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Neurochemical deficits in the cerebellar vermis in child offspring of parents with bipolar disorder

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Abstract

Objectives—We aimed to compare concentrations of N-acetyl aspartate, *myo*-inositol, and other neurometabolites in the cerebellar vermis of offspring at risk for bipolar disorder (BD) and healthy controls to examine whether changes in these neuronal metabolite concentrations occur in at-risk offspring prior to the onset of mania.

Methods—A total of 22 children and adolescents aged 9–17 years with a familial risk for bipolar I or II disorder [at-risk offspring with non-bipolar I disorder mood symptoms (AR)], and 25 healthy controls (HC) were examined using proton magnetic resonance spectroscopy at 3T to study metabolite concentrations in an 8-cc voxel in the cerebellar vermis.

Results—Decreased *myo*-inositol and choline concentrations in the vermis were seen in the AR group compared to HC ($p < 0.01$).

Conclusions—Decreased cellular metabolism and interference with second messenger pathways may be present in the cerebellar vermis in youth at risk for BD as evident by decreased *myo*-inositol and choline concentrations in this region. These results may be limited by a cross-sectional design, co-occurring diagnoses, and medication exposure. Longitudinal studies are necessary to determine whether early neurochemical changes can predict the development of mania. Improved methods for identifying children with certain neurochemical vulnerabilities may inform preventive and early intervention strategies prior to the onset of mania.

Keywords

cerebellar vermis; familial bipolar disorder; lithium; *myo*-inositol; risk

Recent investigations of the neural aspects of emotion have discovered that in addition to regulating motor coordination, balance, and speech, the cerebellum may play an important role in the regulation and monitoring of emotion (1). This is evident by affective disturbances following damage (2) or experimental manipulation (3) to the cerebellum. The cerebellum has rich bidirectional connections to key regions in the cerebral cortex that modulate emotion (4), as suggested by examination of cerebellar projections (5) and demonstration of reduced cerebral gray matter in frontal, parietal, and temporal cortices following cerebellar damage (6). Based on these studies, theories of emotion regulation have

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involved complex interactions between cortical and cerebellar neural circuits during an emotional experience.

In studying the functional topography of the cerebellum, medial portions of lobule VII of the cerebellum appear to be particularly involved in the regulation of certain emotional processes and to connect to limbic circuitry (7). Disruption of the vermis has been associated with a phenomenon called cerebellar cognitive affective syndrome (8), described as a constellation of behavioral and personality changes including flattening of affect or disinhibition. Individuals with this syndrome have been described as being overfamiliar, flamboyant, and impulsive, and as making inappropriate comments or showing regressive and childlike behaviors.

These symptoms are similar to those found in individuals with bipolar disorder (BD), a psychiatric syndrome principally characterized by impulsivity and dysregulation of emotion and attention. Moreover, structural and neurochemical imaging investigations have provided evidence of cerebellar abnormalities in populations with BD. Adults with BD between the ages of 18 and 45 years who had experienced multiple episodes of mania have shown reduced V3 vermal volumes compared to participants with first-episode mania and to healthy volunteers (9), suggesting a neurodegenerative process associated with multiple depressive and manic episodes. This finding in the posterior-inferior cerebellar vermis was replicated by the same group and found to extend to the V2 subregion in individuals with multiepisode BD (10). In an adolescent sample, mean V2 subregion volumes were inversely correlated to number of previous affective episodes, particularly in males (11). However, a different study showed enlargement of total vermal volume in adults with BD compared to healthy controls, driven primarily by male gender (12). Increases in left cerebellar vermal size have been found by voxel-based morphometry in healthy relatives of individuals with BD, suggesting that an enlarged vermis may be related to resilience from expression of BD and more adaptive affect regulation (13).

The above studies may have shown varying results due to variations in size measurement techniques, sample selection as related to stage of illness, or medication exposure. Nevertheless, macroscopic increases or decreases of the cerebellar size in BD suggest underlying cellular and molecular dysfunction at a microscopic level that warrants further investigation. Proton magnetic resonance spectroscopy (^{1}H-MRS) is a noninvasive neuroimaging method that provides biochemical data that can be used to quantitatively examine the potential role of the vermis as a biomarker for developing BD.

Few studies to date have examined neurochemical processes that may be occurring in the vermis leading to the disrupted emotional processes observed in BD. A promising strategy for understanding the early progression of this illness is to study young subjects who are at familial risk for BD (i.e., have a parent with BD), but do not yet have a mood disorder themselves. Specifically, since offspring studies demonstrate that children with a BD parent have an elevated risk of developing BD or associated symptoms of mood dysregulation (14), such offspring are likely to have brain structural, functional, and chemical characteristics that are critical to the pathogenesis of the disorder. One prior MRS study of BD offspring showed increased orbitofrontal *myo*-inositol (*myo*-Ino), a marker for cellular metabolism and related second messenger signaling pathways, and reductions in N-acetyl aspartate (NAA), a healthy nerve cell marker putatively involved in maintaining fluid balance, energy production, and myelin formation in the cerebellar vermis (15). This single investigation of neurochemical characteristics in the cerebellum in familial BD warrants replication in a larger sample to definitively determine the role of the cerebellar vermis in modulating neuronal signaling in individuals who are at familial risk for BD but have not yet developed a fully syndromal manic episode. This line of investigation would help determine whether

altered neurochemical processes in the cerebellar vermis are a consequence of disease progression or represent an endophenotype for BD.

