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Review article

Neurochemical alterations of the brain in bipolar disorder and their implications for pathophysiology: A systematic review of the in vivo proton magnetic resonance spectroscopy findings

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Abstract

Objective: To perform systematic analysis of current proton magnetic resonance spectroscopy (^{1}H MRS) findings in bipolar disorder (BD).
Method: We grouped the ^{1}H MRS studies documenting data on the metabolites of *N*-acetylaspartate (NAA), Choline (Cho), myo-inositol (mI), Glutamate (Glu)/Glutamine (Gln) and Creatine (Cr) separately, for each of the euthymic, manic, depressed adult and child/adolescent bipolar patients.
Results: For NAA resonance, 22 studies involving 328 adult bipolar and 349 control subjects were identified. NAA levels were lower in euthymic bipolar patients in the frontal lobe structures and hippocampus. Lithium seems to have an increasing effect on NAA in those brain regions. Available data in children indicates lower NAA levels in euthymic bipolar patients in dorsolateral prefrontal cortex (DLPFC) and cerebellar vermis. Existing data over 25 studies on 366 adult bipolar and 393 control subjects, although inconsistent, may suggest higher Cho/Cr ratios in the basal ganglia (BG) of euthymic bipolar patients. The metabolite mI seems to be increased both in euthymic and manic bipolar children, while most of the available data does not support such alteration in adults. Glu/Gln levels in adult bipolar patients were higher in all mood states compared to controls. Limited data in children supports such an alteration only in the euthymic state.
Conclusion: The studies reviewed in this paper suggest regional abnormalities of NAA, Cho and Glu/Gln in BD, with the DLPFC, prefrontal and anterior cingulate cortices, hippocampus, and BG being specifically implicated. Systematic analysis of ^{1}H MRS findings so far helps to define future strategies in this field for delineation of actual neurochemical framework in BD.

Keywords: Bipolar disorder; Choline; ^{1}H MRS; Myo-inositol; *N*-acetylaspartate

Contents

Abbreviations: ACC, anterior cingulate cortex; BD, bipolar disorder; BG, basal ganglia; Cho, choline; Cr, creatine; CSF, cerebrospinal fluid; CSI, chemical shift imaging; DLPFC, dorsolateral prefrontal cortex; DSM, diagnostic and statistical manual of mental disorders; FC, frontal cortex; FL, frontal lobe; GABA, gamma-aminobutyric acid; Gln, glutamine; Glu, glutamate; Glx, glutamix; GPC, glycerophosphorylcholine; gm, gray matter; MFC, medial frontal cortex; mI, myo-inositol; MOPF, medial orbital prefrontal; MRS, magnetic resonance spectroscopy; NAA, *N*-acetylaspartate; NAAG, *N*-acetylaspartylglutamate; NC, normal controls; PC, phosphorylcholine; PCr, phosphocreatine; PFC, prefrontal cortex; PI, phosphoinositide; PL, parietal lobe; PubMed, national library of medicine's medline; ^{1}H, proton; ^{1}H MRS, proton magnetic resonance spectroscopy; R, right side; RDC, research diagnostic criteria; ROI, regions of interest; TL, temporal lobe; TNF, tissue necrosis factor.

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1. Introduction

Bipolar disorder (BD) presented by alternating episodes of mania and depression is associated with significant disability in social, marital and occupational functioning. Consequently, according to the World Health Organization, BD is among the 30 leading causes of global burden of disease (Haldane and Frangou, 2004). Type I BD (BDI) is characterized by episodes of mania, whereas hypomanic episodes define type II BD (BDII) (Diagnostic and Statistical Manual of Mental Disorders IV (DSM IV), APA, 1994). Pathophysiological mechanisms underlying expression of BD are yet to be elucidated. Since with magnetic resonance spectroscopy (MRS), neurochemical information of the brain can be obtained in vivo, MRS studies hold considerable promise to illuminate brain mechanisms involved in BD (Glitz et al., 2002). Over the past decade a growing number of proton (^{1}H) MRS studies investigating the neurochemical basis of BD have been accumulated. However, there have been mixed results from these studies, preventing a conclusion on the direction of alterations expected on individual neurochemicals. Presentation of BD with three different mood states, each with a potentially distinct neurochemical profile, makes interpretation of the findings even more difficult. Thus, a structured documentation of the data obtained via ^{1}H MRS in BD is needed, first, to understand what has been found on individual neurochemicals and second, to determine the parts of the puzzle that require additional data. The first generation data obtained so far with ^{1}H MRS served to probe what type of alterations should be expected, in which brain regions and in which mood states. The next generation ^{1}H MRS studies should be driven by prior hypotheses for certain mood states in involved brain regions.

The ^{1}H MRS visible neurochemicals studied in this article are described in the following.

N-acetylaspartate (NAA)/*N-acetylaspartylglutamate* (NAAG): 2.02 ppm: NAA resonance consists predominantly of NAA but also contains smaller contributions from NAAG (Moore and Galloway, 2002). NAA constitutes approximately 3–4% of total brain osmolarity. NAA is synthesized from acetyl coenzyme A and aspartate in neurons by a mitochondrial enzyme (Baslow, 2000). Thus, NAA appears to be sensitive to mitochondrial oxidative phosphorylation (Bertolino et al., 2003). NAA is known to be an acetyl donor for acetyl coenzyme A and lipid biosynthesis such as myelin (Moore and Galloway, 2002). In some neurons a portion of NAA is converted into NAAG from NAA and glutamate (Baslow, 2000). NAA cycles between neurons and oligodendrocytes, among the only cells that contain large amounts of asparto acylase, the NAA catabolic enzyme in the brain. The NAAG appears to undergo a cycle similar to NAA, but with the catabolic enzyme in this case, NAAG peptidase, present on the surface of astrocytes only (Baslow, 2000).

Choline Compounds (Cho): 3.23 ppm: Cho resonance is predominantly composed of phosphorylcholine (PC) and glycerophosphorylcholine (GPC). Therefore, the Cho peak is considered as a potential biomarker for the status of membrane phospholipids metabolism (Moore and Galloway, 2002). Immobile, membrane bound Cho compounds are generally considered MRS invisible; however, phosphatidylcholine has a mobile head group that may be amenable to MR detection. Pathologies marked by membrane breakdown liberate bound Cho moieties into free Cho pool, thus contributing to an increase of this resonance in neurodegenerative states (Moore and Galloway, 2002). Cho peak is notably higher in white matter (Moore and Galloway, 2002).

Myo-inositol (mI): 3.56 ppm: The mI signal represents predominantly mI with minor contributions (<5%) from glycine

and inositol-1-phosphate (Moore and Galloway, 2002). It is a sugar involved in the regulation of neuronal osmolarity, the metabolism of membrane bound phospholipids, and in the phosphoinositide (PI) secondary messenger pathway.

Glutamate (Glu)/*Glutamine* (Gln)/*Gamma-Aminobutyric Acid* (GABA): Glu + Gln + GABA: Glutamix (Glx): 2.3 ppm: At low field strength the broad resonance centered at approximately 2.3 ppm contains overlapping resonances arising from Glu, Gln and GABA, which are often indistinguishable (Glx) (Glitz et al., 2002). Since the concentrations of Glu, Gln, and GABA are 9, 6, and 1 mmol/kg brain tissue, respectively, this resonance is often considered as an indicator of glutamatergic neurotransmission (Michael et al., 2003). Sustained elevated levels of glutamate are toxic (Glitz et al., 2002).

Creatine (Cr)/*Phosphocreatine* (PCr): 3.02 ppm: Cr peak reflects the presence of both Cr and PCr. The equilibrium maintained between Cr and PCr is determined by the cellular demand for the high energy phosphate stored as creatine phosphate (Moore and Galloway, 2002). As its level is considered to be relatively constant, it has often been used as an internal standard for comparison. The gray matter concentration of Cr is greater than the white matter.

This review presents a systematic inspection of the findings so far by addressing the following questions: 1. What are the main regions of interest for ^{1}H MRS studies in BD? In what anatomical regions have significant results been gained? 2. What was the power of the individual studies to detect the differences observed and what sample sizes should be aimed for in future studies? 3. What metabolites have been missed or under-reported? 4. Is there evidence that metabolic changes parallel the short term clinical status "mood states"? 5. Is there evidence of difference between the bipolar subtypes BDI and BDII in regard to metabolic profiles in the brain? 6. Is there any difference between the childhood and adult presentation of bipolar illness as reflected in the metabolic changes in the brain? 7. Is there evidence that medication changes the measurements within individuals? 8. How can the assumed functions of the metabolites of interest be linked to the pathophysiology of BD? 9. Is the neurochemical profile of the brain different in BD as compared to unipolar depressive disorder? 10. What are the technical implications for future studies?

2. Methods

A computer assisted literature search of the National Library of Medicine's Medline (PubMed) system was conducted, restricting dates for publications between 1978-November 2005 and using '^{1}H magnetic resonance spectroscopy' and 'bipolar disorder' as key words. It was complemented by a manual search of bibliographic cross-referencing. ^{1}H MRS studies of in vivo human brain were included in the data documentation if; 1) the report was published in English, 2) research diagnostic criteria (RDC) or DSM-III, DSM-III-R, or DSM-IV criteria were used, 3) bipolar patients in either euthymic, manic, or depressed state were compared to healthy controls. Studies designed to investigate mood stabilizer drugs' effects on ^{1}H MRS detectable metabolites were also included. We grouped studies documenting data on individual metabolites of NAA, Cho, mI, Glx and Cr separately, for adult and child/adolescent patients with BD. The demographic data, diagnostic/medication status and spectral acquisition parameters for each study were documented.

3. Results

3.1. NAA/NAAG

The inclusion process identified 22 studies (two studies provided data both for euthymic and depressed patients) on NAA resonance involving 328 adult BD patients and 349 normal controls (NC) (Table 1-a). In thirteen of these reports euthymic BD patients were compared to NC. Two studies indicated lower NAA levels in the dorsolateral prefrontal cortex (DLPFC) and hippocampus in BD patients (Winsberg et al., 2000; Deicken et al., 2003). Similarly, in a sample of BD patients, most of who were in the euthymic and depressed mood state, Bertolino et al. (2003) reported lower NAA levels in the hippocampus. One study, where some of the subjects were on lithium, found a trend for lower NAA in basal ganglia (BG) on the right side (R) (Ohara et al., 1998). Four studies finding no difference between patients who were mostly on lithium and NC may suggest lithium-induced normalization of NAA levels in anterior cingulate cortex-prefrontal cortex (ACC-PFC), DLPFC, frontal cortex (FC), and parietal lobe (PL) (Amaral et al., 2002; Brambilla et al., 2005; Hamakawa et al., 1999; Stoll et al., 1992). Two studies report lithium-induced increase in NAA levels beyond normalization in the temporal lobe (TL) and BG (Silverstone et al., 2003; Sharma et al., 1992). One study investigating effect of valproate could not find such an NAA increasing effect for that mood stabilizer (Silverstone et al., 2003). Somewhat divergent from the above findings are three reports, one indicating higher NAA levels in BD patients in the thalamus and two no significant difference in NAA levels between BD patients and NC in BG associated structures, including the thalamus; these findings could not be attributed to lithium since, most of the BD subjects in these studies were not taking lithium (Deicken et al., 2001; Kato et al., 1996; Hamakawa et al., 1998). Limited data in manic phases of the illness may suggest decreased NAA levels in patients in medial orbital prefrontal (MOPF) gray matter (gm) (Cecil et al., 2002). The second study finding no significant difference in DLPFC probably suffers from a large type II error due to a small sample size (Michael et al., 2003). One study investigating affective psychosis in manic and depressed patients reported lower NAA in patients in hippocampus. Available data in the depressed phases of illness suggest no significant difference in NAA levels between patients and NC in various regions of interest (ROI). One study of depressed BD patients and NC found a lithium-induced increase in NAA levels in the frontal lobe (FL) and TL (Table 1-a).

