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ABSTRACT

Pediatric bipolar disorder is a severe mental illness whose pathophysiology is poorly understood and for which there is an urgent need for improved diagnosis and treatment. MR spectroscopy is a neuroimaging method capable of in vivo measurement of neurochemicals relevant to bipolar disorder neurobiology. MR spectroscopy studies of adult bipolar disorder provide consistent evidence for alterations in the glutamate system and mitochondrial function. In bipolar disorder, these 2 phenomena may be linked because 85% of glucose in the brain is consumed by glutamatergic neurotransmission and the conversion of glutamate to glutamine. The purpose of this article is to review the MR spectroscopic imaging literature in pediatric bipolar disorder, at-risk samples, and severe mood dysregulation, with a focus on the published findings that are relevant to glutamatergic and mitochondrial functioning. Potential directions for future MR spectroscopy studies of the glutamate system and mitochondrial dysfunction in pediatric bipolar disorder are discussed.

ABBREVIATIONS: ACC = anterior cingulate cortex; ATP = adenosine triphosphate; BD = bipolar disorder; GABA = γ-aminobutyric acid; Gln = glutamine; Glu = glutamate; HC = healthy controls; PCr = phosphocreatine; Pi = inorganic phosphate; tChol = total choline

With an estimated lifetime prevalence of up to 5.1%,[1] bipolar disorder (BD) is a disabling and often fatal brain disease characterized by recurrent episodes of depression and mania. In pediatric BD, the rate of attempted suicide is 40 times that of healthy adolescents,[2] and BD is the diagnosis imparting the greatest risk for completed suicide.[3] Adding to the morbidity and mortality imposed on patients and their families, the annual economic burden of BD in the United States is at least $151 billion.[4] Despite decades of research, the underlying pathophysiology of BD across the life span is yet to be elucidated.[5,6]

The neurobiology of pediatric BD is of particular interest because up to 65% of patients with BD experience its onset before 19 years of age.[7,8] Adolescence is the peak period for the first episode of mania,[9] the mood state that defines the illness. In fact, the World Health Organization ranks BD as the fourth most disabling disease worldwide in persons between 10 and 24 years of age.[10] Leverich et al[11] found that childhood-onset BD is associated with a delay of first treatment of >16 years. Expert consensus has identified the improved definition and diagnosis of pediatric BD, based on its underlying pathophysiology, as a critical barrier to progress in the field.[12] *The National Institute of Mental Health Strategic Plan*[13] and *A Research Agenda for DSM-V*[14,15] both advocate attempts to discover neuroimaging biomarkers of BD. Thus, neuroimaging has an important role to play in translational research in pediatric BD.[16-18]

Converging lines of evidence implicate 2 related systems in the pathophysiology of BD: 1) alterations in glutamatergic neurotransmission,[19-21] and 2) cerebral mitochondrial dysfunction.[22-24] They are interdependent because >80% of all synapses are glutamatergic[25] and approximately 85% of the energy derived from glucose in the brain is used to support glutamatergic neurotransmission and the conversion of glutamate (Glu) to glutamine (Gln).[26,27]

Mood-related alterations in cerebral bioenergetics would presumably have an impact on the glutamate system. Support for this is provided by the fact that inhibition of mitochondrial respiratory chain complexes I, III, and IV in an animal model of depression is reversed by administration of the N-methyl-D-aspartate glutamate receptor antagonist ketamine,[28] a novel intervention for refractory BD.[29,30] MR spectroscopy is a neuroimaging method capable of noninvasive interrogation of specific brain metabolites in vivo. Because it allows measurement of the chemical status of specific brain regions, MR spectroscopy is one potential method for establishing quantitative correlates of illness

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and treatment response in psychiatric conditions such as BD.[31,32] Accordingly, MR spectroscopy has been used extensively in BD research to study both the glutamate system and brain bioenergetics. Two systematic reviews[33,34] and 1 meta-analysis[35] have each concluded that MR spectroscopy studies provide convincing evidence for glutamatergic abnormalities in BD. As reviewed by Stork and Renshaw,[36] the MR spectroscopy literature in BD also provides consistent support for mitochondrial dysfunction. The promising nature of these findings has led to the conjecture that MR spectroscopy studies may represent "a pathway to diagnosis, novel therapeutics, and personalized medicine" in mood disorders.[37]

There is an urgent need for translational pediatric BD research, for the reasons enumerated above and because the data suggest that juvenile BD is continuous with adult BD.[38-40] The MR spectroscopy literature in pediatric major depressive disorder was recently reviewed,[41] but a review of MR spectroscopy studies of child and adolescent BD is lacking. The purpose of this article is to provide a companion review in pediatric BD, with particular attention paid to evidence for alterations in the glutamatergic system and mitochondrial dysfunction, and to discuss opportunities for further study.

MR Spectroscopy Measures Relevant to Bipolar Disorder

A technical description of MR spectroscopy methods for data acquisition and analysis is beyond the scope of this article, but excellent technical reviews are available.[42,43] MR spectroscopy can be used to study a range of atomic nuclei that possess magnetic properties, including hydrogen (^{1}H), phosphorus (^{31}P), lithium (^{7}Li), fluorine (^{19}F), and carbon (^{13}C).[31] To date, the published pediatric BD literature has largely focused on 2 of these: ^{1}H and ^{31}P.

^{1}H-MR Spectroscopy. The most common spectroscopic imaging method used in BD research is ^{1}H-MR spectroscopy because the scans can be obtained on standard low-field clinical systems. Glutamatergic ^{1}H-MR spectroscopy metabolites include Glu, Gln, γ-aminobutyric acid (GABA) and *N*-acetyl aspartylglutamate.[44] At the magnetic field strengths used in clinical research, separation of the Glu and Gln resonance is unreliable[42]; however their combined peak (Glx) can be accurately quantified and therefore is most commonly reported. Although by convention Glx is defined as Glu+Gln, GABA may also contribute to the total Glx signal.[45] However, when conventional MR spectroscopy methods are used, the contribution of GABA to Glx is considered very small.[46]