To address this question, we used ^{1}H-MRS to compare neurochemical levels among children of parents with BD [at-risk offspring with non-bipolar I disorder mood symptoms (AR)] who have some mood symptoms but have not developed a full manic episode and healthy controls (HC). Based on prior studies demonstrating neurometabolite differences in regions involved in emotion regulation, we hypothesized that AR would demonstrate abnormalities in NAA and *myo*-Ino concentrations in the cerebellar vermis as compared to HC, which would then correlate to more severe subsyndromal mood symptomatology. An additional exploratory aim was to compare vermal glutamate- and choline (Cho)-related metabolite concentrations in these populations given their prior association with bipolar illness (16).

Methods and materials

Subjects

Stanford University's Panel of Medical Research in Human Subjects approved this research protocol. After complete description of the study to the subjects and their parents, written informed consent was obtained from the parents, and written assent was obtained from the children. For the AR group, 22 children of parents with bipolar I or II disorder, aged 9–17 years, were recruited from ongoing studies of high-risk offspring within a Pediatric Bipolar Disorders Program and from the community. HC children of parents without any DSM-IV Axis I disorder with comparable age, Tanner stage, race, sex, socioeconomic status, and handedness were recruited for study participation from community advertisements and local schools (n = 25). All participants were evaluated for psychiatric disorders by semistructured interviews. The Structured Clinical Interview for DSM-IV (SCID-P) (17) was administered to all parents by raters with established symptom and diagnostic inter-rater reliability (kappa > 0.9). All children were evaluated for lifetime psychiatric diagnoses using the Affective and Psychotic Modules of the Washington University in St. Louis Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U KSADS) (18) and the Kiddie Schedule of Affective Disorders and Schizophrenia Present and Lifetime version (KSADS-PL) (19), administered separately to parents and children by raters with established symptom and diagnostic reliability (kappa > 0.9). Diagnostic decisions were ultimately made by a board-certified child psychiatrist (KDC) based on personal interview or discussion with a master's-level research assistant. Current and lifetime diagnoses and onsets and offsets of hypomanic episodes were established using DSM-IV criteria.

In addition to a parental BD diagnosis, subjects included in the AR group met criteria for moderate mood dysfunction by a score of > 10 on the Young Mania Rating Scale (YMRS) (20) or a score of > 29 on the Children's Depressive Rating Scale-Revised (CDRS-R) (21), but did not meet symptom duration or severity criteria for a fully syndromal manic episode, either at the time of assessment or historically. Subjects in the AR group received a diagnosis of BD not otherwise specified (NOS) if they were missing only one DSM-IV-TR criterion for mania or had all criteria but only had 2–4 days of episode duration (22) and did not have a concurrent diagnosis of major depression. Global functioning in all participants was determined using the Clinical Global Assessment Scale (CGAS) (23). The HC group was comprised of healthy volunteers with no DSM-IV psychiatric diagnosis or psychotropic medication exposure. In addition, the HC had parents without any psychiatric diagnosis by SCID, and no first- or second-degree relative with BD as assessed by the Family History Research Diagnostic Criteria (24). Exclusion criteria for all subjects included a neurological condition (such as a seizure disorder), substance use disorder, IQ < 80, or presence of metallic implants or braces. All subjects were assessed and scanned in an outpatient setting. Psychostimulant medications were discontinued 24 hours before the MRS, primarily due to

a concurrent, separate functional magnetic resonance imaging (fMRI) study of attention. Other medications including mood stabilizers, atypical antipsychotics, and antidepressants were continued to avoid any risk of mood destabilization. Thorough medication histories were obtained and used for exploratory and covariate analyses of ^{1}H-MRS findings.

Proton magnetic resonance spectroscopy

After psychiatric diagnostic interviews, subjects were scanned by ^{1}H-MRS using a 3 Tesla Signa MRI system with Echospeed gradients (GE Healthcare, Milwaukee, WI, USA) using a custom-built quadrature birdcage receiving head coil with a 50% advantage in signal-to-noise ratio (SNR) over that provided by the standard GE head coil. Forty axial slices (2 mm thick, 3 mm skip) parallel to the anterior-posterior commissure plane and covering the entire brain were acquired with a temporal resolution of 3 minutes using a T2-weighted gradient-echo spiral pulse sequence [fast spin echo, repetition time (TR) = 4,000 msec, echo time (TE) = 68 msec, echo train length = 12, receiver bandwidth = 15.63 kHz, 22 cm field of view; 256 × 256 matrix; acquired resolution = 5.0 × 0.9 × 1.2 mm^3]. Images were then reconstructed as an 18 × 256 × 256 matrix with a 5.0 × 0.9 × 0.9 mm^3 spatial resolution. These T2-weighted images were used to localize and prescribe a voxel in the cerebellar vermis.