In child and adolescent BD patients, four reports indicated decreased NAA levels in the DLPFC and cerebellar vermis for patients in the euthymic state (Table 1-b). In one of these studies

Table 1-a
Proton MRS findings of *N*-acetyl aspartate (NAA) in adult patients with bipolar affective disorder

Study	Study subjects compared	*N* of patients/ control (M)	Age of patients/control, mean±SD	ROI/voxel size	NAA studied	NAA in patients/controls, mean±SD	Result	Direction of change	Technique (device/FS/Acq./ TRms/TEms/Coil)	Comment
Amaral et al. (2002)	BDI–euthymic vs NC	13/15	Not stated	Anterior cingulate-PFC/8 cm^3	NAA/Cr	1.60±0.34/ 1.68±0.34	Nonsignif.	Ns	GE/1.5T/PRESS/ 1500/144/Not stated	On Li for at least 4 weeks, Li may have normalized NAA
Winsberg et al. (2000)	BDI and II (DSM-IV)– euthymic vs NC	20 (9)/20 (9)	37.9±13.8/ 33.5±13.9	DLPFC/8 cm^3	NAA/ Cr (R)	1.63±0.13/ 1.74±0.18	$p<0.03$, $t=-2.30$, $df=38$	Decreased	GE/1.5T/PRESS/ 2000/35/Not stated	Drug free 2 weeks BDI/II: 10/10 Lower NAA/Cr in BDI vs BDII BDI had sign. lower NAA/Cr relative to NC in R and L; BDII only in L
					NAA/ Cr (L)	1.63±0.12/ 1.79±0.18	$p<0.003$, $t=-3.21$, $df=38$	Decreased		
					NAA/ Cho (R)	2.06±0.23/ 2.30±0.31	$p<0.008$, $t=-2.85$, $df=38$	Decreased		
					NAA/ Cho (L)	2.17±0.30/ 2.38±0.33	$p<0.04$, $t=-2.14$, $df=38$	Decreased		
Brambilla et al. (2005)	BDI and II (DSM-IV)– euthymic (1 depressed) vs NC	10 (2)/32 (16)	36.6±13.9/ 34.8±9.9	DLPFC (L)/8 cm^3	NAA	8.36±0.60/ 7.98±0.86	$p=0.20$, $F=1.71$	Ns	GE/1.5T/STEAM/ 1500/20/Not stated	4 BD drug free 2 weeks; off Li 1 month; 6 BD on Li; BDI/II: 8/2. Li group had sign. higher NAA/Cr relative to NC and also drug free BD.
					NAA/Cr	1.41±0.24/ 1.36±0.17	$p=0.32$, $F=1.01$	Ns		
					NAA/ Cho	2.99±1.46/ 2.67±0.80	$p=0.42$, $F=0.68$	Ns		
Hamakawa et al. (1999) *	BDI and II (DSM-III-R)– euthymic vs NC	23 (8)/20 (7)	44.8±11.0/ 37.0±10.0	Frontal cortex/15.6 cm^3	NAA (R)	16.79±5.17/ 19.75±6.57	Nonsignif.	Ns	GE/1.5T/STEAM/ 2000/135/ Quadrature head coil	20 on medicat. (13 Li; 11 AP); 3 drug free 7 days
					NAA (L)	17.68±5.23/ 17.10±3.84	Nonsignif.	Ns		
Silverstone et al. (2003)	BDI (DSM-IV)– euthymic vs NC	9 (2)/11 (6)	42.4±3.0/ 37.3±2.2	Frontal L(L)/ Temporal L cortex (L)/8 cm^3	NAA (Valp)/ vs NC	11.24±0.34/ 11.92±0.28	Nonsig. $p=0.14$, $t=1.56$, $df=18$	Ns, data given as SEM	Magnex/3T/ PRESS/3000/25/ Quadrature head coil	All on 1000 mg Na valproate, taking no other medicat. All euthymic>3 months
						10.53±0.53/ 10.84±0.39	Nonsig. $p=0.14$, $t=0.64$, $df=18$	Ns, data given as SEM		
Silverstone et al. (2003)	BDI and II (DSM-IV)– euthymic vs NC	14 (9; Li) 11 (5; Valp)/18 (8) NC	40.4±2.96 35.5±2.27/ 31.4±2.89 (Li group sign. older)	Temporal L/12 cm^3	NAA/ Cr (Li)/	1.68±0.06/ 1.47±0.06	$p=0.016$, $t=2.56$, $df=30$	Li induced increase, data given as SEM	Magnex/3T/ PRESS/3000/32/ Quadrature head coil	All on Li or valproate All euthymic>3 month All but 3 were on other medicat. (6 AP) No signif diff bw BDI and II
					NAA/Cr (Valp)/vs NC	1.59±0.09/ 1.47±0.06	$p=0.236$, $t=1.21$, $df=27$	Ns, data given as SEM		
Deicken et al. (2003)	BDI (DSM-IV)– euthymic vs NC	15 (15)/20 (20)	39.3±10.3/ 36.0±10.7	Hippocampus/ 1.6 mL	NAA (R)	2.75±0.33/ 3.25±0.48	$p=0.001$	Decreased	Siemens/1.5T/ PRESS/1800/135/ Standard head coil	12 on med. (4 Li; 3 AP) All euthym>2 mo. All had first degree relative w MD Low NAA can't be attributed to voxel tissue differences Sign. negative correlation bw R hippo. NAA and years illness after age adjustment
					NAA (L)	2.87±0.38/ 3.26±0.46	$F=13.23$ (1, 33)			
Stoll et al. (1992)	BD (DSM-III-R)– euthymic vs NC	7 (7)/6 (6)	33.9±8.7/ 31.7±6.3	Parietal L (supralat. to corpus callosum)/27 cm^3	NAA/ Cho	2.18±0.31/ 1.98±0.37	Nonsignif.	Ns	GE/1.5T/STEAM/ 2000/270/Not stated	On Li>6 months
Deicken et al. (2001)	BDI (DSM-IV)– euthymic vs NC	15 (15)/15 (15)	41.1±10.6/ 37.5±11.1	Thalamus/1.5 mL	NAA (R)	13.12±0.16/ 11.79±0.13	$p=0.0097$, $F=7.69$ (1, 28)	Increased	Siemens/1.5T/ PRESS/1960/135/ Standard head coil	13 on medicat. (5 on Li, 2 AP) All patients had a first degree relative w MD All euthymic >2 months
					NAA (L)	13.95±0.12/ 12.77±0.16	$p=0.0017$ $F=12.02$ (1, 28)	Increased		

Ohara et al. (1998)	BDI (DSM-IV)–euthymic vs NC	10 (6)/10 (6)	38.2±14.2/ 39.0±15.2	Basal G (mostly Lenticular nucleus)/8 cm^3	NAA/ Cr (R)	1.42±0.27/ 1.50±0.15	Nonsignif. $p=0.075$, $F=3.6$, $df=1, 17$ nonsignif.	Decreased, Trend	GE/1.5T /PRESS/ 1500/40 / Quadrature head coil	7 on Li; 3 drug free
					NAA/ Cr (L)	1.27±0.16/ 1.32±0.19		Ns		All symptom free >4 weeks
					NAA/ Cho (R)	1.96±0.40/ 1.92±0.48	Nonsignif. $p=0.656$, $F=4.15$, $df=1, 17$	Ns		NAA/Cr and NAA/Cho signif. higher in R than L
					NAA/ Cho (L)	1.72±0.29/ 1.72±0.40	Nonsignif.	Ns		
Kato et al. (1996)	BDI and II (DSM-III-R)–euthymic vs NC	19 (5)/19 (5)	41.6±9.4/ 40.3±6.3	Basal G (include caudate h and lenticular n) /27 cm^3	NAA/ Cr (total)	1.83±0.61/ 1.59±0.47	Nonsignif.	Ns	GE/1.5T/STEAM/ 2000/135/	BDI/II: 10/9
					NAA/ Cr (w Li)	1.68±0.55/ 1.59±0.47	Nonsignif.	Ns	Quadrature head coil	10 on Li>40 days (± other drugs, 6 AP); 9 Li free>30 days (± other drugs, 4 AP)
					NAA/Cr (wo Li)	2.00±0.63/ 1.59±0.47	Nonsignif.	Ns		
Hamakawa et al. (1998) *	BDI–II–NOS (DSM-III-R)–euthymic vs NC	16 (4)/20 (6)	44.4±10.9/ 43.8±9.5	Basal G (L) (include caudate h, putamen, thalamus) /27 cm^3	NAA	16.79±4.03/ 18.48±4.07	Nonsignif.	Ns	GE/1.5T/ STEAM/ 2000/135/	14 on medicat. (6 Li; 6 AP)
					NAA/Cr	1.81±0.68/ 1.71±0.65	Nonsignif.	Ns	Quadrature head coil	Ns effect of BD subtype
Sharma et al. (1992)	BDI (RDC manic type)–remission vs NC	4/ 9 (6)	Not stated/ 31±4.8	Basal G (include caudate h)/15.6 cm^3	NAA/Cr	2.59±0.80/ 1.39±0.23	Significant	Increased	GE/1.5T/STEAM/ 3000/28.5/ Surface coil	All on medication including Li, all stable and cooperative Ns diff in Occipital L
Cecil et al. (2002)	BDI (DSM-V)–manic 9/mixed 8 vs NC	17 (6)/21 (9)	22.3±7.3/ 21.7±5.2 (both groups 16–35)	Medial orbital prefrontal frontal gm and wm/8 cm^3	NAA (gm)	9.8±1.5/ 11.0±1.3	$p=0.026$	Decreased Effect size=0.41	GE/1.5T/PRESS/ 5000/35/Not stated	All on medication (2 Li; 13 AP). Composite AA was sign. higher in BD than NC in orbital frontal white m
					NAA (wm)	15.0±2.0/ 15.7±3.0	$p=0.361$	Ns, ES=0.14		
Michael et al. (2003)	BDI–(DSM-IV)–manic vs NC	8 (6)/8 (6)	40.1±13.9/ 40.7±14.7	DLPFC /3.375 cm^3	NAA	No numeric data available	$p=0.12$, $t=-1.6$	Ns	Siemens/1.5T/ STEAM/2500/20/ Not stated	6 drug naïve; 1 Li; 1 switched to mania after ECT
Blasi et al. (2004)	7 BDI and 10 MDD (DSM-IV)–manic or depressed (all psychotic and first episode) vs NC	17 (10)/17 (10)	26.8±7.6/ 25.5±6.8	Hippocampus/ 1.4 mL	NAA/Cr	1.8±0.22/ 2.0±0.25	$p<0.04$ $F=4.7$, $df=1, 32$	Decreased	GE/1.5T/spin echo slice selection/ 2200/272/ Quadrature head coil	All on AP, 2 Li. All subjects were stabilized on med. for≥4 weeks. No signif change in any metabolites in other regions sampled
Friedman et al. (2004)	BDI and II (DSM-IV)–depressed or mixed (predominantly depressed) put on Li or valp vs NC	21 (9)/12 (5)	30.1±9.1/ 30.6±5.5	Frontal wm/ Cingulate/Caudate/ Putamen/Thalamus/	Δ NAA gm	−0.22±0.78 (Li)/ 0.27±1.25 (Valp)/ −0.26±0.84 (NC)	Nonsignif. $F(2, 26)=0.81$	Ns	GE/1.5T/PEPSI 2D/2000/20 and 272/Custom built bird cage coil	BD patients randomly assigned to Li ($n=12$; 2–7 months) and Valp ($n=9$; 1–5 months) Δ in BD compared to Δ NC (studied at two time points)
				Parietal wm/ Occiput/	Δ NAA wm	−0.41±1.28 (Li)/ 0.15±0.65 (Valp)/ −0.15±0.48 (NC)	Nonsignif. $F(2, 26)=0.88$	Ns		
Dager et al. (2004)	BDI and II (DSM-IV)–depressed or mixed (predominantly depressed) vs NC	32 (14)/26 (12)	30.3±10.8/ 31.9±7.7	Frontal wm/ Cingulate/Caudate/ Putamen/Thalamus/ Parietal wm/ Occiput/Insula/ 1 cm^3 each	NAA (gm)	10.6±1.26/ 10.18±0.43	Nonsignif. $\beta<0.28$, $t\leq1.07$, $p\geq0.32$	Ns	GE/1.5T/PEPSI 2D/2000/20 and 272/Custom built bird cage coil	All drug free ≥8 week. No past AP expos. ROI specific analysis showed increased NAA in L putamen. No signif. diff. bw BDI and II both in gm and in wm
					NAA (wm)	9.76±0.89/ 9.77±0.44	Nonsignif. $F_{1,51}=3.61$, $p=0.06$	Ns		
Hamakawa et al. (1999) *	BDI–II (DSM-III-R)–depressed vs NC	8 (3)/20 (7)	Not stated/ 37.0±10.0	Frontal Cortex/ 15.6 cm^3	NAA (R)	17.81±4.13/ 19.75±6.57	Nonsignif.	Ns	GE/1.5T/STEAM/ 2000/135/	6 on medicat. (2 Li; 4 AP) 2 drug free 7 days
					NAA (L)	16.28±3.95/ 17.10±3.84	Nonsignif.	Ns	Quadrature head coil	

(continued on next page)

Table 1-a (*continued*)

Study	Study subjects compared	*N* of patients/ control (M)	Age of patients/control, mean±SD	ROI/voxel size	NAA studied	NAA in patients/controls, mean±SD	Result	Direction of change	Technique (device/FS/Acq./ TRms/TEms/Coil)	Comment
Moore GJ et al. (2000)	BDI and II (DSM-IV)– depressed vs NC	12 (5)/9 (3)	36.3±–/ 27.1±–	R Frontal /L Temporal/L Parietal/Central Occipital Lobes/each 8 mL	NAA (baseline) NAA (4 weeks Li)	No numeric data available	No diff. in baseline vs control Li lead signf increase $F=5.528$, $p=0.0217$ (data BD and NC combined)	Li induced increase	GE/1.5T/STEAM/ 2000/30/Not stated	Drug free ≥ 14 days BD and NC given Li 4 weeks Positive correlat. bw NAA and gm Li induced increase in all ROI but most in Frontal and Temporal Lobes
Hamakawa et al. (1998) *	BDI–II–NOS (DSM-III-R)– depressed vs NC	11 (2)/20 (6)	48.3±13.4/ 43.8±9.5	Basal G (L) (include caudate h, putamen, thalamus)/27 cm^3	NAA	17.14±3.78/ 18.48±4.07	Nonsignif.	Ns	GE/1.5T/STEAM/ 2000/135/ Quadrature head coil	9 on medicat. (3 Li; 3 AP)
					NAA/Cr	1.54±0.35/ 1.71±0.65	Nonsignif.	Ns		
Soares et al. (1999)	BDI–depres3/ euthymic3 vs NC	6/10	Not stated/ NC age matched	Anterior cingulate/3 cm^3	NAA/Cr	1.17±0.27/ 1.28±0.38 (3 depressed drug free pat.)	Nonsignif.	Ns	GE/1.5T/STEAM / 1500/20/ Quadrature head coil	Abstract
						1.27±0.46/ 1.28±0.38 (3 euthymic pat. On Li)	Nonsignif.	Ns		
Bertolino et al. (2003)	BDI (DSM-IV)– depress 7/manic-hm4/ euthymic 6 vs NC	17 (10)/17 (10)	40.1±12.9/ 37.6±10.3	Hippocampus/ 1.4 mL	NAA/Cr	1.41±0.31/ 1.72±0.36	$p<0.009$, $F=7.3$ (1, 32)	Decreased	GE/1.5T/spin echo slice selection/ 2200/272/ Quadrature head coil	11 on medicat. (5 Li; 4 AP), 6 drug free 2 weeks Ns diff in 6 pat scanned in depressed and manic state Ns diff in the other areas sampled
					NAA/ Cho	1.14±0.23/ 1.29±0.22	$p=0.05$ $F=4.02$ (1, 32)	Decreased		
Yurgelun-Todd et al. (1993)	BD (DSM-III-R)– Not stated vs NC	12/14	Not stated	Temporal Lobe	NAA/ Cr (L) NAA/ Cr (R)	1.17±0.15/ 1.21±0.17 Not stated for BD	Not stated	Statistical comparison bw BD and NC was not reported	GE/1.5T/STEAM/ 2000/30/ Quadrature head coil	Signif. bilat. reduction in NAA/Cr in SCP compared to NC and reduction in L as compared to BD

AA: Amino acid composite including γ-amino butyric acid, aspartate, glutamate and glutamine; AP: Antipsychotic; BD: Bipolar disorder; Δ: Change in metabolite concentrations at two time domains; 2D: Two dimensional; DLPFC: Dorsolateral prefrontal cortex; ECT: Electroconvulsive therapy; FS; Field strength; gm: gray matter; hm: hypomanic; L: Left; M: Male; MD: Mood Disorder; mo: months; NC: Normal Control; Ns: Nonsignificant; PEPSI: Proton echo planar spectroscopic imaging; PFC: Prefrontal cortex; PRESS: Point resolved spectroscopy; R: Right; ROI: Region of interest; SCP: Schizophrenia; SD: Standard deviation; SEM: Standard error of mean; STEAM: Stimulated echo method pulse sequence; TE: Echo time; TR: Repetition time; wm: white matter.