Significant findings in ^{1}H-MR spectroscopy measures considered indicators of mitochondrial dysfunction in BD include the following: decreased NAA, decreased total creatine, increased total choline (tChol), increased Glx, and increased mIns.[36] NAA is synthesized inside neuronal mitochondria from L-aspartate + acetyl coenzyme A by the enzyme L-aspartate-N-acetyl transferase in an energy-dependent process, suggesting that decreased NAA concentrations are consistent with impaired mitochondrial bioenergetics.[36,47] The concentration of NAA by in vivo ^{1}H-MR spectroscopy methods is consistently higher than that found by careful ^{1}H-nuclear MR analysis of freeze-clamped animal brain tissue, suggesting additional contributions to the "NAA" in vivo peak.[48] The total creatine peak is composed of phosphocreatine (PCr), a temporal and spatial buffer of adenosine triphosphate (ATP), and creatine (PCr+Cre). tChol is a trimethylamine peak that is composed of phosphocholine, a membrane phospholipid precursor; glycerophosphocholine, a membrane phospholipid breakdown product; and choline, acetylcholine, carnitine, and acetyl-L-carnitine. The replicated finding of increased tChol in adult BD is hypothesized to be due to increased phospholipid turnover resulting from mitochondrial dysfunction.[36] The Glx peak contains contributions from glutamate, glutamine, and γ-aminobutyric acid. The largest contributors to the Glu resonance are Glu in metabolic pathways and, to a much lesser degree, the neurotransmitter Glu. Increased Glx in BD is hypothesized to reflect Glu-induced neuronal hyperactivation,[36] which places abnormally large demands on neuronal and glial energy metabolism.[46]

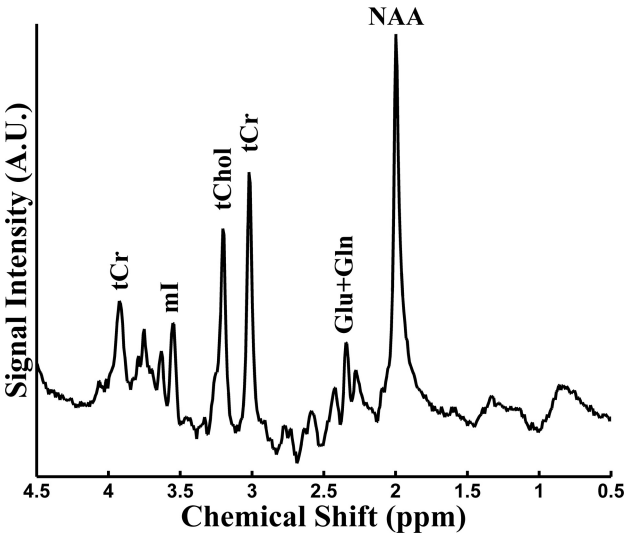

FIG 1. Representative proton-1 MR spectroscopy (^{1}H-MRS) spectrum acquired with parameters TR/TE = 2000/31 ms on a 3T MR imaging scanner.

Notably, the classic medication lithium has a significant normalizing effect on Glx in BD.[49] The mIns resonance consists primarily (>95%) of the cyclic sugar alcohol mIns, with minor contributions from inositol sugar phosphate compounds and glycine.[50] The relevance of mIns to BD stems from its status as a potential indicator of altered membrane metabolism resulting from mitochondrial dysfunction[36] and the fact that a decrease in mIns is associated with administration of the BD medication lithium.[36] A representative ^{1}H-MR spectroscopy spectrum is shown in Fig 1.

^{31}P MR Spectroscopy. Another MR spectroscopy technique used in BD research is ^{31}P-MR spectroscopy, which requires specialized hardware and software, such as a dual-tuned ^{1}H-^{31}P radiofrequency coil, a broadband radio-frequency power amplifier, and customized pulse sequences. Investigator experience with ^{31}P-MR spectroscopy pulse-sequence design and data processing/analysis is also essential because MR imaging system manufacturers do not typically supply these tools. Yet ^{31}P-MR spectroscopy may provide unique insights into BD neurobiology because it is a validated method for in vivo measurement of the ultimate mitochondrial process: ATP synthesis.[51] Few ^{31}P-MR spectroscopy

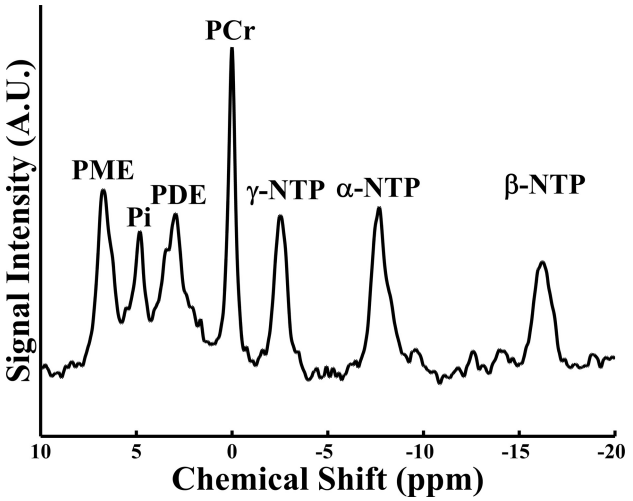

FIG 2. Representative phosphorus 31 MR spectroscopy (^{31}P-MRS) spectrum acquired without proton decoupling on a 3T MR imaging scanner.

studies of adult BD have been reported,[52] and to date, there are just 3 published ^{31}P-MR spectroscopy investigations in the pediatric BD literature.[53-55] ^{31}P-MR spectroscopy measures relevant to mitochondrial function include phosphomonoesters, phosphodiesters, β-nucleoside triphosphate, PCr, inorganic phosphate (Pi), and intracellular pH.[52] The phosphomonoesters signal contains contributions from the membrane precursors phosphoethanolamine and phosphocholine, in addition to sugar and inositol phosphates.[36] Phosphomonoesters are the building block precursors of neuronal membrane phospholipids. Both increased and decreased phosphomonoesters has been observed in studies of BD; thus, changes in the phosphomonoesters resonance may be state-dependent—with increased phosphomonoesters in depression and mania reflecting increased membrane phospholipid turnover, with decreased phosphomonoesters in subjects with euthymic BD possibly reflecting an opposite quiescence.[36]

The phosphodiester signal, made up of contributions from glycerophosphocholine, glycerophosphoethanolamine, and mobile phospholipids, represents the breakdown products of phospholipid membranes.[52] PCr is the buffer storage form of ATP and serves as the substrate reservoir for the creatine kinase reaction.[56] In the mitochondria, this reaction reversibly converts PCr into ATP + creatine in a 1:1 molar ratio.[57,58] Neuronal energy demands are met through a shift in reaction equilibrium, which is designed to maintain constant ATP concentrations.[59-61] β-nucleoside triphosphate predominately measures β-ATP levels and is, therefore, used as a proxy measure of relative ATP concentrations. Pi and adenosine diphosphate are the products of the ATP hydrolysis reaction and are released when ATP is consumed. Intracellular pH can be calculated by using a modified Henderson-Hasselbalch equation and the resonance Pi relative to PCr.[62] Figure 2 presents a representative ^{31}P-MR spectroscopy spectrum.