Spectroscopic data were acquired within a 2 × 2 × 2 voxel that was placed in the cerebellar vermis according to the 18 × 256 × 256 anatomical image set using the following parameters: PRESS localization, TR/TE = 2,000/35 msec, 2 × 2 × 2 cm voxel in the medial cerebellum using a midline T2 anatomical image in the axial plane (see Fig. 1). An investigator blind to group status visually inspected the prescription of each voxel to ensure proper placement in the region of interest. The voxel was placed in the cerebellar vermis posterior to the fourth ventricle to maximize tissue components and minimize cerebrospinal fluid (CSF) contribution. MRS scans used 32 averages, 1 kHz spectral bandwidth, 1 k data points, with water-suppressed and -unsuppressed frames, and a scan length of 1 min 44 sec. The metabolite spectra were reconstructed using the water-suppressed frames, while the water-unsuppressed frames were used by LCModel version 6.20 (25) for *absolute* quantification expressed in institutional units. A field strength of 3T made it possible to obtain adequate SNR with a relatively short acquisition time (26). The fully automated PROBE/SV quantification tool (GE Medical Systems, Milwaukee, WI, USA) was used for data acquisition and LCModel was used to process the MRS data, enabling examination of both absolute and relative to creatine (Cr) concentrations of *myo*-Ino and NAA. The role of other neurometabolites that may be implicated in BD risk, including glutamate, glutamate/glutamine (Glx), and Cho (a composite of phosphocholine and glycerophosphocholine), were also explored (see Fig. 2 for representative spectra). Cramer-Rao spectral inclusion criteria were SD < 15% for *myo*-Ino, NAA, Cho, and Cr, and SD < 25% for glutamate and Glx, to replicate assumptions made by previous research measuring these neurochemicals in youths at risk for BD (27). Measurements not meeting these standards were excluded from group analysis. Voxel segmentation was not performed in this region due to the mixed tissue composition of the cerebellum.

Statistical analysis

All statistical analyses were performed using SAS software, version 8.02 (SAS Institute, Cary, NC, USA). *T*-tests and Fisher's Exact tests were used to compare demographic and clinical characteristics between groups. MRS data were first examined for normality using univariate analyses and demonstrated non-normal distributions, requiring the use of nonparametric statistics (Shapiro-Wilks statistic, $W > 0.76$; $p < 0.0001$). Difference in *myo*-Ino and NAA concentrations in the vermis were considered the primary outcome measures and were compared among groups using Wilcoxon rank sums with a Bonferroni-corrected

significance threshold of $p \leq 0.025$. *Myo*-Ino and NAA as a ratio to Cr was measured to confirm the stability of the absolute *myo*-Ino and NAA concentrations observed between groups. Other absolute and relative to Cr metabolite concentrations, including Cho, glutamate, and Glx, were considered secondary and exploratory, with a significance threshold of $p \leq 0.017$ to adjust for multiple comparisons. Using two-tailed statistical tests, metabolite concentration was the dependent variable and group status (AR or HC) was the independent variable. Effect sizes for group differences in metabolite concentration were calculated to identify the largest difference between groups based on mean values and variance using the equation $d = M_1 - M_2 / s_{pooled}$ where d = effect size, $M_1 - M_2$ is the difference between the two groups' mean values, and s_{pooled} = the pooled standard deviations of the two groups. An effect size of (d) > 0.50 is considered a medium effect and of potential clinical relevance (28).

Pearson correlations were performed to explore relationships between metabolites in the cerebellar vermis and clinical scores for depression (CDRS-R), mania (YMRS), and overall functioning (CGAS). Because of these multiple comparisons, a Bonferroni-type correction was applied to adjust significance threshold to $p < 0.001$ for these exploratory analyses.

Results

Cohort

There were no statistically significant group differences in age, gender, socioeconomic status, or IQ between the two groups (Table 1). There was a wider distribution of ethnicities in the HC group compared to the AR group, but the between-group metabolite differences presented below did not change significantly when matching the two groups on this factor. In the AR group, mood diagnoses included major depressive disorder (MDD) (n = 14) and BD-NOS (n = 6), with subsyndromal level YMRS (mean = 12.5 ± 7.4) and CDRS (mean = 33 ± 6.5) scores, suggesting a mild severity of mood symptoms at the time of the scan. These scores were significantly higher than those of the HC group ($p < 0.05$). Other comorbid disorders in the AR group included attention-deficit hyperactivity disorder (n = 12), oppositional defiant disorder (n = 6), and anxiety disorders including generalized anxiety (n = 10), separation anxiety (n = 2), specific phobia (n = 3), and anxiety disorder NOS (n = 1) (Table 2). None of the subjects in any group had a present or past substance use disorder. Overall level of functioning represented in CGAS scores were significantly higher in the HC group relative to the AR group [$t(38) = 24.4$, $p < 0.0001$].

Nineteen (85%) subjects in the AR group had at some time in their life been exposed to psychotropic medications. Prior to discontinuation of psychostimulants 24 hours before the scan, 32% were being actively treated with psychostimulants, 32% with antidepressants, 27% with atypical antipsychotics, 18% with lamotrigine, and 5% with lithium; no one was treated with valproate. The percentages of subjects in the AR group with lifetime exposure to various medications were as follows: 41% to stimulants; 32% to antidepressants; 45% to atypical antipsychotics and mood stabilizers, including 18% to lamotrigine, 5% to lithium, and 0% to valproate.