* Data from the same study, for the euthymic and depressed bipolar patients has been documented separately.

Table 1-b
Proton MRS findings of *N*-acetyl aspartate (NAA) in child/adolescent patients with bipolar affective disorder

Study	Study subjects compared	*N* of patients/ control (M)	Age of patients/control, mean±SD	ROI/voxel size	NAA studied	NAA in patients/controls, mean±SD	Result	Direction of change	Technique (Device/FS/Acq./ TRms/TEms/Coil)	Comment
Chang et al. (2001)	BDI (DSM-IV)–euthymic vs NC	9/4	12.8±–/13.6±–	DLPFC/2 cm^3	NAACr (R)	1.58±0.13/ 1.66±0.04	$p=0.14$	Ns	Not stated	Abstract All on medicat. All had at least one parent w BDI/II
					NAA/Cr (L)	1.54±0.05/ 1.60±0.08	$p=0.14$	Ns		
Chang et al. (2003)[a]	BDI (DSM-IV)–euthymic vs NC	15 (13)/11 (6)	12.6±2.9 /12.6±2.9	DLPFC/8 cm^3	NAA/Cr (R)	1.61±0.12/ 1.68±0.08	$p<0.02$	Decreased	GE/3T/PRESS/2000/ 35/Custom built head coil	14 on medicat. (6 Li; 7 AP) and All had at least one parent w BDI/ II
					NAA/Cr (L)	1.59±0.13/ 1.61±0.07	$p=0.16$	Ns		
Sassi et al. (2001)	BD Not stated vs NC	7/9	15±3.1/14.8±3.6	DLPFC (L)	NAA	Not stated	Significantly lower levels in BD	Decreased	Not stated	Poster presented at ACNP meeting
Castillo et al. (2000)	BD (DSM-IV)–euthymic vs NC	10 (9)/10 (8)	8±– (range 6–12)/ Non-age matched child	Frontal L/ 8 or 27 cm^3	NAA/Cr (R)	2.51±0.76/ 2.06±0.53	Nonsignif.	Ns	–/1.5T/PRESS/1500/135/ Standard head coil	Drug free for one week
					NAA/Cr (L)	2.20±0.06/ 1.90±0.23	Nonsignif.	Ns		
				Temporal L/ 8 or 27 cm^3	NAA/Cr (R)	2.02±0.76/ 2.13±0.28	Nonsignif.	Ns		Larger frontal lobe lipid resonances in BD patients
					NAA/Cr (L)	2.28±0.76/ 2.19±0.20	Nonsignif.	Ns		
Cecil et al. (2003)	3 BDI–3 BDII–1 BD NOS and 2 MDD (DSM-IV)–euthymic vs NC	9 (5)/10 (6)	9.8±1.4/10.8±1.8	Cerebellar vermis	NAA	13.13±1.61/ 14.19±0.89	Trend, $z=-1.46$, $p=0.07$.	Ns, ES=0.38 Ns Decreased, ES=0.42	GE/1.5T/PRESS/2000/ 35/Not stated	All but one drug free. All had at least one parent w BDI 8% decrease in NAA and Cr (parallel change obscured change in NAA/Cr). No signif diff in metabolite. bw MD and NC in R frontal wm. Similar findings wn 1 MDD case excluded
					NAA/Cr	1.09±0.09/ 1.09±0.09	Nonsignif.			
					NAA/Cho	1.24±0.18/ 1.37±0.08	$z=-1.63$, $p=0.05$			
				Medial frontal cortex/ 8 cm^3 each	NAA	14.44±1.84/ 14.52±2.24	Nonsignif.	Ns		
					NAA/Cr	1.52±0.10/ 1.61±0.22	Nonsignif.	Ns		
					NAA/Cho	2.14±0.19/ 2.28±0.36	Nonsignif.	Ns		
Davanzo et al. (2003)	BDI (DSM-IV)–manic 7 or mixed 3 vs NC	10 (8)/13 (unmatched by age and gender)	9.8±2.0/11.7±3.6	Anterior cingulate cortex/8 cm^3	NAA/Cr	1.07±0.14/ 1.06±0.11	$p=0.88$	Ns	GE/1.5T/PRESS/3000/ 30/Not stated	5 on medicat. (0 Li; 2 AP) Most patients had comorbid diagnosis Ns diff in Occipital L
					NAA	6.50±0.65/ 6.48±0.46	$p=0.90$	Ns		
Davanzo et al. (2001)	BDI and II (DSM-IV)–manic 9/hm 2 vs NC	11 (9)/11 (age and gender matched)	11.4±–/matched	Anterior cingulate cortex/8 cm^3	NAA/Cr (baseline)	1.37±0.38/ 1.23±0.19	$p=0.477$	Ns	GE/1.5T/PRESS/3000/ 30/Not stated	9 on medicat. (0 Li; 5 AP) 6 w comorbid diagnosis 6 rapid cycler
					NAA/Cr (7 days Li)	1.26±0.12/ compared w baseline	$p=0.657$ (baseline vs 7 days Li)	Ns		

AP: Antipsychotic; BD: Bipolar disorder; DLPFC: Dorsolateral prefrontal cortex; ES: Effect size; FS; Field strength; hm: hypomanic; L: Left; M: Male; MDD: Major depressive disorder; MD: Mood Disorder; NC: Normal Control; Ns: Nonsignificant; PRESS: Point resolved spectroscopy; R: Right; ROI: Region of interest; SD: Standard deviation; STEAM: Stimulated echo method pulse sequence; TE: Echo time; TR: Repetition time.

[a] Overlap of subjects with the prior report is probable.

Table 2-a
Proton MRS findings of choline in adult patients with bipolar affective disorder

Study	Study subjects compared	*N* of patients/ control (M)	Age of patients/ control, mean±SD	ROI/voxel size	Choline studied	Choline in patients/ controls Mean±SD	Result	Direction of change	Technique (Device/FS/ Acq./TRms/ TEms/Coil)	Comment
Soares et al. (1999)	BDI–euthymic3 vs NC	3/10	Not stated/age matched	Anterior cingulate/ 3 cm^3	Cho/Cr (on lithium)	1.11±0.52/ 0.84±0.36	Significantly elevated in Li treated patients	Increased Li induced?	GE/1.5T/ STEAM/ 1500/20/ Quadrature head coil	Abstract Increase in Cho is attributed to Li treatment
Amaral et al. (2002)	BDI–euthymic vs NC	13/15	Not stated	Anterior cingulate-PFC/8 cm^3	Cho/Cr	1.13±0.13/ 1.11±0.20	Nonsignif.	Ns	GE/1.5T/PRESS/ 1500/ 144 /Not stated	On Li for at least 4 weeks
Winsberg et al. (2000)	BDI and II (DSM-IV)–euthymic vs NC	20 (9)/20 (9)	37.9±13.8/ 33.5±13.9	DLPFC/8 cm^3	Cho/Cr (R)	0.79±0.07/ 0.76±0.07	Nonsignif.	Ns	GE/1.5T/PRESS/ 2000/	Drug free 2 weeks BDI/II: 10/10
					Cho/Cr (L)	0.76±0.08/ 0.76±0.07	Nonsignif.	Ns	35/Not stated	BDI and II had similar values
Brambilla et al. (2005)	BDI and II (DSM-IV)–euthymic (1 depressed) vs NC	10 (2)/ 32 (16)	36.6±13.9/ 34.8±9.9	DLPFC (L)/8 cm^3	Cho	1.07±0.38/ 1.10±0.30	$p=0.87$ $F=0.03$	Ns	GE/1.5T/ STEAM/1500/	4 BD drug free 2 weeks; off Li
					Cho/Cr	0.55±0.20/ 0.55±0.16	$p=0.85$ $F=0.04$	Ns	20/Not stated	1 month; 6 BD on Li; BDI/II: 8/2.
Hamakawa et al. (1999) *	BDI and II (DSM-III-R)–euthymic vs NC	23 (8) / 20 (7)	44.8±11.0/ 37.0±10.0	Frontal cortex/ 15.6 cm^3	Cho (R)	2.45±0.79/ 2.44±0.76	Nonsignif.	Ns	GE/1.5T/ STEAM/	20 on medicat. (13 Li; 11 AP);
					Cho (L)	2.9±1.18/ 2.52±0.81	Nonsignif.	Ns	2000/135/ Quadrature head coil	3 drug free 7 days
Deicken et al. (2003)	BDI (DSM-IV)–euthymic vs NC	15 (15)/ 20 (20)	39.3±10.3/ 36.0±10.7	Hippocampus / 1.6 mL	Cho (R)	7.67±1.17/ 7.93±1.38	Nonsignif. $p=0.21$	Ns	Siemens/1.5T/ PRESS/	12 on medicat. (4 Li; 3 AP).
					Cho (L)	7.94±1.17/ 8.51±1.02			1800/135/ Standard head coil	All euthymic >2 mo. All had first degree relative w MD
Wu et al. (2004)	BDI (DSM-IV)–euthymic vs NC	9 (2)/11 (6)	42.4±3.0 / 37.3±2.2	Frontal L(L) / Temporal L cortex (L) / 8 cm^3	Cho (Valp)/ vs NC	0.28±0.015/ 0.27±0.028	Nonsig. $p=0.72$, $t=0.367$, $df=18$	Ns, data given as SEM	Magnex/3T/ PRESS/ 3000/25/	All on 1000 mg Na valproate, taking no other medicat.
						0.28±0.016/ 0.26±0.021	Nonsig. $p=0.59$, $t=0.539$, $df=18$	Ns, data given as SEM	Quadrature head coil	All euthymic >3 months
Wu et al. (2004)	BDI and II (DSM-IV)–euthymic vs NC	14 (9; Li) 11 (5; Valp)/18 (8) NC	40.4±2.96 35.5±2.27/ 31.4±2.89 (Li group sign. older)	Temporal L/ 12 cm^3	Cho/Cr (Li)/	1.18±0.07/ 1.46±0.04	$p=0.001$, $t=3.628$, $df=30$	Decreased, data given as SEM	Magnex/3T/ PRESS/ 3000/32/ Quadrature head coil	All on Li or valproate All euthymic >3 month All but 3 were on other medicat. (6 AP)
					Cho/Cr (Valp)/ vs NC	1.12±0.08/ 1.46±0.04	$p=0.002$, $t=4.248$, $df=27$	Decreased, data given as SEM		No signif diff bw BDI and II
Stoll et al. (1992)	BD (DSM-III-R)–euthymic vs NC	7 (7)/6 (6)	33.9±8.7/31.7±6.3	Parietal L (supralat. to corpus callosum)/27 cm^3	Cho/Cr	0.93±0.13/ 0.93±0.07	Nonsignif.	Ns	GE/1.5T/ STEAM/2000/ 270/Not stated	On Li >6 months