MATERIALS AND METHODS

Search Strategy

A computer-assisted literature search by using PubMed and MEDLINE data bases of the National Library of Medicine was conducted to identify reports focusing on pediatric BD samples studied with MR spectroscopy. The following terms were included in the search: "MR spectroscopy," "bipolar disorder," "pediatric or child or adolescent or juvenile or early-onset." A backward search of bibliographic references from the identified references was performed to ensure inclusion of relevant articles; a forward citation search for identified studies was also performed. We also included reports from MR spectroscopy studies of at-risk youth who were the offspring of parents with BD and subjects with severe mood dysregulation,[63] also known as disruptive mood dysregulation disorder,[64] a new mental illness of childhood published in the *Diagnostic and Statistical Manual of Mental Disorders,* 5th ed,[65] the diagnostic manual for US psychiatrists, in May 2013. All relevant articles published in English were included, and due to the small number of studies, no MR spectroscopy methodologic exclusion criteria were applied.

RESULTS

Overview of the Literature

The literature searches yielded 55 citations, of which 26 contained original neuroimaging acquired from subjects younger than 18 years of age. The sample characteristics, scanning acquisition methods, voxel location, and MR spectroscopy metabolite results are presented in Tables 1–4, and the key findings related to glutamatergic and mitochondrial function are summarized below. In addition to the modest number of reports and diversity of study methods and samples, this literature is in its infancy: The first MR spectroscopy study of pediatric BD was published in 2000. Despite this, the investigations conducted to date point to numerous important directions for further study.

Cross-Sectional MR Spectroscopy Studies of Pediatric BD

Cross-Sectional Studies of the Glutamate System. A summary of the cross-sectional MR spectroscopy studies comparing patients with pediatric BD versus healthy controls (HC) is shown in Table 1. Castillo et al[66] were the first to study juvenile patients with BD and controls in 2000, reporting that patients with BD showed elevated Glx in the bilateral frontal lobes and basal ganglia. In a cross-sectional study of stably medicated pediatric patients with BD versus patients with mania, Glx was decreased in mania; this finding, the authors noted, could represent anterior cingulate cortex (ACC) hypometabolism.[67] In another study, decreased ACC Gln was found in pediatric patients with manic BD, compared with both controls and stably medicated patients,[68] while there were no differences in Glu.

Cross-Sectional Studies of Mitochondrial Function. The frontal lobes have been the subject of numerous case-control studies in pediatric BD, with several investigators reporting decreased NAA concentrations in subjects with pediatric BD compared with controls.[69-73] In one report whose findings were in the opposing direction, Patel et al[74] reported increased NAA in the ACC in patients with pediatric BD depression. Two studies reported increased mIns in pediatric BD, compared with both HC[74] and intermittent explosive disorder.[75] One study of pediatric mania found reduced tChol levels compared with HC,[75] while a study of pediatric BD depression found an increase in tChol.[74]

As noted above, 3 recent studies of pediatric BD used ^{31}P-MR

Table 1: Cross-sectional MRS studies of pediatric bipolar disorder

Study	Sample	Methods (Device/FS/TR/TE/Sequence)	Region-of-Interest Voxel Size and Location	Findings
Castillo et al, 2000[66]	10 Patients with BD, mood state not reported, unmedicated, (mean age, 8 yr), 10 non-aged-matched healthy volunteers	Not stated/1.5T/3000/30/PRESS	8 mL or 27 mL in the left and right frontal lobe, 8 mL or 27 mL in the left and right temporal lobe	↑ Glx/tCre in BD in the frontal lobe and basal ganglia; No significant difference in NAA/tCre or tChol/tCre
Davanzo et al, 2001[78]	11 Patients with BD, mixed state ($n = 9$), manic state ($n = 2$), medicated ($n = 9$), unmedicated ($n = 2$), (mean age, 11.4 yr), 11 age- and gender-matched healthy volunteers	Signa[a]/1.5T/1500/135/PRESS	8 mL in the anterior cingulate cortex	Trend ($P = .054$) toward ↑ mIns/tCre in BD
Moore and Galloway, 2002[50]	9 Youth with BD with mean serum lithium level = −0.87 mEq/L, mood state not reported, (mean age, 13.4 yr), 18 adults with BD with mean serum lithium level = 0.78 mEq/L, mood state not reported, (mean age, 37.3 yr)	Signa[a]/1.5T/25,000/not stated/1D-ISIS Lithium-7 MRS was used to measure brain lithium concentrations in vivo	60-mm axial section centered on the superior edge of the ventricles	Mean brain lithium concentration = 0.52 mEq/L in pediatric patients with BD; mean brain lithium concentration = 0.92 mEq/L in adult patients with BD; lower brain-to-serum concentration ratios[b] in youth with BD compared with adults: 0.58 vs 0.92 ($P < .02$); brain-to-serum concentration ratio correlated positively with age ($r = 0.44$; $P < .02$); formula for brain-to-serum lithium concentration ratio[b]; (brain lithium in mEq/L) / (serum lithium in mEq/L)
Chang et al, 2003[70]	15 Patients with BD with at least 1 parent with BD, mood state euthymic ($n = 15$), medicated ($n = 14$), unmedicated ($n = 1$), (mean age, 12.6 yr), 11 healthy volunteers (mean age, 12.6 yr)	Signa[a]/3T/2000/35/PRESS	8 mL in left and right dorsolateral prefrontal cortices	↓ NAA/tCre in BD in the right dorsolateral prefrontal cortex ($P < .02$)