Spectroscopy results

NAA concentrations showed no statistically significant group differences [$Z = 0.42$, $p = 0.68$, (d) = 0.15]. However, *myo*-Ino and Cho concentrations were significantly lower in the AR group than in the HC group [*myo*-Ino: 6.30 ± 2.06 versus 7.19 ± 1.67, respectively; $Z(47) = 2.39$, $p < 0.01$, (d) = 0.47; Cho: 2.22 ± 0.50 versus 2.61 ± 0.53, respectively; $Z(47) = 3.06$, $p < 0.002$, (d) = 0.76] (Table 3; Fig. 3; Fig. 4). These results remained unchanged even after restricting our analyses to unmedicated subgroups. A trend for between-group

differences in *myo*-Ino/Cr concentration [$Z = 1.67$, $p = 0.09$, (d) = 0.27] and significant group difference in Cho/Cr concentration [$Z = 2.67$, $p = 0.008$, (d) = 0.68] supported the primary result observed for absolute concentrations of these metabolites. Cr concentrations between groups were not significantly different but demonstrated the largest effect size for group difference ($d = 0.63$). Exploratory nonparametric tests of glutamate and Glx in absolute and relative concentrations to Cr were not statistically significant for the vermal region examined here (Table 3).

No significant correlations between YMRS, CDRS-R, or CGAS scores and metabolite concentrations were found within the AR group after correcting for multiple comparisons (highest value for Cho/Cr correlated to CDRS: $R = 0.26$, $p = 0.24$).

Discussion

This study aimed to replicate and expand on a previous finding of reduced NAA in the cerebellar vermis in children at risk for BD (15) as a potential early risk marker for bipolar illness. While we did not find any differences in NAA between AR and HC offspring, our findings indicate that AR had decreases in cerebellar vermis *myo*-Ino absolute concentrations, trends for decreases in *myo*-Ino relative to Cr, and decreases in Cho absolute and relative to Cr concentrations in this region compared to HC. *Myo*-Ino reductions may be associated with altered cellular signaling (29) via second messenger pathways, regulation of neuronal osmolarity, and metabolism of membrane-bound phospholipids (16) even prior to the development of a fully symptomatic clinical course of mania. Similarly, reductions in Cho could reflect disruption in cell membrane synthesis, maintenance, and repair (30). Exploratory analyses did not reveal any statistically significant differences in any other metabolites among AR or HC. Moreover, effect sizes for all metabolites examined were, for the most part, modest, suggesting that larger samples would be needed to detect neurochemical differences that may be clinically relevant.

A signal for changes in *myo*-Ino concentrations in youth at risk for BD is partially consistent with and adds to one prior study that showed *myo*-Ino increases rather than decreases in the medial prefrontal cortex in symptomatic children at risk for BD (15). Cecil et al. suggested that elevated *myo*-Ino concentrations may represent phosphoinositide cycle abnormalities in prefrontal regions in individuals with BD, which may be susceptible to treatment with lithium. In a lithium-exposed group, lithium may be working to inhibit inositol monophosphatase and polyphosphate-1-phosphatase (31). Similarly, increased Cho concentrations have been reported in the anterior cingulate cortex in medicated adults with BD compared to HC (32). Given the known functional relationship between the prefrontal cortex and cerebellum (33), it is possible that relative decreases in *myo*-Ino and Cho in the cerebellar vermis observed in our study are due to prefrontal sequestration of these molecules or represent a compensatory down regulation of signaling in an activated frontocerebellar circuit.

Decreased *myo*-Ino and Cho levels have also been reported in individuals who have already developed BD, suggesting the need to consider other mechanisms by which risk for BD might be neurochemically conferred. For example, BD adults with histories of drug abuse showed reduced dorsolateral prefrontal *myo*-Ino concentrations relative to adults with co-occurring BD and alcohol dependence (34). In our study, AR participants did not have any histories of substance use, but Nery et al. (34) did suggest that inositol second messenger systems may be disrupted by mood symptoms that may place individuals at increased risk for developing morbidities like substance dependence. This risk hypothesis was recently supported by a study showing increased rates of substance use disorders in offspring at risk for BD relative to HC (35). High-risk offspring in this study were also more likely to

develop substance use problems during or after the first major mood episode (35). Further prospective analyses in AR youth are warranted to determine whether the combination of decreased brain *myo*-Ino and mood symptoms represents an early risk marker for a subset of individuals who develop both BD and substance use disorders. In medication-free adults with BD, reduced Cho concentrations have also been shown in the left dorsolateral prefrontal cortex compared to HC (36). In our study, reductions in vermal *myo*-Ino and Cho may reflect hypometabolism (37) or an early neurodegenerative process that parallels volumetric reductions seen in the cerebellum of individuals who have already developed BD (9,10).

