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Anterior cingulate cortex choline levels in female adolescents with unipolar versus bipolar depression: A potential new tool for diagnosis

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Abstract

Background—Delayed diagnosis in bipolar disorder (BD) due to misdiagnosis as major depressive disorder (MDD) is a significant public health concern. Thus, identification of relevant diagnostic biomarkers is a critical unmet need, particularly early in the course of illness. The anterior cingulate cortex (ACC) is thought to play an important role in mood disorder pathophysiology. Case-control studies utilizing proton-1 magnetic resonance spectroscopy (¹H-MRS) have found increased total choline levels in several brain regions in MDD. However, there are no published ¹H-MRS reports directly comparing adolescents with MDD and BD. We hypothesized that ACC choline levels would be increased in adolescents with unipolar versus bipolar depression.

Methods—We studied depressed adolescents with MDD ($n=28$; mean age 17.0 ± 2.1 years) and BD ($n=9$; 17.3 ± 3.1 years). A Siemens Verio 3-Tesla clinical MRI system was used to acquire scans, using a single-voxel PRESS sequence. The voxel (18.75 cm^3) was positioned on the ACC in the midsagittal plane. To remove potential gender effects, only female adolescent participants were included. Data were analyzed using the ANOVA and post-hoc Tukey tests.

Results—A significantly increased ACC choline/creatine ratio was observed in participants with MDD (mean= 0.253 ± 0.021) compared to BD (mean= 0.219 ± 0.020) ($p=0.0002$). There were no significant differences in the other ¹H-MRS metabolites.

Limitations—Cross sectional design, single gender sample, limited sample size.

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Conflict of interest

Dr. Renshaw, Dr. Shi and Dr. Kondo are co-inventors on a patent application that describes the use of proton-1 magnetic resonance spectroscopic imaging of the brain as a diagnostic method for differentiating bipolar disorder from major depressive disorder, in patients who present with a major depressive episode. All other authors declare that they have no conflicts of interest.

Conclusions—The present findings suggest that ACC total choline may have the potential to serve as a diagnostic biomarker in adolescent mood disorders.

Keywords

Neuroimaging; Bipolar; Unipolar; Biomarker; Diagnosis; Spectroscopy

1. Introduction

Together unipolar and bipolar mood disorders affect 20.7% of adults (Kessler et al., 2003; Merikangas et al., 2007), and up to 14.3% of adolescents (Merikangas et al., 2010). The identical diagnostic criteria for the major depressive episodes (MDEs) experienced by patients with major depressive disorder (MDD) and bipolar disorder (BD) make the differential diagnosis in juveniles challenging, particularly for non-mental health professionals. In fact, while 50% of BD patients experience the onset of illness during childhood or adolescence (Post et al., 2010), 69% of patients with BD are initially misdiagnosed, consulting a mean of four physicians prior to receiving the correct diagnosis (Hirschfeld et al., 2003). Owing to this and other factors, patients with early-onset BD experience a mean delay to appropriate treatment of >16 years (Leverich et al., 2007). Moreover, even with an established diagnosis of BD on their medical record, a strikingly high proportion of patients are subsequently misdiagnosed with MDD (Stensland et al., 2010). Experts in the field have identified improved diagnosis as one critical barrier to advancing research and patient care for pediatric BD (Carlson et al., 2009). To accomplish this, identifying neuroimaging-based biomarkers is one promising strategy (Cardoso de Almeida and Phillips, 2013; Frey et al., 2013; Houenou et al., 2012; Lewis and March, 2010).

Magnetic resonance spectroscopy (MRS) is the only imaging method for measuring in vivo concentrations of neurochemicals (Stanley, 2002), several of which are relevant to BD and MDD. Proton-1 MRS (^1H -MRS) is the most commonly used technique; brain metabolites measurable with ^1H -MRS include: choline-containing compounds (tCho), N-acetylaspartate/N-acetylaspartyl-glutamate (NAA/NAAG), creatine (Cre) and glutamate/glutamine (Glx). Recent ^1H -MRS studies of pediatric MDD have reported increased tCho in patients compared with controls in the orbitofrontal cortex (Steingard et al., 2000), prefrontal cortex (Farchione et al., 2002; Macmaster and Kusumakar, 2006), and caudate (Gabbay et al., 2007). In adult MDD, two reviews of case-control and intervention studies concluded that increased tCho may be a biomarker for MDD (Yildiz-Yesiloglu and Ankerst, 2006) that decreases with efficacious treatment (Caverzasi et al., 2012). The ^1H -MRS choline resonance is in equilibrium with membrane phospholipids, and is therefore thought to reflect both regional membrane turnover and cellular density (Rae, 2014).