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Study	Sample	Methods (Device/FS/TR/TE/Sequence)	Region-of-Interest Voxel Size and Location	Findings
Davanzo et al, 2003[75]	10 Patients with BD, mood state manic ($n = 2$), mood state mixed ($n = 8$), medicated ($n = 7$), unmedicated ($n = 3$), (mean age, 9.8 yr), 10 patients with intermittent explosive disorder, (mean age, 9.6 yr), 13 healthy volunteers, (mean age, 11.7 yr)	Signa[a]/1.5T/3000/30/PRESS	8 mL in the anterior cingulate cortex, 8 mL in the occipital cortex	↑ mIns and mIns/tCre in anterior cingulate in BD compared with both intermittent explosive disorder and healthy volunteers ($P < 0.02$); ↓ tChol/tCre in anterior cingulate in BD compared with healthy volunteers ($P = .05$); no significant group differences in occipital cortex mIns, mIns/tCre, or tChol/tCre
Sassi et al, 2005[71]	14 Patients with BD, mood state euthymic ($n = 13$), mood state depressed ($n = 1$), medicated ($n = 13$), unmedicated ($n = 1$), (mean age, 15.5 yr), 18 healthy volunteers, (mean age, 17.3 yr)	Signa[a]/1.5T/1500/20/STEAM	8 mL in the left dorsolateral prefrontal cortex	↓ NAA in BD ($P = .03$); tChol was negatively correlated with the number of previous BD episodes ($r = -0.86$; $P = .0001$)
Moore et al, 2007[67]	10 Unmedicated patients with BD mania, (mean age, 11.1 yr), 8 patients with BD on risperidone; mean dose = 2.09 mg; mean duration = 101 weeks (mean age, 10.9 yr)	Signa[a]/1.5T/2000/30/Probe-P(PRESS) and MRSI; TR/TE not stated	4.8 mL in the anterior cingulate cortex	↓ Glx/tCre in BD mania compared with BD risperidone-treatment responders ($P < .05$)

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Study	Sample	Methods (Device/FS/TR/TE/Sequence)	Region-of-Interest Voxel Size and Location	Findings
Moore et al, 2007[68]	22 Patients with BD, euthymic state (n = 2), depressed state (n = 1), manic state (n = 10), mixed state (n = 9), medicated (n = 15), unmedicated (n = 7), (mean age, 12.6 yr), 10 healthy volunteers, (mean age, 12.3 yr)	Varian[c] 4T/2000/30/PRESS	8 mL in the anterior cingulate cortex	↓ Gln in unmedicated BD (n = 7; mean age, 12.9 yr) compared with both medicated BD (P = .003) and healthy volunteers (P = .027); no significant difference in Glu among the 3 groups
Olvera et al, 2007[72]	35 Patients with BD, (mean age, 13.2 yr), mood state not reported, medicated (n = 24), unmedicated (n = 11), 36 healthy volunteers, (mean age, 13.7 yr)	Intera[b]/1.5T/6000/30/PRESS	8 mL in the left dorsolateral prefrontal cortex	↓ NAA in BD (P = .04); no significant difference in Glu, tCre, tChol, or mIns
Patel et al, 2008[74]	28 Unmedicated depressed patients with BD, (mean age, 15.5 yr), 10 healthy volunteers, (mean age, 14.6 yr)	Signa[a]/1.5T/2000/35/Probe-P(PRESS)	8 mL in the anterior cingulate cortex, and the left and right ventral lateral prefrontal cortices	↑ NAA in BD in the anterior cingulate cortex, (P = .0002) and the left (P = .0008) and right (P = .002) ventral lateral prefrontal cortices; ↑ tChol in BD in the left (P = .001) and right (P = .01) ventral lateral prefrontal cortices; ↑ mIns in BD in the right (P = .002) ventral lateral prefrontal cortex; in general, patients with BD had higher neurometabolite concentrations than healthy volunteers

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Study	Sample	Methods (Device/FS/TR/TE/Sequence)	Region-of-Interest Voxel Size and Location	Findings
Caetano et al, 2011[73]	43 Patients with BD, euthymic state ($n = 8$), depressed state ($n = 11$), manic state ($n = 12$), mixed state ($n = 12$), medicated ($n = 31$), unmedicated ($n = 12$), (mean age, 13.2 yr), 38 healthy volunteers, (mean age, 13.9 yr)	Inter[b]/1.5T/1500/272/MRSI	8 mL in bilateral medial prefrontal cortex, dorsolateral prefrontal cortex, anterior and posterior cingulate cortices, and occipital lobe	↓ NAA in BD in the left ($P = .002$) and right ($P = .004$) medial prefrontal cortices; ↓ GPC+PC in BD in left ($P = .006$) and right ($P = .002$) right) medial prefrontal cortices; ↓ PCr+Cr in BD in the left medial prefrontal cortex ($P = .005$); ↓ NAA in BD in the left dorsolateral prefrontal cortex ($P = .013$); ↓ PCr+Cr in BD ($P = .011$) in the left dorsolateral prefrontal cortex
Shi et al, 2012[53]	14 Depressed patients with BD, medicated ($n = 6$), unmedicated ($n = 8$), (mean age, 15.6 yr), 24 healthy volunteers, (mean age, 15.7 yr)	Trio[d]/3T/3000/2.3/^{31}P-MRSI; No ^{1}H decoupling; dual-tuned ^{1}H and ^{31}P head coil	15.625 mL in the frontal lobe	↓ Pi/TP in unmedicated BD vs healthy controls; ↑ PCr/Pi ratio in unmedicated BD compared with healthy volunteers (24%; $P = .013$) and with medicated BD (39%; $P = .002$)
Sikoglu et al, 2013[54]	8 Patients with BD, mood state euthymic ($n = 3$), mood state mixed, manic, or depressed ($n = 5$), medicated ($n = 8$), unmedicated ($n = 0$), (mean age, 16.9 yr), 8 healthy volunteers, (mean age, 15.5 yr)	Varian[c]/4T/3000/1.2/^{31}P-MRSI; no ^{1}H decoupling; dual-tuned ^{1}H and ^{31}P head coil	540 mL global sagittal whole-brain slab, 108 mL in the frontal lobe	↓ Global Pi/TP in BD ($P = .021$); ↑ PCr/Pi global ratio in BD ($P = .05$); Frontal pHi increased with age in BD (Spearman $\rho = 0.64$)

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Study	Sample	Methods (Device/FS/TR/TE/Sequence)	Region-of-Interest Voxel Size and Location	Findings
Weber et al, 2013[55]	19 Unmedicated patients with manic BD, (mean age, 15.5 yr), and 14 unmedicated patients with euthymic BD, (mean age, 16.1 yr), 20 healthy volunteers, (mean age, 15.4 yr)	Varian[c]/4T/500/not stated/^{31}P-MRSI and Varian[c]/4T/2000/23/PRESS; no ^{1}H decoupling; dual-tuned ^{1}H and ^{31}P head coil	11-mL effective voxel size in the anterior cingulate cortex	↓ pHi in manic BD vs HC ($P = .03$); ↓ ADP in manic BD vs HC ($P = .01$)

Note:—TR and TE are expressed in milliseconds. FS indicates field strength; 1D-ISIS, adiabatic 1D image-selected in vivo spectroscopy; PRESS, point-resolved spectroscopic sequence; Probe-P(PRESS), proton brain examination single-voxel PRESS; MRSI, multivoxel MRS imaging; ^{31}P-MRSI, multivoxel phosphorus MRS imaging; ↓, decreased; ↑, increased; ^{31}P-MRS, phosphorus 31MRS; ADP, adenosine diphosphate; GPC, glycerophosphocholine; PC, phosphocholine; pHi, intracellular pH; tCre, total creatine; TP, total ^{31}P signal.

