistry as they relate to cognition in BD may therefore provide insight into the onset and trajectory of BD.

Converging evidence from neuroimaging and neuropsychological studies suggests that metabolite alterations and cognitive abnormalities are a characteristic of BD (Etkin et al., 2013). However, there is limited research examining brain chemistry and its potential relationship to neurocognitive deficits in BD. Research studies with healthy adults have shown that performance on neuropsychological tests is correlated with concentrations of neurochemicals in the brain, particularly NAA (Patel et al., 2014). ^{1}H-MRS has been used to investigate the lenticular nucleus and cognitive functioning in BD and HC adults. Specifically, decreased NAA and lower performance on the WCST was observed for BD adults when compared to controls (Zhang et al., 2015). Despite these findings, there is limited research that has examined in vivo brain chemistry and its potential relationship to neurocognitive function, especially in youth.

While, a growing number of studies have examined cognitive impairments in bipolar illness, there are few studies with bipolar youth that explore these deficits using advanced imaging approaches. Magnetic resonance spectroscopy provides important information regarding brain chemistry and metabolism that can be used to explore the neural substrates which underlie the cognitive deficits in youth with BD. In particular, understanding cognitive impairments in BD at a mechanistic level may help to identify treatment “targets” which are vital to the National Institute of Mental Health's (NIMH's) experimental therapeutics model for clinical trials. The current study was a pilot study to examine the relationship between cognitive deficits and proton metabolites in youth with bipolar disorder. To our knowledge, this is the first ^{1}H-MRS study to evaluate executive functioning deficits in bipolar youth and their potential relationship to neurometabolites in the frontal lobe.

2. Methods

2.1. Participants

Two groups of participants were recruited, one with BD and a comparison group with no evidence of BD or other psychiatric diagnoses, or clinically significant medical conditions. Capable of impacting outcome data Participants were recruited using radio advertisements, informational flyers, posting in local news letters, an Internet website, and advertisements on local public transit. The University of Utah Internal Review Board (IRB) approved all recruitment methods and study procedures.

Participants with BD were males and females between the ages of 13–21 who were in a current depressive episode. All participants with BD met the DSM-IV-TR criteria for bipolar I, bipolar II, or bipolar-not otherwise specified (NOS) according to a clinician administered structured interview. Participants had to be depressed for ≥ 2 weeks and experienced mania or hypomania at least once during their lifetime. All bipolar disorders (bipolar I, II, or NOS) were grouped together into one bipolar group. Due to the possibility that NAA and GABA concentrations could be altered by substance use (Prescot et al., 2011, 2013), we excluded participants who met criteria for a current substance use disorder. Additionally, this was confirmed with a negative drug screen prior to obtaining ^{1}H-MRS. Twenty participants (13 females) with bipolar disorder consented to participate in the study. One participant with bipolar disorder was not able to finish the scan, so their data was excluded from the analyses. An age- and sex-matched non-affected comparison group was included in the study in order to provide a comparison to adolescents with bipolar disorder. Ten non-affected comparison participants (5 females), ages 13–21, completed the study (see Table 1).

2.2. Screening measures

After providing permission, assent, and consent for the study, all participants were screened for study eligibility. Participants completed psychiatric and mood measures to determine eligibility. Specifically, participants completed a diagnostic interview and depression, mania, and suicide rating scales. The *Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime* version (K-SADS-PL; Kaufman and Schweder, 2003) was given to the parent(s) and all adolescent participants between the ages of 13 and 17. Participants who were 18–21 were administered the *Structured Clinical Interview for DSM-IV* (SCID I/P; First et al., 1997). The *Children's Depression Rating Scale-Revised* (CDRS-R; Poznanski and Mokros, 1996) and the *Montgomery-Asberg Depression Rating Scale* (MADRS; Montgomery and Asberg, 1979) were