Bruhn et al. (1993)	BD (not stated)–euthymic vs NC	8/8	31 (23–52)/ 30 (18–72)	Parietal L gm and wm	Cho/Cr (gm)	0.22±0.02/ 0.20±0.01	Nonsignif.	Ns, data given as SEM	Siemens/2T/ STEAM/3000 gm–6000wm/20/	All on Li for 6–40 mo
					Cho/Cr (wm)	0.32±0.01/ 0.32±0.01	Nonsignif.	Ns, data given as SEM	Not stated	
					Cho (wm)	1.51±0.08/ 1.49±0.04	Nonsignif.	Ns, data given as SEM		
Deicken et al. (2001)	BDI (DSM-IV)–euthymic vs NC	15 (15)/ 15 (15)	41.1±10.6/ 37.5±11.1	Thalamus/ 1.5 mL	Cho (R)	1.82±0.31/ 1.69±0.35	Nonsignif. $F=1.4$, $df=1,28$, $p=0.246$	Ns	Siemens/1.5T/ PRESS/1960/135/	13 on medicat. (5 on Li, 2 AP).
					Cho (L)	1.86±0.50/ 1.69±0.43	Nonsignif. $F=0.09$, $df=1,28$, $p=0.762$	Ns	Standard head coil	All patients had a first degree relative w MD. All euthym >2 mo
Ohara et al. (1998)	BDI (DSM-IV)–euthymic vs NC	10 (6)/10 (6)	38.2±14.2/ 39.0±15.2	Basal G (mostly Lenticular nucleus)/8 cm^3	Cho/Cr (R)	0.74±0.16/ 0.82±0.14	Nonsignif.	Ns	GE/1.5T/PRESS/ 1500/40/	7 on Li; 3 drug free. All symptom free >4 weeks
					Cho/Cr (L)	0.76±0.15/ 0.79±0.12	Nonsignif.	Ns	Quadrature head coil	
Lafer et al. (1994)	BDI (DSM-III-R)–euthymic vs NC	19/14	Not stated	Basal Ganglia/ not stated	Cho/Cr	0.58±0.16/ 0.44±0.18	$p=0.04$	Increased	GE/1.5T/ STEAM/ 2000/30/ Quadrature head coil	12 on Li; 7 Li free. No signif diff bw BD patients treated w Li and wo Li; findings are not attributed to Li
Hamakawa et al. (1998)*	BDI–II–NOS (DSM-III-R)–euthymic vs NC	16 (4)/20 (6)	44.4±10.9/ 43.8±9.5	Basal G (L) (include caudate h, putamen, thalamus)/ 27 cm^3	Choline	2.16±1.13/ 1.68±0.61	Nonsignif.	Ns	GE/1.5T/ STEAM/ 2000/135/ Quadrature head coil	14 on medicat. (6 Li; 6 AP). Ns effect of BD subtype. Ns effect of medicat on Cho
					Cho/Cr	0.78±0.39/ 0.55±0.28	$p<0.05$, $t=1.92$	Increased		
					Cho/NAA	0.43±0.16/ 0.32±0.10	$p<0.05$, $t=2.47$	Increased		
Kato et al. (1996)	BDI and II (DSM-III-R)–euthymic vs NC	19(5) /19(5)	41.6±9.4/ 40.3±6.3	Basal G (include caudate h and lenticular n)/27 cm^3	Cho/Cr (total)	0.75±0.38/ 0.52±0.26	$p<0.05$, $t=2.1$, $df=36$	Increased	GE/1.5T/ STEAM/ 2000/135/ Quadrature head coil	BDI/II: 10/9 10 on Li >40 days (± other drugs, 6 AP); 9 Li free > 30 days (± other drugs, 4 AP) Cho higher in BD pat. treated w AD than wo AD Higher Cho/Cr wo Li group is not attributed to AD Cho/Cr higher in BDII than BDI
		10/19			Cho/Cr (w Li)	0.63±0.36/ 0.52±0.26	Nonsignif.	Ns		
		9/19			Cho/Cr (wo Li)	0.89±0.35/ 0.52±0.26	$p<0.01$, $t=2.9$, $df=26$	Increased		
		19/19			Cho/NAA (total)	0.41±0.15/ 0.32±0.09	Ns, $p=0.057$, $t=2.6$, $df=36$	Ns		
		10/19			Cho/NAA (w Li)	0.37±0.14/ 0.32±0.09	Nonsignif.	Ns		
		9/19			Cho/NAA (wo Li)	0.45±0.15/ 0.32±0.09	$p<0.05$, $t=2.6$, $df=26$	Increased		
Kato et al. (1994)*	BDI–II–NOS (DSM-III-R)–euthymic vs NC	17/22 (5)	Not stated/ 37.9±8.4	Basal Ganglia/ 27 cm^3	Cho/Cr (L)	0.75±0.38/ 0.55±0.27	Nonsignif.	Ns	GE/1.5T/ STEAM/ 2000/135/ Not stated	All on medicat. Ns diff bw patients treated w Li and wo Li
					Cho/NAA (L)	0.41±0.16/ 0.33±0.10	Nonsignif.	Ns		

(continued on next page)

Table 2-a (*continued*)

Study	Study subjects compared	*N* of patients/ control (M)	Age of patients/ control, mean±SD	ROI/voxel size	Choline studied	Choline in patients/ controls Mean±SD	Result	Direction of change	Technique (Device/FS/ Acq./TRms/ TEms/Coil)	Comment
Sharma et al. (1992)	BDI (RDC manic type)– remission vs NC	4/9 (6)	Not stated/ 31±4.8	Basal G (include caudate h)/ 15.6 cm^3	Cho/Cr (on Li)	1.22±0.35/ 0.87±0.24	Significant elevations in patients	Increased (Li induced)	GE/1.5T/ STEAM/ 3000/28.5/ Surface coil	All on Li ± other medications. All stable and cooperative. Ns diff in Occipital L
Cecil et al. (2002)	BDI (DSM-IV)–manic 9/ mixed 8 vs NC	17 (6)/21 (9)	22.3±7.3/21.7±5.2 (both groups 16–35)	Medial orbital prefrontal frontal gm and wm/8 cm^3	Choline (gm)	1.6±0.3/ 1.8±0.2	Trend $p=0.057$	Decreased, Trend, ES=0.37	GE/1.5T/PRESS/ 5000/ 35/Not stated	All on medication (2 Li; 13 AP)
					Choline (wm)	2.8±0.5/ 3.0±0.4	Nonsignif. $p=0.129$	N s , ES=0.26		
Michael et al. (2003)	BDI–(DSM-IV)–manic vs NC	8 (6)/8 (6)	40.1±13.9/ 40.7±14.7	DLPFC/ 3.375 cm^3	Cho	No numeric data available	Nonsignif. $p=0.34$, $t=-0.99$	Ns	Siemens/1.5T/ STEAM/ 2500/20/ Not stated	6 drug naïve; 1 Li; 1 switched to mania after ECT
Blasi et al. (2004)	7 BDI and 10 MDD (DSM-IV)–manic or depress. (all psychotic 1st episode) vs NC	17 (10)/ 17 (10)	26.8±7.6/ 25.5±6.8	Hippocampus/ 1.4 mL	Cho/Cr	No numeric data available	Nonsignif. $p=0.85$, $F=0.04$, $df=1,32$	Ns	GE/1.5T/ spin echo slice selection/ 2200/272/ Quadrature head coil	All on AP, 2 Li. All subjects were stabilized on med. for ≥4 weeks. No signif change in any metabolites in other ROIs
Friedman et al. (2004)	BDI and II (DSM-IV)– depressed or mixed (predominantly depressed) put on Li or valp vs NC	21 (9)/12 (5)	30.1±9.1/ 30.6±5.5	Frontal wm/ Cingulate/ Caudate/ Putamen/ Thalamus/ Parietal wm/Occiput/	Δ Cho gm	0.09±0.31 (Li)/ −0.12±0.31 (Valp)/ −0.13±0.22 (NC)	Nonsignif. $F(2, 26)=0.33$	Ns	GE/1.5T/PEPSI 2D/2000/ 20 and 272/ Custom built bird cage coil	BD patients randomly assigned to Li ($n=12$; 2–7 months) and Valp ($n=9$; 1–5 months) Δ in BD compared to Δ NC (studied at two time points)
					Δ Cho wm	0.06±0.38 (Li)/ 0.08±0.30 (Valp)/ 0.08±0.29 (NC)	Nonsignif. $F(2, 26)=0.16$	Ns		
Dager et al. (2004)	BDI and II (DSM-IV)– depressed or mixed (predominantly depressed) vs NC	32 (14)/ 26 (12)	30.3±10.8/ 31.9±7.7	Frontal wm/ Cingulate/ Caudate/ Putamen/ Thalamus/ Parietal wm/Occiput/ Insula/1 cm^3 each	Cho (gm)	2.52±0.66/ 2.30±0.26	Nonsignif. $\beta<0.28$, $t\leq1.07$, $p\geq0.32$	Ns	GE/1.5T/PEPSI 2D/2000/20 and 272/Custom built bird cage coil	All drug free ≥8 week. No past AP expos.No signif. diff. bw BDI and II both in gm and in wm
					Cho (wm)	2.59±0.35/ 2.49±0.28	Nonsignif. $F_{1, 51}=3.61$, $p=0.06$	Ns		
Moore GJ et al. (2000)	BDI–(DSM-IV)–depressed vs NC	9 (5) 27 mrs for R; 23 mrs for L/ 14 (6) 13 mrs for R; 14 mrs for L	37.9±9.7/ 36.1±10.5	Anterior cingulate cortex/2 cm^3	Cho/Cr (R)	0.86±0.23/ 0.63±0.12	$p<0.005$, $t=3$, $df=43$	Increased	GE/1.5T/ STEAM/2000/ 30/Not stated	All on mood stab ± AD (5 Li; 0 AP). Ns diff in metabolite ratios on L. In L HAM-D ratings correlated positively w Cho/Cr.
					Cho/Cr (R; wo AD 4)	0.95±0.30/ 0.63±0.12	$p<0.005$	Increased		
					Cho/Cr (R; w Li 5)	0.86±0.26/ 0.63±0.12	$p<0.003$	Increased		

					Cho/Cr (R; w Valp 4)	0.85±0.34/ 0.63±0.12	$p<0.014$	Increased		AD use correlated w lower Cho/Cr
					Cho/Cr (L)	0.91±0.59/ 0.84±0.23	Nonsignif.	Ns		
Moore et al. (1999)	11 BDI and 1 BDII (DSM-IV)–depressed vs NC	12 (5)/9 (3) 36 mrs for each ROI	36.3 (22–56)/ 27.1 ±–	R Frontal L/ L Temporal/ L Parietal/ C Occipital/ 8 mL each	Cho (baseline) Cho (4 weeks Li)	No numeric data available	Li caused significant decrease in choline in frontal lobe	Li induced decrease	GE/1.5T/ STEAM/ 2000/30/Not stated	All went through min. two weeks wash out then administered Li 4 weeks; depression scores decreased w Li; Ns diff in other ROI
Hamakawa et al. (1999) *	BDI and II (DSM-III-R)–depressed vs NC	8 (3)/20 (7)	Not stated/37.0±10.0	Frontal Cortex/ 15.6 cm^3	Cho (R)	2.0±0.65/ 2.44±0.76	Nonsignif.	Ns	GE/1.5T/ STEAM/ 2000/135/ Quadrature head coil	6 on medicat. (2 Li; 4 AP) 2 drug free 7 days
					Cho (L)	2.05±0.59/ 2.52±0.81	Nonsignif.	Ns		
Hamakawa et al. (1998) *	BDI–II–NOS (DSM-III-R)–depressed vs NC	11 (2)/20 (6)	48.3±13.4/43.8±9.5	Basal G (L) (include caudate h, putamen, thalamus)/27 cm^3	Choline	2.70±1.46/ 1.68±0.61	$p<0.05$, $t=2.19$	Increased	GE/1.5T/ STEAM/ 2000/135/ Quadrature head coil	9 on medicat. (3 Li; 3 AP)
					Cho/Cr	0.88±0.51/ 0.55±0.28	$p<0.05$, $t=1.92$	Increased		
					Cho/NAA	0.56±0.29/ 0.32±0.10	$p<0.05$, $t=2.72$	Increased		
Kato et al. (1994) *	BDI–II–NOS (DSM-III-R)–depressed vs NC	11/22 (5)	Not stated/37.9±8.4	Basal Ganglia/ 27 cm^3	Cho/Cr (L)	0.88±0.47/ 0.55±0.27	$p<0.01$	Increased	GE/1.5T/ STEAM/ 2000/135/Not stated	All on medicat. Ns diff bw patients treated w Li and wo Li
					Cho/NAA (L)	0.56±0.27/ 0.33±0.10	$p<0.01$	Increased		
Bertolino et al. (2003)	BDI (DSM-IV)–depress 7/manic-hm4/ euthymic 6 vs NC	17 (10)/ 17 (10)	40.1±12.9/ 37.6±10.3	Hippocampus/ 1.4 mL	Cho/Cr	No numeric data available	$p>0.5$, $F=0.23$ (1, 32)	Ns	GE/1.5T/spin echo slice selection/2200/ 272/Quadrature head coil	11 on medicat. (5 Li; 4 AP), 6 drug free 2 weeks Ns diff in 6 pat scanned in depressed and manic state Ns diff in the other areas sampled

AA: Amino acid composite including γ-amino butyric acid, aspartate, glutamate and glutamine; AD: Antidepressant; AP: Antipsychotic; BD: Bipolar disorder; C: Central; Δ: Change in metabolite concentrations at two time domains; DA: Dexro-amphetamine; DLPFC: Dorsolateral prefrontal cortex; 2D: Two dimensional; ECT: Electroconvulsive therapy; FS; Field strength; gm: gray matter; HAM-D: Hamilton Depression Rating Scale; hm: hypomanic; L: Left; M: Male; mo: months; MD: Mood Disorder; NC: Normal Control; Ns: Nonsignificant; PEPSI: Proton echo planar spectroscopic imaging; PFC: Prefrontal cortex; PRESS: Point resolved spectroscopy; R: Right; ROI: Region of interest; SCP: Schizophrenia; SD: Standard deviation; SEM: Standard error of mean; STEAM: Stimulated echo method pulse sequence; TE: Echo time; TR: Repetition time; wm: white matter.

* Data from the same study, for the euthymic and depressed bipolar patients have been documented separately.