[a] GE Healthcare, Milwaukee, Wisconsin.
[b] Philips Healthcare, Best, the Netherlands.
[c] Varian, Palo Alto, California.
[d] Siemens, Erlangen, Germany.

spectroscopy to study cerebral energy metabolism: Shi et al[53] focused on the frontal lobe, Sikoglu et al[54] reported global or "whole brain" findings, and Weber et al[55] interrogated the ACC. Most interesting, none of the studies reported a significant difference between BD and HC in β-nucleoside triphosphate (a proxy measure for ATP), but 2 investigators reported a significant decrease in Pi and an increased PCr/Pi ratio,[53,54] neither of which has been reported in studies of adult BD. In the most recent ^{31}P-MR spectroscopy study of pediatric BD, manic subjects had reduced intracellular pH and lower adenosine diphosphate concentrations in the ACC.[55]

Longitudinal Treatment MR Spectroscopy Studies of Pediatric BD and High-Risk Samples

Longitudinal Studies of the Glutamate System. Strawn et al[76] treated pediatric patients with BD in a manic or mixed episode with valproic acid and performed ^{1}H-MR spectroscopy at baseline, day 7, and day 28 (Table 2). In subjects who achieved clinical remission with valproic acid, the investigators found a decreased baseline Glx and a correlation between a change in the Young Mania Rating Scale[77] scores and decreased Glu in the left ventrolateral prefrontal cortex.[76]

Longitudinal Studies of Mitochondrial Function. Repeated-measures MR spectroscopy studies of treatment response have been conducted in pediatric BD and in high-risk samples of children with a parent with BD. Davanzo et al[78] treated pediatric inpatients with manic BD with lithium and found that decreased mIns was associated with treatment, an effect that was stronger in treatment responders. Patel et al[79] treated adolescents with BD depression with lithium and found that mIns concentrations did not significantly change from baseline, though pretreatment cortical mIns was significantly lower in patients who achieved remission. The same investigators later reported a significant decrease in NAA levels in response to treatment with lithium.[80] DelBello et al[81] treated pediatric patients with mania with olanzapine and found that increased tChol was associated with treatment; in addition, treatment remitters demonstrated increased NAA while nonremitters showed a decrease in NAA. Chang et al[82] randomized subjects with pediatric BD depression to quetiapine or placebo and found that decreased mIns levels were associated with a positive treatment response. One repeated-measures MR spectroscopy study has been performed with a high-risk sample of youth with subsyndromal mood symptoms and at least 1 parent with BD: Chang et al[83] found no significant alterations in NAA, tChol, or mIns associated with valproic acid treatment. However, a large effect size was noted for decreased posttreatment NAA in the right dorsolateral prefrontal cortex.[83]

Cross-Sectional MR Spectroscopy Studies of Youth at Risk for BD

Cecil et al[69] conducted a study of mood-disordered children with a familial risk for BD and found increased mIns and decreased NAA in the high-risk subjects compared with HC (Table 3). Gallelli et al[84] studied children of parents with BD in 3 groups: those with BD, those with subsyndromal BD symptoms, and HC. Measuring NAA, mIns, and tChol, the investigators found no signifi-

Table 2: Longitudinal MRS studies of pediatric bipolar disorder and youth at risk for bipolar disorder

Study	Sample	Methods (Device/FS/TR/TE/Sequence)	Region-of-Interest Voxel Size and Location	Findings
Davanzo et al, 2001[78]	11 Patients with BD mania, medicated ($n = 9$), unmedicated ($n = 2$), (mean age, 11.4 yr), Treatment with lithium for 1 week (mean lithium level = 0.64 mEq/L), Scans obtained at baseline and day 7	Signa[a]/1.5T/3000/30/PRESS	8 mL in the anterior cingulate cortex	↓ mIns/tCre was associated with acute lithium treatment ($P = .047$); ↓ mIns/tCre in lithium responders ($P < .012$); mIns/tCre was not significantly different in lithium nonresponders ($P < .655$); NAA/tCre was the metabolite least affected by lithium
DelBello et al, 2006[81]	19 Unmedicated manic or mixed patients with BD treated with olanzapine, 10–20 mg/day for 4 weeks, (mean age, 14.7 yr), 10 healthy volunteers, (mean age, 15 yr),	Signa/1.5T/2000/35/PRESS	8 mL in the medial ventral prefrontal cortex, 8 mL in the left and right ventral lateral prefrontal cortices, Scans obtained at baseline, day 7, and day 28	↑ tChol in medial ventral prefrontal cortex ($P = .0001$) associated with olanzapine treatment; ↑ baseline tChol in the medial ventral prefrontal cortex associated with remission at 4 weeks ($P = .001$); ↑ NAA for 4 weeks in the medial ventral prefrontal cortex in olanzapine remitters ($n = 11$) vs ↓ NAA in nonremitters ($n = 8$) ($P = .006$); ↑ NAA for 4 weeks was associated with reduction in YMRS scores ($r = 0.68$; $P = .004$)
Patel et al, 2006[79]	28 Unmedicated depressed patients with BD, (mean age, 15.5 yr), Treatment with lithium for 42 days, titrated to serum levels of 1.0–1.2 mEq/L	Signa/1.5T/2000/35/PRESS	8 mL in the medial prefrontal cortex, 8 mL in the left and right lateral prefrontal cortices, Scans obtained at baseline, day 7, and day 42	mIns in medial prefrontal cortex did not significantly differ among baseline, day 7, or day 42; ↓ baseline mIns in medial prefrontal cortex in lithium remitters ($n = 8$) vs non-remitters ($n = 20$) ($P = .003$)
Chang et al, 2009[83]	10 Offspring of BD parents with mood symptoms but not BD, medicated ($n = 3$), unmedicated ($n = 7$), (mean age, 11.3 yr), Treatment with divalproex for 12 weeks; mean serum VPA level = 82 μg/mL	Signa/3T/2000/35/ PRESS	8 mL in the left and right dorsolateral prefrontal cortices, Scans obtained at baseline and 12 weeks	No significant difference in NAA in the left ($P = .88$) or right ($P = .13$) dorsolateral prefrontal cortex associated with 12 weeks of divalproex treatment; Effect size for decreased NAA = 0.94 for the right dorsolateral prefrontal cortex; Exploratory analyses showed no significant differences in tChol or mIns