One potential benefit of examining AR youth is that they may be medication naïve or have limited lengths of medication exposure. Although 86% of our AR youth had been exposed to at least one medication in their lifetime, only one person had been exposed to lithium, whose exclusion from our analysis yielded the same results. Lithium may increase brain concentrations of *myo*-Ino (38) and exert its mood-stabilizing effects by normalizing the phosphoinositol second messenger system (39). An indication of lithium effects on peripheral *myo*-Ino is illustrated by decreased serum *myo*-Ino concentrations found in lithium-naïve adults with BD relative to lithium-treated individuals with BD and to HC (40). Although serum *myo*-Ino levels were not measured in our study, decreased *in vivo* brain *myo*-Ino in our lithium-naïve AR group is consistent with decreased peripheral *myo*-Ino in lithium-naïve adults with BD. In another study, reduced Cho concentrations in frontotemporal regions did not appear to be influenced by chronic lithium or valproate exposure in euthymic adults with BD (41), suggesting that even chronic exposure to these agents is unlikely to confound our Cho result. Although several previous MRS studies have implicated inositol in the pathophysiology of BD [see Potter et al. (42) for review], it is not yet clear whether early exposure to lithium or other medications would confer neuroprotection from progression to mania in children who may be at familial risk for developing BD. Future studies with larger sample sizes are needed to clarify the impact of medication exposure on *in vivo* neurochemistry.

Other studies have found no significant brain *myo*-Ino or Cho differences in individuals at risk for BD (43,44). These differences might be due to diagnostic and developmental heterogeneity, mood state at the time of scan, partial volumes of gray and white matter in the region of interest, and other demographic variables. Systematic reviews of the MRS studies to date in individuals with BD suggest developmental differences in that children with BD appear to show increases in *myo*-Ino both in euthymic and manic states, whereas this is not typically seen in adults (16). Similarly, frontal lobe decreases in Cho concentrations have been reported for adolescents and young adults during manic or mixed mood states (30). Our data did not appear to show any mood state-related influences on metabolite concentrations, and therefore might represent a trait rather than state finding of early abnormalities in this metabolic system. Further prospective examination of acute and chronic changes of *myo*-Ino and Cho in the brain and their response to treatment is warranted to understand its relationship to different stages of bipolar illness.

Several limitations need to be acknowledged for the current study. Voxel placement was based on anatomical landmarks that provided some framework for reliable placement but still may have varied slightly across subjects. Due to limitations in scanning children for prolonged periods of time, scanner drift and the possibility of overlapping resonances due to the short TE (35 msec) may have caused sources of variance in our spectral measurements across all groups. We capitalized on the higher 3T field strength used in our study to overcome these issues by providing better peak separation and SNR compared to 1.5 T magnets, although at field strengths greater than 3T the SNR and spectral separation for ^{1}H NMR spectroscopy may be superior (45). Segmentation of the voxel placed in the cerebellar

vermis was not performed and may be a limitation of this study in that variable tissue composition within that voxel might affect metabolite concentrations in that region. However, the cerebellum has a highly uniform cytoarchitecture compared to the cerebral cortex (46), which would likely be consistent across all of our participants. Moreover, we sought to place the voxel posterior to the fourth ventricle to maximize tissue components (47) and minimize CSF contributions or size differences across groups. Sample heterogeneity due to co-occurring diagnoses and medication exposure limit this analysis due to insufficient sample sizes to examine individual effects of these factors. Finally, not all individuals with a familial risk for BD and non-bipolar I disorder mood symptoms may go on to develop fully syndromal mania. Future longitudinal studies are warranted to substantiate that vermal deficits in *myo*-Ino and Cho represent endophenotypes for BD.

Our findings suggest that AR children exhibit deficits in *myo*-Ino and Cho concentrations in the cerebellar vermis relative to HC even prior to the onset of fully syndromal mania. Potential for cell signaling deficits due to these metabolite reductions may have important implications in the evolution of mood symptoms in this high-risk sample. Further longitudinal studies are necessary to determine whether early chemical changes can predict the development of mania. Improved methods for identifying children with certain neurochemical vulnerabilities may inform preventive and early intervention strategies prior to the onset of a fully syndromal bipolar syndrome.