Table 2-b
Proton MRS findings of choline in child/adolescent patients with bipolar affective disorder

Study	Study subjects compared	*N* of patients /control (M)	Age of patients/control, mean±SD	ROI/voxel size	Choline studied	Choline in patients/ controls, mean ±SD	Result	Direction of change	Technique (Device/FS/Acq./ TRms/TEms/Coil)	Comment
Chang et al. (2001)	BDI (DSM-IV)– euthymic vs NC	9/4	12.8±–/13.6±–	DLPFC/2 cm^3	Cho/Cr (R) Cho/Cr (L)	No numeric data available	Nonsignif. Nonsignif.	Ns Ns	Not stated	Abstract All on medicat. All had at least one parent w BDI/ II
Chang et al. (2003)[a]	BDI (DSM-IV)– euthymic vs NC	15 (13)/11 (6)	12.6±2.9/12.6±2.9	DLPFC/8 cm^3	Cho/Cr (R) Cho/Cr (L)	0.77±0.08/ 0.77±0.06 0.78±0.07/ 0.75±0.07	$p=0.84$ $p=0.16$	Ns Ns	GE/3T/PRESS/2000/35/ Custom built head coil	14 on medicat. (6 Li; 7 AP) and All had at least one parent w BDI/II 13/15 comorbid dgn
Castillo et al. (2000)	BD (DSM-IV)– euthymic vs NC	10 (9)/10 (8)	8 ±– (range 6–12)/ Non-age matched child	Frontal L/8 or 27 cm^3 Temporal L/8 or 27 cm^3	Cho/Cr (R) Cho/Cr (L) Cho/Cr (R) Cho/Cr (L)	1.15±0.14/ 1.10±0.13 1.16±0.17/ 1.09±0.09 1.04±0.07/ 1.11±0.15 1.04±0.12/ 1.06±0.08	Nonsignif. Nonsignif. Nonsignif. Nonsignif.	Ns Ns Ns Ns	–/1.5T/ PRESS /1500/135 / Standard head coil	Drug free for one week, larger frontal lobe lipid resonances in BD patient
Cecil et al. (2003)	3 BDI–3 BDII–1 BD NOS and 2 MDD (DSM-IV)–euthymic vs NC	9 (5)/10 (6)	9.8±1.4/10.8±1.8	Cerebellar vermis Medial frontal cortex/8 cm^3 each	Cho Cho/Cr Cho/mI Cho Cho/Cr Cho/mI	3.66±0.72/ 3.51±0.15 0.90±0.21/ 0.79±0.06 1.37±0.21/ 1.29±0.13 2.29±0.27/ 2.19±0.37 0.71±0.06/ 0.71±0.09 1.07±0.15/ 1.20±0.16	Nonsignif. Ns, ES=0.34 Nonsignif. Nonsignif. Nonsignif. Nonsignif.	Ns Ns Ns Ns Ns Ns	GE/1.5T/PRESS/2000/35/ Not stated	All but one drug free. All had at least one parent w BDI. No signif diff in metabolite. bw MD and NC in R frontal wm. Similar findings wn 1 MDD case excluded
Davanzo et al. (2003)	BDI (DSM-IV)– manic 7 or mixed 3 vs NC	10 (8)/13 (unmatched by age and gender)	9.8±2.0/11.7±3.6	Anterior cingulate cortex/8 cm^3	Cho/Cr Cho	0.19±0.01/ 0.20±0.02 1.16±0.16/ 1.25±0.13	$p=0.05$ $p=0.19$	Decreased	GE/1.5T/PRESS/ 3000/30/Not stated	5 on medicat. (0 Li; 2 AP) Most patients had comorbid diagnosis Ns diff in Occipital L
Davanzo et al. (2001)	BDI and II (DSM-IV)–manic 9/ hm 2 vs NC	11 (9)/11 (age and gender matched)	11.4±–/matched	Anterior cingulate cortex/8 cm^3	Cho/Cr (baseline) Cho/Cr (7 days Li)	0.92±0.26/ 0.80±0.17 0.79±0.11	Ns, $p=0.424$ Ns, $p=0.131$ (baseline vs 7 days Li)	Ns Ns	GE/1.5T/ PRESS/ 3000/30/Not stated	9 on medicat. (0 Li; 5 AP) 6 w comorbid diagnosis 6 rapid cycler

AP: Antipsychotic; BD: Bipolar disorder; dgn: Diagnosis; DLPFC: Dorsolateral prefrontal cortex; ES: Effect size; FS; Field strength; gm: gray matter; hm: hypomanic; L: Left; M: Male; MDD: Major depressive disorder; MD: Mood Disorder; NC: Normal Control; Ns: Nonsignificant; PRESS: Point resolved spectroscopy; R: Right; ROI: Region of interest; SD: Standard deviation; STEAM: Stimulated echo method pulse sequence; TE: Echo time; TR: Repetition time; wm: white matter

[a] Overlap of subjects with the prior report is probable.

(Chang et al., 2001, $N=9$), although the initial findings were non-significant due to type II error, in the extended sample, the same authors later detected significance (Chang et al., 2003, $N=15$). One study in the FL and TL and another in the medial frontal cortex found no difference in NAA levels in euthymic patients compared to NC. Limited data in manic patients found no difference in NAA levels in ACC of BD patients and NC (Table 1-b).

3.2. Cho

The inclusion process identified 25 studies (three studies provided data both for euthymic and depressed patients and one study investigated two brain regions) on the Cho resonance in adult patients with BD ($N=366$) compared to NC ($N=393$) (Table 2-a); 17 of these reports were on euthymic BD patients. Three studies reported higher Cho levels in euthymic BD patients compared to NC in the BG, a finding not attributable to lithium since most of the subjects on these studies were not taking lithium (Lafer et al., 1994; Hamakawa et al., 1998; Kato et al., 1996). In one of these studies the non-significant difference in the lithium-treated group compared to NC may be explained by the normalization or decreasing effect of lithium on Cho (Kato et al., 1996). Similarly, six other studies where subjects were mostly on lithium could not detect any significant difference in Cho levels between patients and controls in ACC-PFC, DLPFC, PL, and BG. (Amaral et al., 2002; Brambilla et al., 2005; Stoll et al., 1992; Bruhn et al., 1993; Ohara et al., 1998; Kato et al., 1994). Wu et al. (2004) reported lower Cho levels in BD patients treated by lithium or valproate compared to NC in the TL. However, same authors in a separate sample of BD patients treated by valproate did not detect a significant difference between BD patients and NC either in the FL or in the TL (Wu et al., 2004). Two other studies with very small sample sizes reported higher Cho levels in BD patients treated by lithium in the ACC and BG (Soares et al., 1999; Sharma et al., 1992, Table 2-a). Four reports in the DLPFC, FC, hippocampus, and thalamus showed no significant difference between BD patients and NC (Table 2-a). Since most subjects in these studies were not taking lithium the negative findings could not be associated with lithium treatment. Two of the three studies in manic patients (one on affective psychosis) reported no significant difference in Cho levels between BD patients and NC (Michael et al., 2003; Blasi et al., 2004). In the other study a trend for a decrease in Cho in MOPF gm was observed (Cecil et al., 2002). In depressed BD subjects, three studies reported higher Cho levels in patients compared to controls in the ACC and BG (Moore CM et al., 2000; Hamakawa et al., 1998; Kato et al., 1994). In one of these studies, while depression scores correlated positively with Cho, antidepressant treatment resulted in decreased Cho levels (Moore CM et al., 2000; Moore GJ et al., 2000). In another study, 4 weeks of lithium treatment while resulting in an improvement in depression scores also caused a decrease in Cho levels in the frontal lobe of BD patients (Moore et al., 1999).

In child/adolescent bipolar patients four studies with patients in the euthymic state indicated no alteration of Cho in the DLPFC, medial frontal cortex (MFC), FC, and TL (Table 2-b). In two studies available in manic patients one study reported lower Cho in lithium-free BD patients in the ACC. In another study, 7 days of lithium resulted in a decrease in Cho, which was not significant, most likely due to a type II error (Davanzo et al., 2001).

3.3. mI

Ten studies investigating mI resonance in adult BD patients ($N=159$) compared to NC ($N=149$) were identified (Table 3-a). Among the five studies on euthymic BD patients only one reported a trend for higher mI levels in drug free BD patients (Winsberg et al., 2000). In three studies reporting no significance, patients were either on lithium or valproate. In contrary, one study with a very small sample size reported higher mI in patients on lithium compared to NC (Sharma et al., 1992). While one study in manic patients and two in depressed BD patients found no significance in mI, one study reported a lithium-induced decrease in mI (Moore et al., 1999) and another a trend for a lithium-induced increase in depressed BD patients (Friedman et al., 2004) (Table 3-a).

In three studies of euthymic bipolar children one reported a significant increase in mI levels in the medial frontal cortex (Table 3-b). Patients were mostly drug free on this study, while in the other two with non-significant results all patients were on medication. Two studies in manic children also reported higher mI levels in the ACC and in one of these studies 7 days of lithium treatment resulted in a significant decrease in mI levels (Table 3-b).

3.4. Glu/Gln/GABA (Glx)

Only four studies reporting on Glx resonance in adult bipolar patients ($N=69$) compared to NC ($N=54$) were identified (Table 4-a). Available data consistently suggested higher Glx levels in gm in all phases of BD (Table 4-a). One study showed a lithium-induced decrease in gm Glx levels (Friedman et al., 2004). Further, Cecil et al. (2002) observed higher levels of composite amino acids that include Glu, Gln, and GABA in BD patients in orbital frontal white matter. In one study 20% higher lactate levels were also observed in BD patients in gm, which could be explained by neurotoxic effects of increased Glutamate (Dager et al., 2004).

In drug free children with BD higher Glx levels in the euthymic state have been observed both in the FL and TL (Table 4-b). In manic bipolar children who were mostly on medication but not on lithium such an elevation in Glx could not be observed (Table 4-b).

3.5. Cr/PCr

Nine studies were identified which reported on Cr resonance in adult bipolar patients ($N=157$) compared to NC ($N=174$) (Table 5-a). Among the five studies available in euthymic BD patients one study reported decreased Cr in the hippocampus, one study increased Cr in the thalamus and three studies non-significance in the BG, FC and DLPFC (Table 5-a). Two studies

Table 3-a
Proton MRS findings of myo-inositol in adult patients with bipolar affective disorder

Study	Study subjects compared	*N* of patients /control (M)	Age of patients/ control, mean±SD	ROI/voxel size	mI studied	mI in patients/ controls, mean±SD	Result	Direction of change	Technique (Device/FS/Acq./ TRms/TEms/Coil)	Comment
Winsberg et al. (2000)	BDI and II (DSM-IV)– euthymic vs NC	20 (9)/20 (9)	37.9±13.8/ 33.5±13.9	DLPFC/8 cm^3	mI/Cr (R)	0.64±0.05/ 0.61±0.04	Trend $p=0.06$, $t=2.0$, $df=38$	Increased, Trend	GE/1.5T/PRESS/ 2000/35/Not stated	Drug free 2 weeks BDI/II: 10/10 BDI and II had similar values
					mI/Cr (L)	0.61±0.06/ 0.62±0.04	Nonsignif.	Ns		
Silverstone et al. (2002)	BDI (DSM-IV)– euthymic vs NC	9 (2)/11 (6)	42.4±3.0/ 37.3±2.2	Frontal L(L)	mI (Valp) / vs NC	7.33±0.89/ 7.42±0.66	Nonsig. $p=0.79$, $F=0.9$, $df=1$	Ns, data given as SEM	Magnex/3T/ PRESS/3000/ 25/Quadrature ead coil	All on 1000 mg Na valproate, taking no other medicat. All euthymic >3 months
				/Temporal L cortex (L)/ 8 cm^3		7.44±1.02/ 7.47±0.67	Nonsig. $p=0.94$, $F=0.4$, $df=1$	Ns, data given as SEM		
Silverstone et al. (2002)	BDI and II (DSM-IV)– euthymic vs NC	16 (10; Li) 11 (5; Valp)/19 (9) NC	42.9±3.18 36.8±2.52/ 30.6±2.79 (Li group sign. older)	Temporal L/ 12 cm^3	mI/Cr (Li)/ mI/Cr (Valp)/ vs NC	0.26±0.01/ 0.22±0.02 0.23±0.03/ 0.22±0.02	$p=0.24$, $F=1.49$, $df=2$	Ns, data given as SEM	Magnex/3T/ PRESS/3000/32/ Quadrature head coil	All on Li or valproate All euthymic >3 months. Most of the subjects were on other medicat. No signif diff bw BDI and II
Bruhn et al. (1993)	BD (not stated)– euthymic vs NC	8/8	31 (23–52)/30 (18–72)	Parietal L gm and wm	mI/Cr (gm)	0.76±0.02/ 0.75±0.01	Nonsignif.	Ns, data given as SEM	Siemens/2T/ STEAM/3000 gm–6000wm/20/ Not stated	All on Li for 6–40 mo
					mI/Cr (wm)	0.71±0.04/ 0.70±0.02	Nonsignif.	Ns, data given as SEM		
					mI (wm)	3.15±0.41/ 3.28±0.14	Nonsignif.	Ns, data given as SEM		
Sharma et al. (1992)	BDI (RDC manic type)– remission vs NC	4/9 (6)	Not stated/ 31±4.8	Basal G (include caudate h)/ 15.6 cm^3	mI/Cr (on Li)	0.74±0.39/ 0.45±0.13	Significant elevations in patients	Increased (Li induced)	GE/1.5T/STEAM/ 3000/28.5/Surface coil	All on Li ± other medications. All stable and cooperative. Ns diff in Occipital L
Cecil et al. (2002)	BDI (DSM-IV)– manic 9/ mixed 8 vs NC	17 (6)/21 (9)	22.3±7.3/ 21.7±5.2 (both groups 16–35)	Medial orbital prefrontal frontal gm and wm/8 cm^3	mI (gm)	3.2±0.5/ 3.3±0.5	Nonsignif. $p=0.411$	Ns, ES=0.14	GE/1.5T/PRESS/ 5000/35/Not stated	All on medication (2 Li; 13 AP)
					mI (wm)	4.7±1.2/ 4.1±0.8	Nonsignif. $p=0.093$	Ns, ES=0.29		