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Study	Sample	Methods (Device/FS/TR/TE/Sequence)	Region-of-Interest Voxel Size and Location	Findings
Strawn et al, 2012[76]	25 Unmedicated manic or mixed patients with BD (mean age, 14.5),	Varian[b]/4T/3000/23/PRESS	8 mL in the anterior cingulate cortex (gray matter),	↓ Glx at baseline in the left ventrolateral prefrontal cortex in treatment remitters ($P = .01$);
			8 mL in left and right ventrolateral prefrontal cortices (white matter),	In divalproex treatment remitters, change in Glu in the left ventrolateral prefrontal cortex correlated with change in YMRS score ($r = 0.82$; $P = .03$)
	Treatment with divalproex for 28 days, titrated to a serum VPA level of 85–125 μg/mL		Scans obtained at baseline, day 7, and day 28	
Chang et al, 2012[82]	26 Unmedicated depressed patients with BD, Treatment with either quetiapine ($n = 16$) or placebo ($n = 10$) for 8 weeks, (mean age, 15.6 yr)	Signa/3T/2000/26/ PRESS and Varian/4T/2000/26/PRESS	8 mL in the anterior cingulate cortex, 8 mL in the left dorsolateral prefrontal cortex, 8 mL in the right dorsolateral prefrontal cortex	↓ Posttreatment mIns in the ACC in quetiapine responders (5 of 16 patients); no significant change in NAA between the quetiapine and placebo groups

Note:—TR and TE are expressed in milliseconds. FS indicates field strength; PRESS, point-resolved spectroscopic sequence; ↓, decreased; ↑, increased; tCre, total creatine; VPA, valproic acid; YMRS, Young Mania Rating Scale.

[a] GE Healthcare, Milwaukee, Wisconsin.

[b] Varian, Palo Alto, California.

cant between-group differences. Singh et al[85] studied an at-risk sample of offspring of parents with BD, focusing first on the ACC and then on the cerebellar vermis.[86] In the ACC, the authors found decreased absolute Glu concentrations in BD compared with both HC and offspring with subsyndromal BD symptoms.[85] Then, studying at-risk offspring without BD and HC, Singh et al[86] reported decreased cerebellar mIns and tChol. Finally, Wozniak et al[87] measured ACC Glu in children with at least 1 parent with BD, dividing their sample into children with high-versus-low scores on a Child Behavior Checklist[88] profile proposed as a correlate of pediatric BD.[89,90] No group differences in ACC Glu were found, but in the high-score group, there was a positive correlation between Glu levels and Child Behavior Checklist profile scores.[87]

Cross-Sectional and Repeated-Measures MR Spectroscopy Studies of Severe Mood Dysregulation

The publication of the *Diagnostic and Statistical Manual of Mental Disorders,* 5th ed[65] in May 2013 introduced disruptive mood dysregulation disorder as a new mood disorder of childhood (Table 4). Designed to differentiate children who present with severe, nonepisodic irritability from those with BD,[91] disruptive mood dysregulation disorder is closely related to the severe mood dysregulation syndrome defined by Leibenluft[63] and Leibenluft et al.[92] Dickstein et al[93] conducted a series of prescient MR spectroscopy investigations of severe mood dysregulation. In a case-control study, the investigators used ^{1}H-MR spectroscopy to interrogate the frontal, temporal, and parietal cortices in severe mood dysregulation versus HC; their main finding was reduced mIns in the temporal cortex, though female subjects with severe mood dysregulation showed trends toward increased temporal tCr and Glx. The authors then conducted a randomized controlled trial of lithium in severe mood dysregulation, selecting this intervention on the basis of its potential effects on irritability, aggression, and neurometabolism.[94] MR spectroscopy scans were acquired at baseline and repeated following 6 weeks of treatment with lithium or a placebo. A significant treatment Group × Time interaction was found for parieto-occipital Glx, which increased in the lithium group and decreased in placebo group.[94]

DISCUSSION

Pediatric BD is a prevalent and disabling illness, for which progress in timely diagnosis and effective treatment is urgently needed. Research in psychiatry is increasingly focused on biomarker discovery,[95,96] and a consensus is emerging that MR neuroimaging investigations,[16] including multimodal approaches that include MR spectroscopy,[17] offer significant promise in elucidating the pathophysiology of BD.[97]

Findings Related to the Glutamate System in Pediatric BD

It has been proposed that MR spectroscopy studies of the glutamate system may hold the key to elucidating the pathophysiology of BD and to identifying novel treatment interventions.[37] In adults, a consistent pattern has emerged in meta-analyses of the MR spectroscopy mood disorder literature: increased cerebral Glx levels in BD[33,35] and decreased Glx in major depressive disorder.[33,98] In comparison, there have been relatively few pediatric