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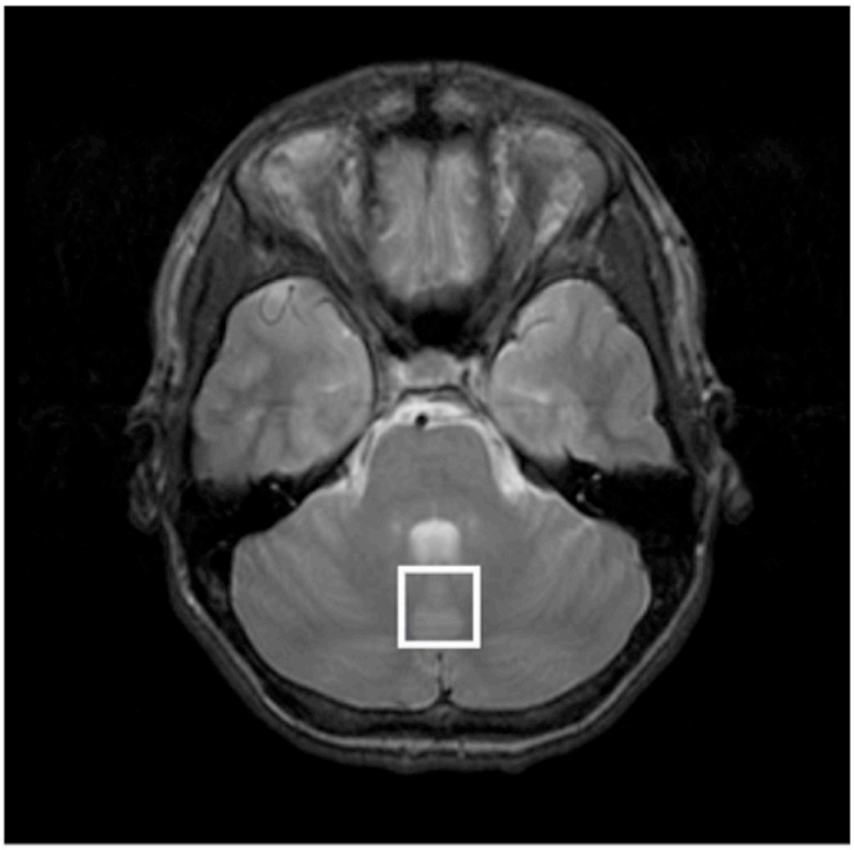

Fig. 1.
Anatomical localization of cerebellar vermis sampled in this study.

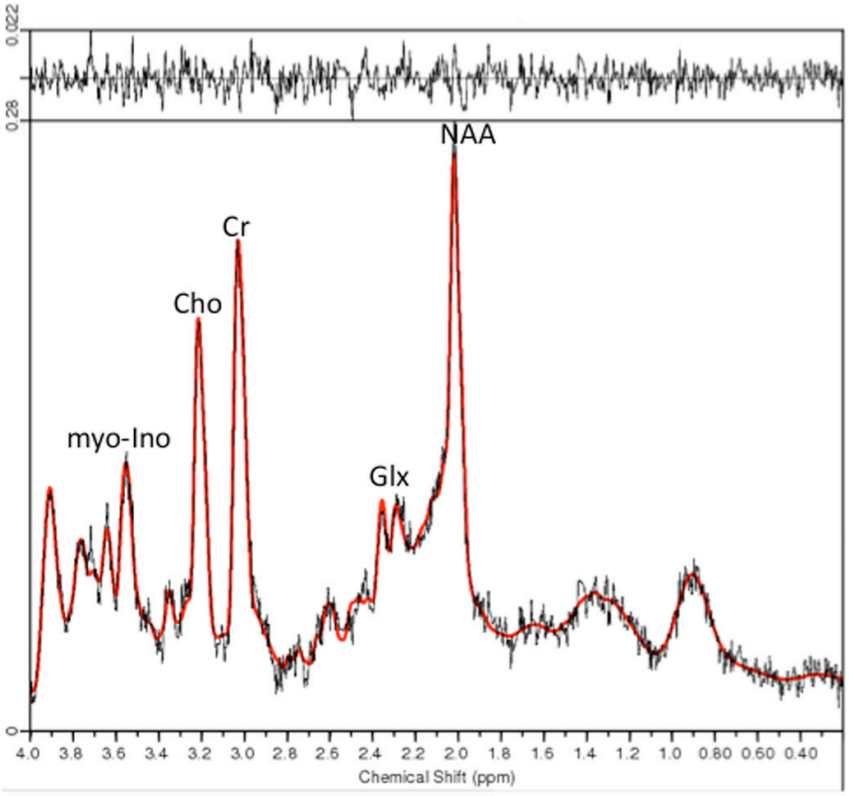

Fig. 2.

Sample magnetic resonance spectrum in LCModel (version 6.20) (25). *myo*-Ino = *myo*-inositol; Cho = choline; Cr = creatine; Glx = glutamate + glutamine; NAA = N-acetyl aspartate.