Friedman et al. (2004)	BDI and II (DSM-IV)–depressed or mixed (predominantly depressed) put on Li or valp vs NC	21 (9)/12 (5)	30.1±9.1/ 30.6±5.5	Frontal wm/ Cingulate/ Caudate/ Putamen/ Thalamus/ Parietal wm/Occiput/	Δ mI gm	0.53±0.67 (Li)/−0.10± 0.73 (Valp)/− 0.14±0.54 (NC)	p=0.05, F(2, 25)= 3.31	Increased in Li group, Trend	GE/1.5T/PEPSI 2D/2000/20 and 272/Custom built bird cage coil	BD patients randomly assigned to Li (n=12; 2–7 months) and Valp (n=9; 1–5 months) Δ in BD compared to Δ NC (studied at two time points). Ns diff in baseline mI bw BD and NC
					Δ mI wm	−0.57±0.69 (Li)/0.10±0.75 (Valp)/−0.12± 0.66 (NC)	Nonsignif. F(2, 25)= 2.16	Ns		
Dager et al. (2004)	BDI and II (DSM-IV)–depressed or mixed (predominantly depressed) vs NC	32 (14)/26 (12)	30.3±10.8/ 31.9±7.7	Frontal wm/ Cingulate/ Caudate/ Putamen/ Thalamus/ Parietal wm/ Occiput/Insula/ 1 cm^3 each	mI (gm)	4.59±0.98/ 4.36±0.50	Nonsignif. β<0.28, $t \leq 1.07$, $p \geq 0.32$	Ns	GE/1.5T/PEPSI 2D/2000/20 and 272/Custom built bird cage coil	All drug free ≥ 8 weeks. No past AP expos. No signif. diff. bw BDI and II both in gm and in wm
					mI (wm)	4.50±0.62/ 4.25±0.75	Nonsignif. $F_{1, 51}$= 3.61, p=0.06	Ns		
Moore et al. (1999)	11 BDI and 1 BDII (DSM-IV)–depressed vs NC	12 (5)/9 (3) 36 mrs for each ROI at 3 time domains	36.3 (22–56)/ 27.1 ±–	R Frontal L/ L Temporal/ L Parietal/ C Occipital/ 8 mL each	mI R Frontal (baseline) mI R Frontal (1 weeks Li) mI R Frontal (4 weeks Li)	No numeric data available	Li induced decrease 30% p = 0.04, t=2.46, df=8, p=0.04, t=2.46, df=8	Li induced decrease	GE/1.5T/STEAM/ 2000/30/Not stated	All went through min. two weeks wash out then administered Li 4 weeks; depression scores decreased w Li; Ns diff in other ROI
Moore CM et al. (2000)	BDI–(DSM-IV)–depressed vs NC	9 (5) 27 mrs for R; 23 mrs for L/14 (6) 13 mrs for R; 14 mrs for L	37.9±9.7/ 36.1±10.5	Anterior cingulate cortex/2 cm^3	mI/Cr (R)	0.54±0.24/ 0.59±0.46	Nonsignif.	Ns	GE/1.5T/STEAM/ 2000/30/Not stated	All on mood stab ± AD (5 Li; 0 AP). Ns diff in metabolite ratios on L
					mI/Cr (R; wo AD 4)	0.56±0.20/ 0.59±0.46	Nonsignif.	Ns		
					mI/Cr (R; w Li 5)	0.52±0.18/ 0.59±0.46	Nonsignif.	Ns		
					mI/Cr (R; w Valp 4)	0.57±0.29/ 0.59±0.46	Nonsignif.	Ns		
					mI/Cr (L)	0.66±0.35/ 0.50±0.17	Nonsignif.	Ns		

AD: Antidepressant; AP: Antipsychotic; BD: Bipolar disorder; Δ: Change in metabolite concentrations at two time domains; 2D: Two dimensional; DLPFC: Dorsolateral prefrontal cortex; FS; Field strength; gm: gray matter; L: Left; M: Male; mo: months; NC: Normal Control; Ns: Nonsignificant; PEPSI: Proton echo planar spectroscopic imaging; PRESS: Point resolved spectroscopy; R: Right; ROI: Region of interest; SD; Standard deviation; SEM: Standard error of mean; STEAM: Stimulated echo method pulse sequence; TE: Echo time; TR: Repetition time; wm: white matter.

Table 3-b
Proton MRS findings of myo-inositol in child/adolescent patients with bipolar affective disorder.

Study	Study subjects compared	*N* of patients / control (M)	Age of patients/ control, mean±SD	ROI/voxel size	Choline studied	Choline in patients/ controls, mean±SD	Result	Direction of change	Technique (Device/ FS/Acq./TRms/ TEms/Coil)	Comment
Chang et al. (2001)	BDI (DSM-IV)–euthymic vs NC	9/4	12.8±–/13.6±–	DLPFC/2 cm^3	mI/Cr (R) mI/Cr (L)	No numeric data available	Nonsignif. Nonsignif.	Ns Ns	Not stated	Abstract All on medicat. All had at least one parent w BDI/II
Chang et al . (2003)[a]	BDI (DSM-IV)–euthymic vs NC	15 (13)/11 (6)	12.6±2.9/12.6±2.9	DLPFC/8 cm^3	mI/Cr (R) mI/Cr (L)	0.47±0.05/ 0.46±0.03 0.46±0.05/ 0.49±0.07	$p=0.47$ $p=0.55$	Ns Ns	GE/3T/PRESS/ 2000/35/Custom built head coil	14 on medicat. (6 Li; 7 AP) and all had at least one parent w BDI/II 13/15 comorbid dgn
Cecil et al. (2003)	3 BDI–3 BDII–1 BD NOS and 2 MDD (DSM-IV)–euthymic vs NC	9 (5)/10 (6)	9.8±1.4/10.8±1.8	Cerebellar vermis	mI mI/Cr	5.71±0.36/ 5.87±0.39 0.65±0.09/ 0.61±0.04	Nonsignif. Nonsignif.	Ns Ns	GE/1.5T/PRESS/ 2000/35/Not stated	All but one drug free. All had at least one parent w BDI. No signif diff in metabolite. bw MD and NC in R frontal wm.
				Medial frontal cortex/8 cm^3 each	mI mI/Cr	4.62±0.41/ 4.00±0.90 0.67±0.07/ 0.60±0.10	$p=0.03$, $z=1.89$ $p=0.06$, $z=1.5$	Increased, ES=0.41 Increased, ES=0.35		Similar findings wn 1 MDD case excluded mI %16 higher in BD
Davanzo et al. (2001)	BDI and II (DSM-IV)–manic 9/ hm 2 vs NC	11 (9)/11 (age and gender matched)	11.4±–/matched	Anterior cingulate cortex/8 cm^3	mI/Cr (baseline) mI/Cr (7 days Li)	1.09±0.61/ 0.82±0.15 0.82±0.28	Trend $p=0.054$ $p=0.047$ (baseline vs 7 days Li)	Increased, Trend Li induced decrease	GE/1.5T/PRESS/ 3000/30/Not stated	9 on medicat. (0 Li; 5 AP) 6 w comorbid diagnosis 6 rapid cycler Decrement in mI signif in Li responders; ns in nonresponders
Davanzo et al. (2003)	BDI (DSM-IV)–manic 7 or mixed 3 vs NC	10 (8)/13 (unmatched by age and gender)	9.8±2.0/11.7±3.6	Anterior cingulate cortex/ 8 cm^3	mI/Cr mI	0.75±0.12/ 0.66±0.06 4.55±0.50/ 4.05±0.38	$p=0.02$ $p=0.02$	Increased	GE/1.5T/PRESS/ 3000/30/Not stated	5 on medicat. (0 Li; 2 AP) Most patients had comorbid diagnosis. Ns diff in Occipital L YMRS scores correlated positively w mI

AP: Antipsychotic; BD: Bipolar disorder; dgn: Diagnosis; DLPFC: Dorsolateral prefrontal cortex; ES: Effect size; FS; Field strength; gm: gray matter; hm: hypomanic; L: Left; M: Male; MDD: Major depressive disorder; MD: Mood Disorder; NC: Normal Control; Ns: Nonsignificant; PRESS: Point resolved spectroscopy; R: Right; ROI: Region of interest; SD: Standard deviation; TE: Echo time; TR: Repetition time; wm: white matter; YMRS: Young Mania Rating Scale.

[a] Overlap of subjects with the prior report is probable.

Table 4-a
Proton MRS findings of glutamate in adult patients with bipolar affective disorder

Study	Study subjects compared	*N* of patients/ control (M)	Age of patients/ control, mean±SD	ROI/voxel size	Glutamate studied	Glutamate in patients/ controls, mean ±SD	Result	Direction of change	Technique (Device/FS/Acq./ TRms/TEms/ Coil)	Comment
Bruhn et al. (1993)	BD (not stated)–euthymic vs NC	8/8	31 (23–52)/ 30 (18–72)	Parietal L gm	Glx/Cr (gm)	1.42±0.07/ 1.21±0.03	Not stated	Increased?, data given as SEM	Siemens/2T/ STEAM/3000/ 20/Not stated	All on Li for 6–40 mo
Michael et al. (2003)	BDI–(DSM-IV)–manic vs NC	8 (6)/ 8 (6)	40.1±13.9/ 40.7±14.7	DLPFC/3.375 cm^3	Glx	27.20±14.9/ 10.3±4.3	$p=0.008$, $t=-3.1$	Increased	Siemens/1.5T/ STEAM/2500/ 20/Not stated	6 drug naïve; 1 Li; 1 switched to mania after ECT Glx sign. higher in pats wn ECT-induced manic patient excluded
Friedman et al. (2004)	BDI and II (DSM-IV)–depressed or mixed (predominantly depressed) put on Li or valp vs NC	21 (9)/ 12 (5)	30.1±9.1/ 30.6±5.5	Frontal wm/ Cingulate/Caudate/ Putamen/Thalamus/ Parietal wm/Occiput/	Δ Glx gm	−1.76±2.79 (Li)/0.77±1.28 (Valp)/0.30± 1.67 (NC)	$p=0.03$, $F(2, 25)=4.01$	Li induced decrease	GE/1.5T/PEPSI 2D/2000/20 and 272/Custom built bird cage coil	BD patients randomly assigned to Li ($n=12$; 2–7 months) and Valp ($n=9$; 1–5 months) Δ in BD compared to Δ NC (studied at two time points) Glx sign higher in BD at baseline $p=0.002$, $t(29)=3.38$.
					Δ Glx wm	0.67±2.24 (Li)/ −0.34±2.05 (Valp)/−0.50± 1.80 (NC)	Nonsignif. $F(2, 25)=0.94$	Ns		
Dager et al. (2004)	BDI and II (DSM-IV)–depressed or mixed (predominantly depressed) vs NC	32 (14)/ 26 (12)	30.3±10.8/ 31.9±7.7	Frontal wm/ Cingulate/Caudate/ Putamen/Thalamus/ Parietal wm/Occiput/ Insula/1 cm^3 each	Glx (gm)	17.80±2.51/ 16.18±1.85	10% increase, $p=0.007$, $\beta=0.35$, $t=2.83$	Increased	GE/1.5T/PEPSI 2D/2000/20 and 272/Custom built bird cage coil	All drug free ≥8 week. No past AP expos. No signif. diff. bw BDI and II in gm-wm Glx higher in BDII vs NC both gm-wm %20 increase in lactate in BD in gm; sign BDI, trend BDII.
					Glx (wm)	15.69±2.60/ 14.51±1.99	Nonsignif. $F_{1, 51}=3.61$, $p=0.06$	Ns		↑Glu→↑neuronal firing→↑utilization glycolysis→↑lactate

AP: Antipsychotic; BD: Bipolar disorder; Δ: Change in metabolite concentrations at two time domains; 2D: Two dimensional; DLPFC: Dorsolateral prefrontal cortex; ECT: Electroconvulsive therapy; FS; Field strength; Glx: Peak resonance including γ-amino butyric acid, glutamate and glutamine; gm: gray matter; L: Left; M: Male; mo: months; NC: Normal Control; Ns: Nonsignificant; PEPSI: Proton echo planar spectroscopic imaging; R: Right; ROI: Region of interest; SD: Standard deviation; SEM: Standard error of mean; STEAM: Stimulated echo method pulse sequence; TE: Echo time; TR: Repetition time.

Table 4-b
Proton MRS findings of glutamate in child/adolescent patients with bipolar affective disorder

Study	Study subjects compared	*N* of patients / control (M)	Age of patients/ control, mean±SD	ROI/voxel size	Glutamate studied	Glutamate in patients/controls, mean±SD	Result	Direction of change	Technique (Device/ FS/Acq./TRms/ TEms/Coil)	Comment
Castillo et al. (2000)	BD (DSM-IV)– euthymic vs NC	10 (9)/10 (8)	8±– (range 6–12)/ Non-age matched child	Frontal L/ 8 or 27 cm^3	Glx/Cr (R)	0.78±0.48/ 0.34±0.21	Significant	Increased	–/1.5T/PRESS/ 1500/135/Standard head coil	Drug free for one week. Larger frontal lobe lipid resonances in BD patients
					Glx/Cr (L)	0.72±0.52/ 0.45±0.15	Significant	Increased		
				Temporal L/ 8 or 27 cm^3	Glx/Cr (R)	0.76±0.34/ 0.34±0.10	Significant	Increased		
					Glx/Cr (L)	0.63±0.11/ 0.36±0.10	Significant	Increased		
Davanzo et al. (2001)	BDI and II (DSM-IV)–manic 9/ hm 2 vs NC	11 (9)/11 (age and gender matched)	11.4±– /matched	Anterior cingulate cortex/8 cm^3	Glx/Cr (baseline)	4.16±1.57/ 4.31±1.40	$p=0.790$	Ns	GE/1.5T/PRESS/ 3000/30/Not stated	9 on medicat. (0 Li; 5 AP) 6 w comorbid diagnosis 6 rapid cycler
					Glx/Cr (7 days Li)	3.83±0.74	$p=0.594$ (baseline vs 7 days Li)	Ns		
Davanzo et al. (2003)	BDI (DSM-IV)– manic 7 or mixed 3 vs NC	10 (8)/13 (unmatched by age and gender)	9.8±2.0/11.7±3.6	Anterior cingulate cortex/8 cm^3	Glx/Cr	2.19±0.22/ 2.21±0.18	$p=0.95$	Ns	GE/1.5T/PRESS/ 3000/30/Not stated	5 on medicat. (0 Li; 2 AP). Most patients had comorbid diagnosis. Ns diff in Occipital L
					Glx	13.44±1.86/ 13.54±1.18	$p=1.00$	Ns		

AP: Antipsychotic; BD: Bipolar disorder; ES: Effect size; FS; Field strength; Glx: Peak resonance including γ-amino butyric acid, glutamate and glutamine; gm: gray matter; hm: hypomanic; L: Left; M: Male; NC: Normal Control; Ns: Nonsignificant; PRESS: Point resolved spectroscopy; R: Right; ROI: Region of interest; SD: Standard deviation; TE: Echo time; TR: Repetition time; wm: white matter.