Table 3: Cross-sectional MRS studies of youth at risk for bipolar disorder

Study	Sample	Methods (Device/FS/TR/TE/Sequence)	Region-of-Interest Voxel Size and Location	Findings
Cecil et al, 2003[69]	9 Patients with euthymic mood disorder with at least 1 parent with BD, medicated (n = 1), unmedicated (n = 8), (mean age, 9.9 yr), 10 healthy volunteers, (mean age, 10.6 yr)	Signa[a]/1.5T/2000/35/PRESS	8 mL in the cerebellar vermis, 8 mL in the medial frontal cortex, 8 mL in frontal lobe white matter	↑ mIns/tCre levels in patients with mood disorder in the medial frontal cortex (16%); ↓ NAA/tCre in patients with mood disorder in the cerebellar vermis (8%); no significant differences in NAA/tCre, tChol/tCre, or mIns/tCre in frontal lobe white matter
Gallelli et al, 2005[84]	60 Offspring of parents with BD, 32 patients with BD, medicated (n = 28), unmedicated (n = 4), (mean age, 14.1 yr), 28 patients with subsyndromal BD symptoms, medicated (n = 20), unmedicated (n = 8), (mean age, 12.2 yr), mood state not reported, though "most subjects were not experiencing a manic or depressive episode at the time of scan," 26 unaffected controls, (mean age, 14.2 yr)	Signa/3T/2000/35/ PRESS	8 mL in the left and right dorsolateral prefrontal cortices	No significant group difference in NAA/tCre in the left (P = .99) or right (P = .75) dorsolateral prefrontal cortex; no significant group difference in mIns/tCre in the left (P = .15) or right (P = .19) dorsolateral prefrontal cortex; no significant group difference in tChol/tCre in the left (P = .31) or right (P = .46) dorsolateral prefrontal cortex
Singh et al, 2010[85]	20 Patients with euthymic BD, medicated (n = 17), unmedicated (n = 3), (mean age, 15.9 yr), 20 euthymic patients with subsyndromal BD, medicated (n = 17), unmedicated (n = 3), (mean age, 12.9), 20 healthy volunteers, (mean age, 15.1 yr)	Signa/3T/2000/35/ PRESS	8 mL in the anterior cingulate cortex	↓ Glu in BD compared with both healthy volunteers (P < .04) and subsyndromal BD (P < .04); no significant group differences in NAA or mIns

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Study	Sample	Methods (Device/FS/TR/TE/Sequence)	Region-of-Interest Voxel Size and Location	Findings
Singh et al, 2011[86]	22 Euthymic youth at risk for BD with a parent with BD, medicated ($n = 17$), unmedicated ($n = 5$), psychostimulants discontinued 24 hours prior to scan, (mean age, 13.3 yr), 25 healthy volunteers, (mean age, 13.5 yr)	Signa/3T/2000/35/PRESS	8 mL in the cerebellar vermis	↓ mIns in children at risk for BD ($P < .01$); ↓ tChol in children at risk for BD ($P < .01$)
Wozniak et al, 2012[87]	24 Euthymic youth at risk for BD, with a parent with BD, medicated ($n = 11$), unmedicated ($n = 13$), (mean age, 11.8 yr), 13 healthy volunteers (mean age, 11.5 yr)	Varian[b]/4T/2000/30/PRESS	8 mL in the anterior cingulate cortex	Positive correlation between emotional dysregulation score and Glu (Pearson correlation = 0.659; $P < .02$)

Note:— TR and TE are expressed in milliseconds. FS indicates field strength; PRESS, point-resolved spectroscopic sequence; ↓, decreased; ↑, increased; tCre, total creatine.

[a] GE Healthcare, Milwaukee, Wisconsin.

[b] Varian, Palo Alto, California.

BD studies of the glutamate system. In line with the adult BD literature, Castillo et al[66] reported elevated Glx in pediatric BD compared with HC. Moore et al[67] reported decreased Glx in BD mania compared with subjects with BD stably treated with risperidone. Using high-field 4T scans, these investigators were also able to parse the Gln and Glu resonances in the ACC. Most intriguing, they found decreased Gln in untreated youths with BD compared with both stably medicated patients with BD and HC.[67] Taken together with the fact that there was no difference in Glu among the 3 groups,[67] this finding suggests that the Gln/Glu ratio measured in adult BD investigations[99,100] merits further study in pediatric BD. Finally, in a longitudinal valproic acid treatment study, Strawn et al found decreased baseline Glx in treatment remitters and decreases in Young Mania Rating Scale scores correlated with decreased Glu concentrations.[76] The authors concluded that the predictive value of MR spectroscopy neuroimaging "may relate to a disturbance in either glutamine or GABA, or in the homeostatic equilibrium of Glu and glutamine,"[76] providing further support for the exploration of the Gln/Glu ratio as a potential biomarker in pediatric BD.

Findings Related to Mitochondrial Dysfunction in Pediatric BD

There are 5 reports of decreased cortical NAA concentrations in pediatric BD,[69-73] and 1 study of adolescent BD depression that found increased NAA in the left ventral lateral prefrontal cortex, right ventral lateral prefrontal cortex, and ACC.[74] In addition, Castillo et al[66] reported no difference in cortical NAA between BD and HC, though the study may have been limited by its sample size. Most interesting, Chang et al[70] found normal NAA levels in the dorsolateral prefrontal cortex of youth at risk for BD who had not yet experienced mania, suggesting that alterations in NAA may be a marker for fully syndromal cases of in BD.[101] Longitudinal studies of NAA have shown mixed results: increased prefrontal NAA in BD manic olanzapine remitters[81]; decreased prefrontal NAA in depressed adolescents with BD treated with lithium[80]; and no significant change in NAA following treatment with lithium,[78] quetiapine in BD depression,[82] or youth at risk for BD treated with valproic acid.[83] While additional work will be required to confirm the role of NAA in pediatric BD, the 5 case-control studies[69-73] showing decreased NAA are in agreement with the findings in the adult literature.

Studies of mIns have reported an increase in pediatric BD in both the manic[75,78] and depressed mood state.[74] In addition, Davanzo et al[78] showed that decreased ACC mIns is associated with a positive response to acute lithium treatment, a finding that is consistent with the molecular mechanism common to mood-stabilizing medications.[102]

To date, only three ^{31}P-MR spectroscopy studies of pediatric BD have been published. Shi et al[53] studied 14 depressed subjects with BD and 24 HC and found that unmedicated BD had decreased ACC Pi compared with both HC (17%; $P = .038$) and medicated BD (24%; $P = .022$). In a study of 8 subjects with BD and 8 HC, Sikoglu et al[54] reported that compared with HC, subjects with BD had reduced global Pi. The relevance of Pi to mitochondrial dysfunction in BD may be the fact that Pi is a regulator of oxidative phosphorylation, the metabolic pathway for ATP

Table 4: Cross-sectional and repeated-measures MRS studies of severe mood dysregulation