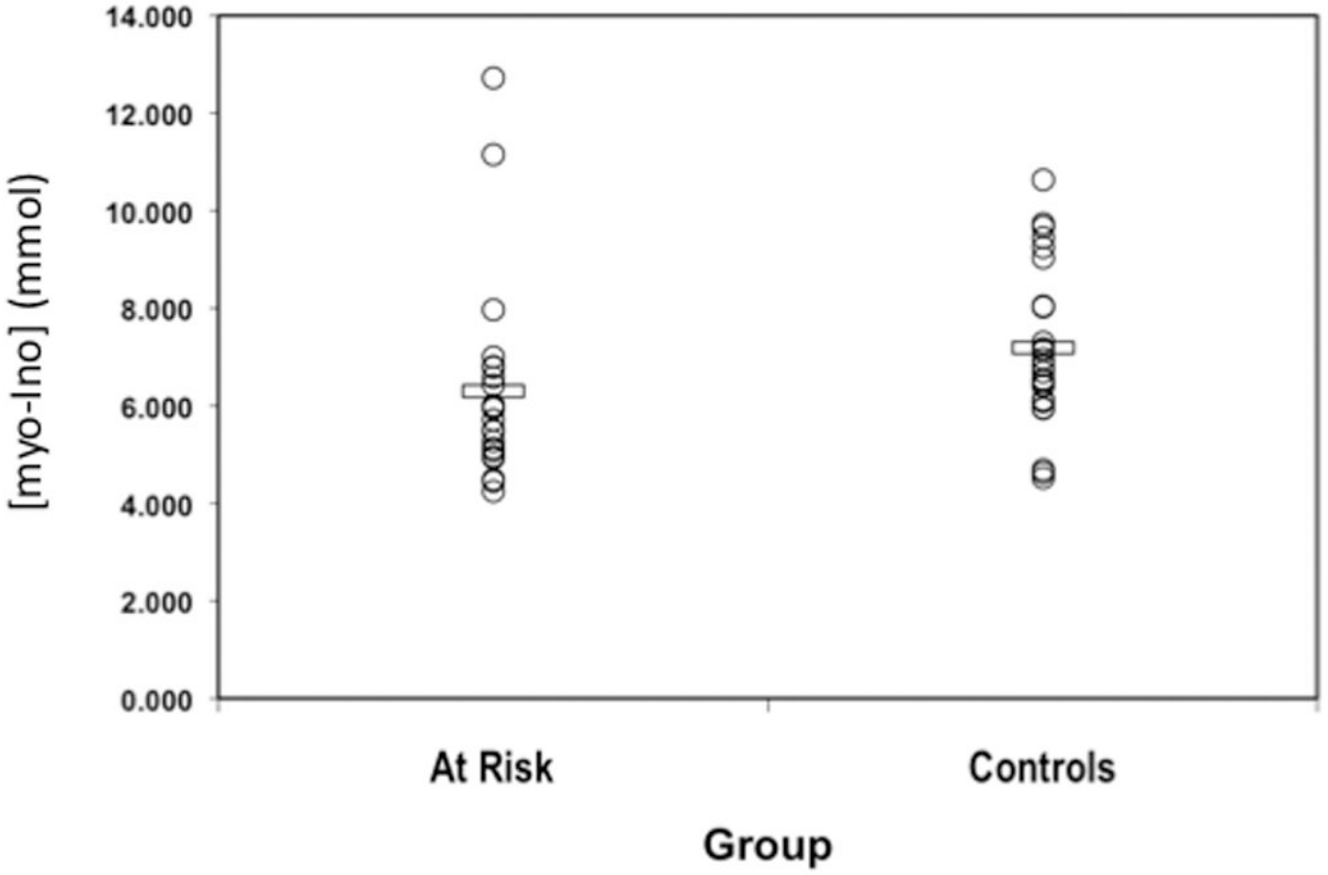

Fig. 3.
Myo-inositol (*myo*-Ino) concentrations in at-risk and control groups.