Table 5-a
Proton MRS findings of creatine in adult patients with bipolar affective disorder

Study	Study subjects compared	*N* of patients / control (M)	Age of patients/ control, mean±SD	ROI/voxel size	Creatine studied	Creatine in patients/ controls, mean±SD	Result	Direction of change	Technique (Device/ FS/Acq./TRms/ TEms/Coil)	Comment
Deicken et al. (2003)	BDI (DSM-IV)–euthymic vs NC	15 (15)/20 (20)	39.3±10.3/ 36.0±10.7	Hippocampus/ 1.6 mL	Cr (R)	2.77±0.32/ 3.25±0.47	$p=0.002$, $F=11.57$ (1, 33)	Decreased	Siemens/ 1.5T/PRESS/ 1800/135/ Standard head coil	12 on med. (4 Li; 3 AP). All euthym>2 mo. All had first degree relative w MD. Low Cr can't be attributed to voxel tissue differences
					Cr (L)	2.87±0.38/ 3.24±0.53		Decreased		
Deicken et al. (2001)	BDI (DSM-IV)–euthymic vs NC	15 (15)/15 (15)	41.1±10.6/ 37.5±11.1	Thalamus/1.5 mL	Cr (R)	1.38±0.52/ 1.15±0.12	$p=0.031$, $F=5.16$ (1, 28)	Increased	Siemens/ 1.5T/PRESS/ 1960/135/ Standard head coil	13 on medicat. (5 on Li, 2 AP). All patients had a first degree relative w MD. All euthymic >2 months. Ns diff bw R and L. High Cr can't be attributed to voxel tissue differences
					Cr (L)	1.38±0.13/ 1.24±0.15		Increased		
Hamakawa et al. (1998) *	BDI–II–NOS (DSM-III-R)–euthymic vs NC	16 (4)/20 (6)	44.4±10.9/ 43.8±9.5	Basal G (L) (include caudate h, putamen, thalamus) /27 cm^3	Cr	8.25±2.64/ 9.70±3.25	Nonsignif.	Ns	GE/1.5T/ STEAM/2000/135/ Quadrature head coil	14 on medicat. (6 Li; 6 AP). Ns effect of BD subtype AP treatm. associated w higher Cr
Hamakawa et al. (1999) *	BDI and II (DSM-III-R)–euthymic vs NC	23 (8)/20 (7)	44.8±11.0/ 37.0±10.0	Frontal cortex/ 15.6 cm^3	Cr (R)	8.65±2.90/ 8.76±2.24	Nonsignif.	Ns	GE/1.5T/ STEAM/2000/135/ Quadrature head coil	20 on medicat. (13 Li; 11 AP); 3 drug free 7 days
					Cr (L)	9.46±2.71/ 8.18±2.37	Nonsignif.	Ns		
Brambilla et al. (2005)	BDI and II (DSM-IV)–euthymic (1 depressed) vs NC	10 (2)/32 (16)	36.6±13.9/ 34.8±9.9	DLPFC (L)/8 cm^3	Cr	6.44±1.14/ 6.23±0.73	$p=0.64$, $F=0.23$	Ns	GE/1.5T/STEAM/ 1500/20/Not stated	4 BD drug free 2 weeks; off Li 1 month; 6 BD on Li; BDI/II: 8/2.
Michael et al. (2003)	BDI– (DSM-IV)–manic vs NC	8 (6)/8 (6)	40.1±13.9/ 40.7±14.7	DLPFC/3.375 cm^3	Cr	No numeric data available	$p=0.095$	Ns	Siemens/1.5T/ STEAM/2500/20/ Not stated	6 drug naïve; 1 Li; 1 switched to mania after ECT
							$t=-1.8$ (lower in BD)			
Cecil et al. (2002)	BDI (DSM-IV)–manic 9/mixed 8 vs NC	17 (6)/21 (9)	22.3±7.3/ 21.7±5.2 (both groups 16–35)	Medial orbital prefrontal frontal gm and wm/8 cm^3	Cr (gm)	7.4±1.3/ 7.8±0.9	$p=0.295$	Ns, ES=0.20	GE/1.5T/ PRESS/5000/35/ Not stated	All on medication (2 Li; 13 AP). Composite AA was sign. higher in BD than NC in orbital frontal white m
					Cr (wm)	9.4±1.4/ 9.2±1.3	$p=0.602$	Ns, ES<0.10		

(continued on next page)

Table 5-a (*continued*)

Study	Study subjects compared	*N* of patients / control (M)	Age of patients/ control, mean±SD	ROI/voxel size	Creatine studied	Creatine in patients/ controls, mean±SD	Result	Direction of change	Technique (Device/ FS/Acq./TRms/ TEms/Coil)	Comment
Friedman et al. (2004)	BDI and II (DSM-IV)–depressed or mixed (predominantly depressed) put on Li or valp vs NC	21 (9)/12 (5)	30.1±9.1/ 30.6±5.5	Frontal wm/ Cingulate/Caudate/ Putamen/Thalamus/ Parietal wm/ Occiput/	Δ Cr gm	0.10±0.64 (Li)/0.09±0.89 (Valp)/−0.08± 0.80 (NC)	Nonsignif. $F(2, 26) = 0.33$	Ns	GE/1.5T/PEPSI 2D/ 2000/20 and 272/ Custom built bird cage coil	BD patients randomly assigned to Li ($n=12$; 2–7 months) and Valp ($n=9$; 1–5 months) Δ in BD compared to Δ NC (studied at two time points)
					Δ Cr wm	−0.28±0.89 (Li)/−0.22± 0.69 (Valp)/ 0.13±1.00 (NC)	Nonsignif. $F(2, 26)=0.16$	Ns		
Dager et al. (2004)	BDI and II (DSM-IV)–depressed or mixed (predominantly depressed) vs NC	32 (14)/26 (12)	30.3±10.8/ 31.9±7.7	Frontal wm/ Cingulate/Caudate/ Putamen/Thalamus/ Parietal wm/Occ./ Insula/1 cm^3 each	Cr (gm)	9.4±0.74/ 9.11±0.73	Nonsignif. $\beta<0.28$, $t \leq 1.07$, $p \geq 0.32$	Ns	GE/1.5T/PEPSI 2D/ 2000/20 and 272/Custom built bird cage coil	All drug free ≥8 weeks. No past AP expos. Inverse correlation bw wm Cr and HAM-D scores
					Cr (wm)	7.98±0.84/ 7.58±0.63	Nonsignif. $F_{1, 51}=3.61$, $p=0.06$	Ns		No signif. diff. bw BDI and II both in gm and in wm
Hamakawa (1999)*	BDI–II (DSM-III-R)–depressed vs NC	8 (3)/20 (7)	Not stated / 37.0±10.0	Frontal Cortex/ 15.6 cm^3	Cr (R)	7.48±1.87/ 8.76±2.24	Nonsignif.	Ns	GE/1.5T/STEAM/2000/ 135/Quadrature head coil	6 on medicat. (2 Li; 4 AP) 2 drug free 7 days For 8 cases scanned twice Cr was signif decreased L in depressed as compared to euthymic state in L Ns effect of subtype
					Cr (L)	6.57±1.40/ 8.18±2.37 NC/ 9.46±2.71 euthymic	Nonsignif. $p<0.05$, $F=4.49$, $df=2$	Ns vs NC Decreased as compared to euthymic		
Hamakawa et al. (1998)*	BDI–II–NOS (DSM-III-R)–depressed vs NC	11 (2)/20 (6)	48.3±13.4/ 43.8±9.5	Basal G (L) (caudate h, putamen, thalamus)/ 27 cm^3	Cr	9.36±2.17 /9.70± 3.25	Nonsignif.	Ns	GE/1.5T/STEAM/2000/ 135/Quadrature head coil	9 on medicat. (3 Li; 3 AP) Benzod. treatment associated w lower Cr

AA: Amino acid composite including γ-amino butyric acid, aspartate, glutamate and glutamine; AP: Antipsychotic; BD: Bipolar disorder; Δ: Change in metabolite concentrations at two time domains; 2D: Two dimensional; DLPFC: Dorsolateral prefrontal cortex; ECT: Electroconvulsive therapy; FS; Field strength; gm: gray matter; HAM-D: Hamilton Depression Rating Scale; L: Left; M: Male; MD: Mood Disorder; mo: months; NC: Normal Control; Ns: Nonsignificant; Occ.: Occiput; PEPSI: Proton echo planar spectroscopic imaging; PRESS: Point resolved spectroscopy; R: Right; ROI: Region of interest; SD: Standard deviation; STEAM: Stimulated echo method pulse sequence; TE: Echo time; TR: Repetition time; wm: white matter.

* Data from the same study, for the euthymic and depressed bipolar patients has been documented separately.

Table 5-b
Proton MRS findings of creatine in child/adolescent patients with bipolar affective disorder

Study	Study subjects compared	*N* of patients / control (M)	Age of patients/ control, mean±SD	ROI/voxel size	Creatine studied	Creatine in patients/controls, mean±SD	Result	Direction of change	Technique (Device/ FS/Acq./TRms/ TEms/Coil)	Comment
Sassi et al. (2001)	BD Not stated vs NC	7/9	15±3.1/ 14.8±3.6	DLPFC (L)	Cr	Not stated	Significantly lower levels in BD	Decreased	Not stated	Poster presented at ACNP meeting
Cecil et al. (2003)	3 BDI–3 BDII–1 BD NOS and 2 MDD (DSM-IV)– euthymic vs NC	9 (5)/10 (6)	9.8±1.4/ 10.8±1.8	Cerebellar vermis	Cr	13.14±1.69/ 14.18±0.72	$p=0.07$, $z=-1.46$	Decreased trend, ES=0.38	GE/1.5T/PRESS/ 2000/35/Not stated	All but one drug free. All had at least one parent w BDI. No signif diff in metabolite. bw MD and NC in R frontal wm Similar findings wn 1 MDD case excluded MD: 8% decrease Cr
				Medial frontal cortex/8 cm^3 each	Cr	10.30±0.75/ 9.77±0.74	Nonsignif.	Ns		
Davanzo et al. (2003)	BDI (DSM-IV)– manic 7 or mixed 3 vs NC	10 (8)/13 (unmatched by age and gender)	9.8±2.0/ 11.7±3.6	Anterior cingulate cortex/8 cm^3	Cr	6.16±0.85/ 6.13±0.41	$p=0.85$	Ns	GE/1.5T/PRESS/ 3000/30/Not stated	5 on medicat. (0 Li; 2 AP). Most patients had comorbid diagnosis. Ns diff in Occipital L

AP: Antipsychotic; BD: Bipolar disorder; DLPFC: Dorsolateral prefrontal cortex; ES: Effect size; FS; Field strength; M: Male; MDD: Major depressive disorder; NC: Normal Control; Ns: Nonsignificant; PRESS: Point resolved spectroscopy; ROI: Region of interest; SD: Standard deviation; TE: Echo time; TR: Repetition time.

in manic and four in depressed phases of illness reported no significant difference between BD patients and NC in frontal lobe structures and the BG. One study reported lower Cr levels in depressed versus euthymic BD patients (Hamakawa et al., 1999, Table 5-a).

In children with BD one study reported lower Cr in the DLPFC (Table 5-b). One study in euthymic bipolar children observed an 8% decrease in Cr in the cerebellar vermis. The other study in manic bipolar children found no difference in Cr compared to NC in the ACC.

4. Discussion

As indicated by the data presented a considerable progress has been accomplished with the ^{1}H MRS investigations of BD. For determining meaning of the findings and future directions in the field we discuss each of the questions raised in the introduction in the light of the reviewed literature.

4.1. What are the main regions of interest for ^{1}H MRS in BD? In what anatomical regions have significant results been gained?

Structural studies indicating volumetric reductions in the DLPFC, PFC, ACC, and hippocampus and functional studies reporting that the activity of the dorsal PFC and ACC are closely associated with mood symptoms imply involvement of those brain regions in BD (Anand and Shekhar, 2003; Haldane and Frangou, 2004). Accumulated ^{1}H MRS evidence mostly suggests that NAA levels may be decreased in euthymic BD patients in the DLPFC, ACC, PFC and hippocampus. Limited data available in manic phases of illness from similar brain regions also support a reduction of NAA levels in patients. Lithium seems to have an increasing effect on NAA to or beyond normal levels in these brain regions. Findings in BG related structures are somewhat more controversial and need reinvestigation in drug free patients. Although existing data on Cho is inconsistent, there is some evidence suggesting increased Cho levels in the BG of BD patients. Lithium may have a normalizing or decreasing effect on Cho. Higher Cho levels in the ACC, FC, and BG have been reported in depressed BD patients compared to NC. While most of the available data on mI is confounded by possible mI lowering/normalizing effects of mood stabilizers, one study indicated a strong trend for higher mI in medication-free euthymic BD patients in the DLPFC. All the available data on Glx indicate increased Glx levels in BD patients in different phases of illness, especially in gm structures. In summary, MRS studies of brain biochemistry have also revealed changes suggestive of neuronal dysfunction within the DLPFC, PFC, ACC, hippocampus, and the BG. Interpretation of the ^{1}H MRS findings in BD under a functional neuroanatomy framework strengthen our belief in the involvement of those brain regions in the pathophysiology of BD. While the primary sensory cortex receives sensory information from the sensory organs and thalamus, the association cortex, which includes PFC, ACC and DLPFC, integrates information to create representation of experience and thereby participates in regulation of cognition and emotion. The basal ganglia structures caudate and putamen receive input from the motor cortex and project to the glabus pallidus, which relays the neostriatal input to the thalamus. The thalamus in turn projects back to the cortical areas that gave rise to the corticostriatal projections, thereby closing the cortico–striato–pallido–thalamocortical loop. This loop is involved in the generation and control of motor behavior. Another BG structure, the ventral striatum or nucleus accumbens, is connected with the amygdala, hippocampus, and hypothalamus, and is therefore considered part of the limbic system. Reciprocal connections between the hippocampus and prefrontal cortex are very important for fine processing of memory. It has been proposed that hippocampal formation is recruited via these connections to regulate emotion or to modulate information processing by attaching limbic valence to sensory stimuli. An intricate balance of hippocampus and frontal lobe structures ensures that the constructive process of memory encoding and retrieval creates accurate representation of experience. Hence, interactions between the hippocampus and frontal cortex are crucial for the formation of memory, conscious awareness and self-awareness, which are all somewhat distorted in BD (Heckers, 2004).