While spectroscopic imaging is increasingly employed to study adolescents with BD (Kondo et al., 2014) and MDD (Kondo et al., 2011), to date no report has directly compared the ^1H -MRS results of adolescents with both disorders. To facilitate early intervention, there is a critical unmet need for tools to aid clinicians in the differential diagnosis of MDD vs. an emerging bipolar-spectrum disorder in young people (Scott et al., 2013). To accomplish this, neuroimaging studies that directly compare patients with unipolar vs. bipolar depression are

urgently needed (Cardoso de Almeida and Phillips, 2013). The present study was undertaken to investigate whether ^1H -MRS data can be used to parse adolescent females with MDD from those with bipolar depression. Because of the evidence implicating it in the pathophysiology of mood disorders (Drevets et al., 2008), we selected the anterior cingulate cortex (ACC) as the region-of-interest for this study. We hypothesized that ACC choline would be increased in participants with MDD compared with BD.

2. Methods

Participants were recruited into two clinical trials for adolescent females with treatment-resistant MDD (NCT01601210) and depressed adolescents of both genders with BD (NCT01805440). The studies were approved by the University of Utah Institutional Review Board, and written informed consent was obtained from participants and their parents. Diagnoses were established with the Kiddie-Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS) (Kaufman et al., 1997), or the Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID) (First et al., 2007). Depressive symptoms were measured using the Children's Depression Rating Scale-Revised (CDRS-R) (Poznanski et al., 1984) and the Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979). The study inclusion criteria were: primary diagnosis of MDD or bipolar disorder I, II or NOS, age 13–20 years inclusive, and a CDRS-R raw score ≥ 40 or MADRS score ≥ 25 . Participants with MDD trial were required to have failed an adequate trial of a selective serotonin reuptake inhibitor (SSRI) antidepressant; the treatment resistance criteria were adopted from the TORDIA trial (Brent et al., 2008). The study exclusion criteria were: positive pregnancy test, unstable comorbid psychiatric or medical illness, known or suspected intellectual disability, significant suicidal/homicidal risk or contraindication to MRI scanning.

Scanning was performed at 3 T on a MAGNETOM Verio clinical MRI system (Siemens Medical Solutions, Erlangen, Germany) with Avanto gradients (40 mT/m strength and 150 T/m/s slew rate) using a 12-channel head coil. Spectra were acquired using a PRESS pulse sequence with a 18.75 cm^3 single voxel positioned on the ACC in the mid-sagittal plane, TR/TE 2000/31 ms, receiver bandwidth 1 kHz, averages of 64 and vector size 1024. Metabolite concentrations were estimated using an LCModel 6 (Provencher, 1993). Each participant's ACC choline concentration was normalized by expressing it as the ratio of tCho to the creatine resonance (tCho/Cr). Participants were instructed that they could discontinue scanning at any time if they experienced discomfort (e.g. claustrophobic anxiety). Because our MDD trial enrolls only female adolescents, to eliminate the potential for gender effects on ACC metabolite levels, male BD study participants were excluded from the analysis. Data were analyzed in R (R Foundation for Statistical Computing, Vienna, Austria) and JMP Pro 10 (SAS Institute, Cary, NC), using the ANOVA and post-hoc Tukey Honestly Significant Difference tests.

3. Results

We enrolled $n=28$ female participants with SSRI-resistant MDD (mean age 17.0 ± 2.1 years) and $n=9$ depressed adolescents with BD (17.3 ± 3.1 years). The demographic, clinical and

spectroscopic imaging results from our study sample are shown in Table 1. There were no significant between-group differences in mean age, CDRS-R score, MADRS score, or the volume percentage of gray matter (GM), white matter (WM) or cerebrospinal fluid (CSF) within the ACC voxel. We observed a significantly increased ACC tCho/Cre ratio (%) in participants with MDD (mean 0.25 ± 0.02) compared with BD (mean 0.22 ± 0.02) ($p=0.0002$). There were no significant differences in the other ^1H -MRS metabolites. We next conducted a receiver operating characteristic (ROC) curve analysis (Perlis, 2011; Youngstrom, 2014) to evaluate how accurately tCho/Cre categorized participants according to diagnosis. With a cutoff point of 0.233, the area under the ROC curve (AUC) was 0.883 (sensitivity 85.7%; specificity 77.8%; Ir eta 0.711; intercept -19.923 ; slope 89.359). The distribution of tCho/Cre values in participants with BD and MDD, and the ROC curve are shown in Fig. 1.

4. Discussion

The authors report what is, to the best of our knowledge, the first ^1H -MRS study to compare the brain chemistry of adolescents with unipolar and bipolar depression. Based upon published reports of increased cortical tCho/Cre in pediatric MDD (Farchione et al., 2002; Macmaster and Kusumakar, 2006; Steingard et al., 2000), and decreased (Caetano et al., 2011; Davanzo et al., 2003) or non-significantly different (Cecil et al., 2003; Gallelli et al., 2005; Patel et al., 2008) cortical tCho/Cre in pediatric BD, we hypothesized that depressed adolescents with BD would demonstrate lower tCho/Cre in the ACC compared with adolescents with SSRI-resistant MDD. While our hypothesis was confirmed in this sample, it will require replication in larger studies at multiple sites. These results also serve to demonstrate the feasibility of this approach, in the search for imaging-based biomarkers of adolescent MDD and BD.