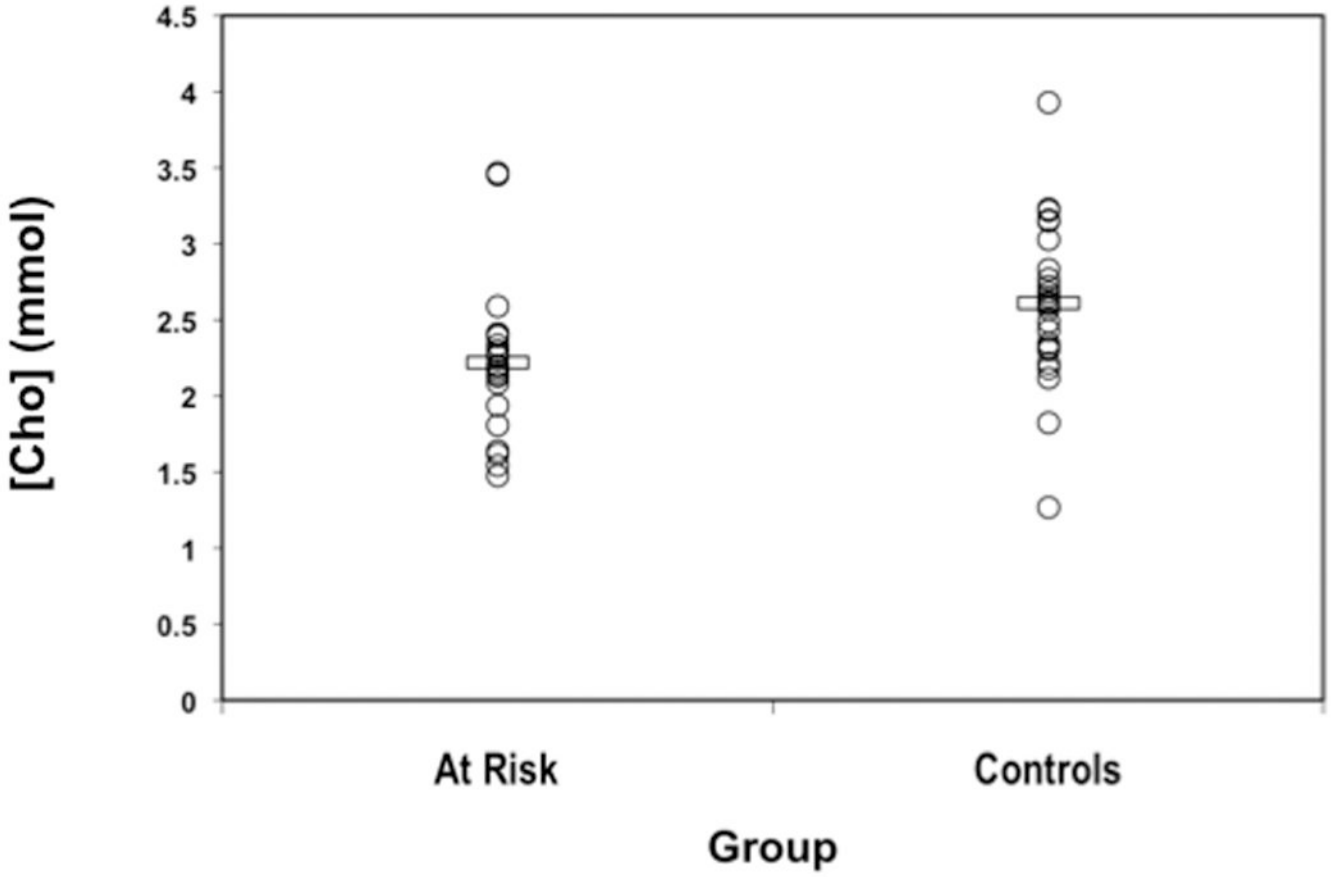

Fig. 4.
Choline (Cho) concentrations in at-risk and control groups.

Table 1

Demographic and clinical characteristics of study participants

	At-risk offspring (n = 22)	Healthy controls (n = 25)
Age, years, mean (SD)	13.3 (2.8)	13.5 (2.5)
Gender, female, n (%)	12 (55)	11 (44)
Right-handedness, n (%)	20 (91)	22 (92)
Ethnicity, n (%)[a]		
African American	0 (0)	1 (4)
Asian	0 (0)	7 (29)
Caucasian	18 (90)	14 (58)
Hispanic	2 (10)	2 (8)
IQ, mean (SD)[a]	112.2 (11.1)	116.3 (11.9)
YMRS score, mean (SD)[a]	12.5 (7.4)	0.8 (1.1)
CDRS-R score, mean (SD)[a]	33.0 (6.5)	18.0 (1.0)
CGAS score, mean (SD)[a]	58.9 (10.0)	88.0 (6.9)

YMRS = Young Mania Rating Scale; CDRS-R = Childhood Depression Rating Scale-Revised; CGAS = Childhood Global Assessment Scale.

[a]Significant group difference at $p < 0.05$.

Table 2

Clinical characteristics of youth at risk for bipolar disorder

Variable, n (%)	At-risk offspring (n = 22)
Diagnoses	
MDD	14 (64)
BD-NOS	6 (27)
ADHD	12 (55)
ODD	6 (27)
Anxiety disorders[a]	16 (73)
Psychotropic medications at time of MRS	
Atypical antipsychotics	6 (27)
Antidepressants	7 (32)
Stimulants	7 (32)
Lithium	1 (4.5)
Valproate	0 (0)
Lamotrigine	4 (18)
Lifetime exposure to any psychotropic medication	19 (86)

MDD = major depressive disorder; BD-NOS = bipolar disorder not otherwise specified; ADHD = attention-deficit hyperactivity disorder; ODD = oppositional defiant disorder; MRS = magnetic resonance spectroscopy.

[a]Including: generalized anxiety (n = 10), separation anxiety (n = 2), specific phobias (n = 3), and anxiety not otherwise specified (n = 1).

Table 3

Cerebellar proton magnetic resonance spectroscopy concentrations in at-risk offspring of parents with bipolar disorder versus healthy controls

Subject group	At risk (n = 22)	Healthy control (n = 25)	Two-sided *Z*-statistic	p-value	Effect size, *d*
Creatine (Cr)	7.84 (0.92)	8.39 (0.81)	1.77	0.08	0.63
N-acetyl aspartate (NAA)[a]	6.64 (1.50)	6.87 (1.51)	0.42	0.68	0.15
NAA/Cr	0.87 (0.12)	0.84 (0.11)	0.69	0.49	0.26
Myo-inositol[a]	6.30 (2.06)	7.19 (1.67)	2.40	0.017	0.47
Myo-inositol/Cr	0.80 (0.21)	0.85 (0.16)	1.67	0.09	0.27
Glutamate[a]	8.42 (1.34)	8.62 (1.77)	0.62	0.53	0.13
Glutamate/Cr	1.10 (0.18)	1.06 (0.20)	1.04	0.30	0.21
Glutamate/glutamine (Glx)[a]	14.03 (2.52)	14.68 (4.28)	0.99	0.32	0.19
Glx/Cr	1.80 (0.27)	1.74 (0.46)	0.22	0.82	0.16
Choline	2.22 (0.50)	2.61 (0.53)	3.06	0.002	0.76
Choline/Cr	0.28 (0.05)	0.31 (0.04)	2.67	0.008	0.68

[a]Absolute concentrations to tissue water using LCModel.