Study	Sample	Methods (Device/FS/TR/TE/Sequence)	Region-of-Interest Voxel Size and Location	Findings
Dickstein et al, 2008[93]	36 Euthymic unmedicated patients with severe mood dysregulation, (mean age, 12.2 yr),	Signa[a]/1.5T/2000/30/PRESS	8 mL in the right frontal cortex,	↓ mIns/tCre in severe mood dysregulation in the left temporal lobe ($P = .03$);
			8 mL in the left temporal cortex,	no significant group differences in mIns/tCre, NAA/tCre, or Glx/tCre in the other regions of interest;
	43 healthy volunteers, (mean age, 12.9 yr)		8 mL in the central parieto-occipital lobe,	females with severe mood dysregulation showed trends toward
			8 mL in the left parietal lobe	↓ mIns/tCre in the left temporal cortex ($P = .07$), ↑ tCre in the left temporal cortex ($P = .08$), and ↑ Glx/tCre in the left parietal lobe ($P = .08$)
Dickstein et al, 2009[94]	25 Euthymic unmedicated patients with severe mood dysregulation, randomized to 6 weeks of treatment with	Signa/1.5T/2000/30/PRESS	8 mL in the right frontal cortex,	There was a significant Group × Time interaction for Glx/tCre in the parieto-occipital lobe ($P = .01$), with ↑ Glx/tCre in the lithium group and ↓ Glx/tCre in the placebo group;
	lithium ($n = 14$; mean age, 10.8 yr; mean serum lithium level = 0.82 mmol/L)		8 mL in the left temporal cortex,	Group × Time interactions for mIns/tCre, NAA/tCre, and Glx/tCre in the other regions of interest were nonsignificant
	or		8 mL in the central parieto-occipital lobe,	
	placebo ($n = 11$; mean age, 12.1 yr)		8 mL in the left parietal lobe, scans obtained at baseline and 6 weeks	

Note:—TR and TE are expressed in milliseconds. FS indicates field strength; PRESS, point-resolved spectroscopic sequence; ↓, decreased; ↑, increased; tCre, total creatine.

[a] GE Healthcare, Milwaukee, Wisconsin.

production.[78,103] Furthermore, it is thought that the only Pi that is detectable by nuclear MR imaging is involved in oxidative phosphorylation.[104,105] Mammalian cells in which oxidative phosphorylation is impaired can reduce the concentration of free Pi via compartmentation to the inner mitochondrial membrane, which immobilizes the phosphorus ions and renders them invisible to MR spectroscopy.[106-108] In addition, Pi has a direct effect in vitro on glucose use in cortical neurons.[109]

It has been posited that decreased ATP consumption leads to a fall in cytosolic Pi, to a level that balances ATP synthesis and use,[110,111] thus stabilizing the phosphorylation potential of the cell.[107,108] Additional support for the potential relevance of Pi in the pathophysiology of BD is provided by the observation that the activity of sodium–potassium adenosine triphosphatase (Na+ / K ± ATPase), an enzyme partially regulated by Pi,[97-101,112-114] is altered in patients with BD.[115] In the third and most recent ^{31}P-MR spectroscopy study of pediatric BD, Weber et al[55] found reduced intracellular pH and decreased adenosine diphosphate concentrations in the ACC. These results are in line with the consistent finding of reduced intracellular pH in studies of adult BD[36] and with the discovery of Chance et al[116] that adenosine diphosphate is one of the principal controllers of oxidative metabolism.

Limitations of Pediatric MR Spectroscopy Studies

Despite the consistent difference in the glutamatergic entity Glx between patients with BD and controls found by 3 independent analyses of the adult MR spectroscopy literature[33-35] and the reports of glutamatergic alterations in pediatric BD discussed here, there are uncertainties associated with MR spectroscopy measures of Glu. In the brain, Glu plays at least 3 key roles: It is the major excitatory neurotransmitter, it serves as the precursor for the major inhibitory neurotransmitter GABA, and it is involved in the synthesis of smaller metabolites, including glutathione, as well as larger peptides and proteins.[117] Glu is involved in a variety of metabolic pathways, including the neuronal tricarboxylic acid cycle, the astrocytic tricarboxylic acid cycle, pyruvate carboxylation, and the glutamate-glutamine cycle that links neuronal and astrocytic metabolism.[118] This metabolic compartmentation leads to spatial uncertainty because Glu is present in glutamatergic neurons, GABAergic neurons, and astrocytes, in addition to extracellular spaces. The published studies of pediatric BD do not parse these multiple Glu pools in terms of either function or location.

Another important limitation of the extant pediatric BD MR spectroscopy literature is the static nature of the measurements reported. Static measures are likely to be insufficient in generating a comprehensive picture of BD pathophysiology because brain metabolism is predominantly made up of dynamic processes (ie, enzyme-catalyzed reactions and the transfer of chemical groups through metabolic pathways). Therefore, elucidation of BD etiopathogenesis may require the use of techniques capable of dynamic in vivo measures. Two examples of these that may find application in the study of BD are magnetization transfer, which can be used to measure the K_f of the creatine kinase reaction,[56] and dynamic ^{13}C MR spectroscopy, which has been validated as a method for studying neuronal bioenergetics and Glu neurotransmission and cycling.[119]

Future Translational Directions in MR Spectroscopy Studies of Pediatric BD

Improved diagnosis and treatment for pediatric BD are urgently needed: While the evidence suggests that pediatric bipolar illness is continuous with adult BD,[38-40] the delay to first appropriate treatment experienced by individuals with childhood-onset BD averages more than 16 years.[11] To date, MR spectroscopy studies of pediatric BD comprise a small, albeit rapidly expanding, literature. On the basis of its ability to measure neurochemical entities relevant to glutamatergic and mitochondrial function in vivo, MR spectroscopy will play a vital role in future translational studies of pediatric BD diagnosis, treatment development, and personalized medicine.[37,120] Cross-sectional studies are needed to determine whether MR spectroscopy can reliably distinguish pediatric BD from disorders with overlapping symptoms, such as disruptive mood dysregulation disorder, attention deficit/hyperactivity disorder, and, especially, major depressive disorder.[121] Comparison with MR spectroscopy studies of normal brain development[122] will shed light on the natural history of BD and point investigators toward opportunities for intervention. Longitudinal studies may determine the predictors of continuity with adult BD and whether timely treatment is capable of altering the course of BD in at-risk individuals. Novel study designs combining MR spectroscopy with other neuroimaging methods in a multimodal approach can be used to increase the dimensionality of the information gleaned from a study sample.[17,123,124] Finally, future studies would benefit from larger sample sizes because it has been calculated that MR spectroscopy investigations require analyzable data on at least 39 affected subjects and 39 HC to have adequate power to detect a 10% group difference in neurometabolite concentrations.[125,126]

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