Perhaps more than in any area of psychiatry, biomarkers to improve diagnostic efficiency are needed to assist pediatric health-care professionals with the differential diagnosis of unipolar vs. bipolar depression. The cumulative incidence of MDD approaches 20% by age 18 (Birmaher et al., 2007), and approximately 60% of patients with BD experience their onset during childhood or adolescence (Leverich et al., 2007; Lish et al., 1994; Post et al., 2008). Given that 71% of first episodes in BD are depressive (Etain et al., 2012), and delayed diagnosis in BD is associated with grave and lifelong consequences (Post et al., 2010; Scott and Leboyer, 2011), the initial diagnosis in juvenile MDEs represents a crucial juncture in the natural history of the illness. Among the competing pathways to diagnostic biomarkers in psychiatry, neuroimaging is one promising area of investigation (Fu and Costafreda, 2013; Houenou et al., 2012; Ozomaro et al., 2013; Savitz et al., 2013).

In our sample, we found that ACC tCho/Cre demonstrated reasonable accuracy in classifying female adolescents with unipolar vs. bipolar depression. The tCho ^1H -MRS signal at 3.2 ppm arises from the nine protons in the N-methyl moiety of choline-containing compounds. These consist of phosphocholine and glycerophosphocholine, with a minor contribution from free choline (Miller et al., 1996). Studies of healthy volunteers with no history of psychiatric or neurological disease have shown that when normalized to water, the cortical tCho resonance is negatively correlated with both intelligence (Jung et al., 1999), and positive effect (Jung et al., 2002). Although the mechanistic contributions have yet to be

definitively elucidated, changes to the ^1H -MRS choline resonance are believed to reflect non-steady state alterations to the rate of membrane synthesis and breakdown, and/or changes in cell density (Rae, 2014). In addition to the findings reported here in adolescents, studies in adults with BD have found no difference in choline between BD and healthy controls (Amaral et al., 2006; Kraguljac et al., 2012; Scherk et al., 2009). However, because the tCho concentration is known to display regional differences in normal brain of up to 46% (Bracken et al., 2011), is thought to vary with mood state (Charles et al., 1994), and can potentially be affected by drugs lithium and valproic acid (Moore et al., 2000; Silverstone et al., 2004), our findings must be considered limited in their applicability to the ACC, in depressed patients not currently taking mood stabilizing medications.

This study has several limitations. Sample size is a weakness of most spectroscopic imaging studies of juvenile mood disorders, and ours is no exception. The minimum acceptable sample size for psychiatric MRS studies has been estimated at $n=78$ subjects (Steen et al., 2005), a standard very few studies have achieved. In addition our study used a single voxel, located in a single brain region. Importantly, our study's participants were all female, although in a previous study we reported finding no gender effect on cortical tCho/Cre ratio in adolescent MDD (Steingard et al., 2000). Finally, some investigators have reported that tCho concentrations appear to be altered by antidepressant medication (Charles et al., 1994; Sonawalla et al., 1999)—although this could be an indication that tCho is a marker of mood state, rather than an indicator of antidepressant exposure per se. The participants in this study were on a variety of psychotropic medication regimens, a well-recognized issue in studies of this kind (Phillips et al., 2008).

This report adds to the expanding efforts to identify and validate biomarkers of MDD (Schneider and Prvulovic, 2013) and BD (Frey et al., 2013). Because their evidence-based treatments are so dissimilar, a reliable diagnostic biomarker capable of differentiating unipolar and bipolar depressive episodes in adolescents would have a significant impact on psychiatric morbidity and mortality. Toward that end, serum samples were collected from the majority of this cohort, and we are endeavoring to develop a non-genetic serum biomarker test, using an algorithm similar to that used in a study of MDD in adults (Papakostas et al., 2013). Future directions for this work include studies that recruit adolescents of both genders, studies of treatment-naïve (i.e. first episode) participants, and studies that utilize multinuclear MRS with the addition of phosphorus-31 and/or carbon-13 spectroscopic imaging.

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Fig. 1. Anterior cingulate choline in bipolar disorder versus major depressive disorder and receiver operating characteristic curve results.

Table 1

Participant demographic, clinical and neuroimaging results.

Mean	Bipolar disorder (<i>n</i> =9)	Major depressive disorder (<i>n</i> =28)	<i>p</i> -value (ANOVA)
Age (years)	17.3±3.1	17.8±2.1	0.71
CDRS-R raw score	55.4±9.6	57.3±6.6	0.52
MADRS score	25.8±9.0	25.6±5.8	0.96
Gray matter (%)	63.84±3.04	62.46±3.36	0.28
White matter (%)	26.80±3.38	27.95±3.19	0.36
CSF (%)	9.36±2.96	9.59±3.80	0.87
tCho/Cr	0.22±0.02	0.25±0.02	0.0002
Glx/Cr	1.56±0.09	1.66±0.21	0.18
(NAA+NAAG)/Cr	1.27±0.14	1.32±0.13	0.36

CDRS-R, Children's Depression Rating Scale-Revised; MADRS, Montgomery–Asberg Depression Rating Scale; CSF, cerebrospinal fluid; tCho, choline-containing compounds; Cr, creatine; Glx, glutamate/glutamine; NAA, N-acetylaspartate; NAAG, N-acetylaspartylglutamate.