4.2. What was the power of the individual studies to detect the differences observed and what sample sizes should be aimed for in future studies?

Many of the individual studies reported non-significant differences between patients and controls raising the question of whether they had sufficient power to detect the effect sizes observed. Some of the more optimistic effect sizes (effect size = mean difference divided by the standard deviation, Cohen, 1988) obtained in the studies for each of the adult metabolites NAA, Cho, mI, Glx, and Cr were 0.52, 0.85, 0.42, 0.97, and 0.43, respectively, and the studies which obtained these effect sizes had total sample sizes (patients and controls) 38, 30, 38, 16, and 30, respectively, yielding power to detect these effect sizes as 34%, 60%, 24%, 44% and 21%, respectively. Therefore most studies were underpowered to detect the slight differences in metabolites between the patients and controls as seemed to be the case upon close of the experiments. In order for each of the studies to have 80% power to detect the effect sizes observed they would have needed total sample sizes (patients and controls) 120, 46, 182, 36, and 168, respectively, numbers that may be unfeasibly large for the expense of performing these experiments. The unfeasibility of performing larger experiments makes meta-analysis an appealing approach for combining the individual studies. But the problem with performing a meta-analysis in this review and the reason it was not done is that the heterogeneity of the studies in terms of the patient populations, medication use, and acquisition parameters. In the future we hope that more studies will contribute findings in each of the different patient populations either with individually large enough sample sizes or by enabling individual meta-analyses

within patient subgroups. New studies should not aim for sample sizes fewer than 40.

4.3. What metabolites have been missed or under-reported?

Although lithium-induced decreases in mI levels have been reported and mI is directly involved in the PI secondary messenger system, available data on mI in BD is both limited and inconsistent. Studies of this metabolite in drug free BD patients in different mood states are needed. Although consistent, available data on Glx in different mood states is insufficient and needs replication at high field magnets given the low signal to noise ratio and overlapping resonances of those metabolites. Cr resonance needs special attention because its levels are assumed to be relatively constant and are often used as an internal standard for comparison. However, the validity of this approach has recently been called into question because of some reports suggesting alteration of this metabolite by disease or medication state (Deicken et al., 2001, 2003; Hamakawa et al., 1998). Thus, further data on Cr resonance in drug free BD patients in different mood states are urgently warranted.

In general, ^{1}H MRS data in manic and depressive BD patients are limited for all metabolites of interest. This is mostly due to the urgency of treatment and the intolerance of patients for scanning in these mood states. To enable successful completion of brain scans–*without head motion*–in those patients that are often agitated and non-cooperative, stringent requirements of well-designed investigations must be balanced with feasibility of MRS applications. For example, study designs allowing pharmacologic sedation with a particular agent without sacrificing homogeneity of data acquisition may be a feasible strategy in MRS investigations of manic or depressed BD patients.

4.4. Is there evidence that metabolic changes parallel short term clinical status-mood states?

Decreased NAA levels in the euthymic and manic phases of BD have been observed in frontal lobe structures and in the hippocampus, whereas no alteration in NAA levels in the depressed state could be detected. A negative correlation between NAA levels in the R hippocampus and illness duration has been reported (Deicken et al., 2003). Available data suggest higher Cho levels in the ACC and BG in bipolar depression and especially in the BG in euthymia. A positive correlation between depression scores and Cho levels in the ACC has also been reported (Moore CM et al., 2000; Moore GJ et al., 2000). Such alterations in Cho were not observed in the manic phases of illness in the three studies that were available. However, in one of these studies a trend for lower Cho in manic bipolar patients was observed (Cecil et al., 2002). One study reported lower Cr levels in the frontal cortex in depressed versus euthymic BD patients (Hamakawa et al., 1999). To understand if opposite polarity in clinical state is reflected in the metabolites of interest or whether the findings detected are trait- or state-dependent, longitudinal ^{1}H MRS studies comparing homogenous populations of BD patients in each of the special mood states to normal controls are required.

4.5. Is there evidence of a difference between the bipolar subtypes BDI and BDII with regard to metabolic profiles in the brain?

Studies comparing regions of prefrontal, frontal, and temporal cortices, as well as areas of the limbic system and basal ganglia in BDI and BDII have generally not found structural and/or functional differences between these two BD subtypes (McGrath et al., 2004). ^{1}H MRS studies in this area are very limited. Four studies reported no significant difference in the metabolic profiles of BDI and II subtypes (Hamakawa et al., 1998; Silverstone et al., 2003; Wu et al., 2004; Dager et al., 2004). Winsberg et al. (2000) observed lower NAA levels in BDI relative to BDII and similar Cho and mI levels in BDI and BDII in the DLPFC. Whereas Kato et al. (1996) reported higher Cho levels in BDII relative to BDI in the BG, Silverstone et al. (2002) reported similar mI levels in BDI and II. Overall these results do not suggest consistent differences between the BDI and II subtypes.

4.6. Are there any differences between childhood and adult presentations of bipolar illness as reflected in metabolic changes in the brain?

Structural imaging studies indicating change in opposite directions of amygdala volumes (smaller in childhood/adolescence and larger in adult) in young versus adult BD patients as compared to controls may suggest a developmental disruption. It is possible that BD in adolescence reflects disruption of critical events related to brain maturation in involved regions with regards to growth, myelination, and pruning (Olvera et al., 2004; Anand and Shekhar, 2003; Haldane and Frangou, 2004). Limited available data suggest lower NAA in the DLPFC and cerebellar vermis in bipolar children in the euthymic state. However, no alteration in Cho in the euthymic state in children with BD is indicated. In manic bipolar children no alteration in NAA and a decrease in Cho have been shown, however, these findings need replication. No study in the depressed state of BD in pediatric patients is available. While one study of mI levels in the MOFC of adult BD patients in manic state reported similar values in patients and NC (Cecil et al., 2002), two studies in manic children reported higher mI levels in the ACC (Davanzo et al., 2001, 2003). In the study by Davanzo et al. (2003), Young Mania Rating Scale scores correlated positively with mI. Lithium-induced decreases in mI have been observed in manic children and depressed adults with BD (Davanzo et al., 2001; Moore et al., 1999). In three studies available in euthymic bipolar children one reported a significant increase in mI levels in the medial frontal cortex (Cecil et al., 2003). In that study patients were mostly drug free, while in the other two they were all on medication. Thus, mI seems to be increased in both euthymic and manic bipolar children, while most of the available data does not support such an alteration in bipolar adults. The preliminary studies in children with BD, where reduced NAA levels and altered mI levels were found, suggest that such abnormalities are already present early in the course of illness. Although limited, all of the available data suggest increased Glx levels in adult BD patients in all mood states.

Again limited data in children supports such an alteration only in the euthymic state. Although two out of ten studies reported decreased Cr levels in euthymic BD patients in the hippocampus and thalamus, most of the available data in adult BD patients did not indicate a change in Cr. Studies in children may suggest lower Cr in the DLPFC and cerebellar vermis.

4.7. Is there evidence that medication changes measurements intra-individually?

There is convincing evidence indicating NAA normalization and/or increasing effects of lithium (Moore CM et al., 2000; Moore GJ et al., 2000; Silverstone et al., 2003). Very limited available data on valproate do not support a similar effect for that mood stabilizer (Silverstone et al., 2003). Frontal gm NAA has also been shown to increase after 4 weeks of olanzapine treatment (DelBello and Strakowski, 2004). Available data suggest that lithium may have a decreasing effect on Cho (Moore et al., 1999; Kato et al., 1996; Wu et al., 2004). Kato et al. (1996) found higher Cho levels to be associated with antidepressant treatment, but another well-designed study by Moore CM et al., (2000), Moore GJ et al., (2000) found lower Cho levels to be associated with antidepressant use. Hamakawa et al. (1998) reported no significant effect of psychotropic medication on the metabolites measured in the BG. There is evidence suggesting a decreasing effect of lithium on mI in the R frontal lobe and ACC of BD (Moore et al., 1999; Davanzo et al., 2001). Hamakawa et al. (1998) observed an association between antipsychotic treatment and higher Cr and between benzodiazepine treatment and lower Cr. In addition to the precise elucidation of the effects of the classical mood stabilizers on brain biochemistry, MRS studies examining the effects of treatment with other commonly prescribed mood regulating agents, such as atypical antipsychotics, lamotrigine or carbamazepine, are required.

4.8. How could the assumed functions of the metabolites of interest be linked to the pathophysiology of BD?

Recent re-investigations into the localization of NAA have revealed that NAA can be expressed in mature oligodendrocytes, that is, myelin, and enter into an inter-compartmental cycling between neurons and oligodendrocytes. Thus, the role or interpretation of NAA may no longer solely indicate neuronal viability, but also the formation and maintenance of myelin and an essential component of neuron↔glia signaling (Baslow, 2000). By using this code, neurons can continuously request metabolic cooperation, insulation (oligodendrocytes), and sustenance (astrocytes) from supporting cells (Baslow, 2000). If neuron↔glia signaling is altered, especially during early development, a deconstruction of the nervous system may be initiated with consequent neuropathology at any developmental stage (Baslow, 2000). Although speculative at this point, if there is a pathological alteration in this chemical code and related cell-to-cell signaling in the brain, as reflected in the lower NAA levels in BD patients in the FL structures and hippocampus, a deconstruction of the nervous system may be provoked, resulting in the symptomatic phases of BD. During these symptomatic phases, with the help of mood stabilizing/neuroprotective agents, NAA levels may be normalized until the underlying defect grounds the next decompensatory phase.

The fact that synthesis of NAA takes place in mitochondria, is reduced by mitochondrial respiratory chain inhibitors, and a mitochondrial pathology being hypothesized in BD, is interesting (Kato, 2003). MRS research indicating decreased intracellular pH and increased lactate in BD patients suggests a shift a way from oxidative phosphorylation toward glycolysis, thus reducing total energy output. These findings and prior implications of mitochondrial dysfunction in BD have recently prompted Stork and Renshaw (2005) to propose an integrative hypothesis that involves impaired oxidative phosphorylation, a resultant shift toward glycolytic energy production, a decrease in total energy production and/or substrate availability, and an altered phospholipids metabolism in BD. In this excellent review authors hypothesize that the majority of MRS findings in BD can be fit into that model. Yet, it remains to be elucidated how lithium, valproate and other mood regulating agents such as atypical antipsychotics and/or lamotrigine can alleviate symptoms of BD within this model.

Analysis of available data on the Cho signal may suggest higher Cho resonance intensities in the BG of bipolar patients. Cho has reportedly increased in neuronal degenerative diseases such as Alzheimer's disease (Meyerhoff et al., 1994), Huntington's disease (Jenkins et al., 1993), and active plaques in multiple sclerosis (Kato et al., 1998) due to accelerated membrane phospholipid turnover and has been accompanied by decreases in NAA. Thus, it has been suggested that decreased NAA, along with elevated Cho signal, may be an indicator of neuronal loss (active neurodegeneration) associated with increased membrane turnover (Winsberg et al., 2000; Rajkowska, 2000). Recent postmortem studies in BD suggest more pronounced alterations of glial than neuronal structures. In addition, the findings indicate a specific pattern of glial loss that is different than the classic morphometric signature of gliosis, i.e., glial hypertrophy in conjunction with glial proliferation similar to that previously observed in the brain from late-stage Huntington's disease (Öngür et al., 1998; Rajkowska et al., 2001). The findings suggest that glial pathology is not a response to ongoing neurodegeneration in the cortex. Given the fact that both in the developing and mature brain, neuronal activity is dependent upon properly functioning glia, these alterations may represent an underlying glial defect, which results in malfunctioning glia providing a defective support/signaling environment for neurons, and thus provokes a subtle neurodegenerative process in BD. Findings of decreased cerebral volume in young multiple-episode patients and studies noting the association of worse neuropsychological performance with illness severity are supportive of such neurodegenerative process in BD (Olvera et al., 2004). Such a mechanism would involve lower NAA and higher Cho in the same brain region. It may be possible that available data coming largely from cross-sectional studies with medicated subjects might have failed to identify such alterations of Cho in the FL related structures and hippocampus or of NAA in the basal ganglia. Indeed, alteration of Cho in the FL of BD patients is indicated

by a longitudinal study of lithium in medication-free bipolar patients by Moore et al. (1999), which reported a significant decrease (compared with baseline) in the FL Cho concentration after chronic lithium administration. Alternatively, the findings of lower NAA in the FL related structures and hippocampus and higher Cho in the BG of bipolar patients may indicate brain region-specific alterations of these metabolites, possibly one reflecting a trait dependent actual pathology and the other reflecting a state dependent disease-related alteration. Future longitudinal studies in drug free bipolar patients will hopefully clarify the actual case.

Recent research demonstrates that glutamate-receptor-mediated excitotoxic cell death might be an important mechanism of cell injury not only in neurons, but also in astrocytes and oligodendrocytes. Injection of excitotoxins acting at Glu receptors causes transient disappearance of glial fibrillary acidic protein positive astrocytes and triggers a process of demyelination that lasts for several days (Haydon, 2001; Gallo and Ghiani, 2000). Glu receptor agonists cause tissue necrosis factor-α (TNF-α) release from microglia, which in turn would activate TNF-α receptors on astrocytes, oligodendrocytes and neurons. Considering findings of decreased glia and neurons in the PFC (Öngür et al., 1998; Rajkowska et al., 2001) and findings of increased Glx in BD patients (Table 4-a), the hypothesis of a hyperglutamatergic state induced neuro- and/or glia-toxicity being involved in pathophysiology of BD deserves further investigation. As an intriguing possible link between Glu excess and the neurobiology of BD, lamotrigine that inhibits the effects of excitatory amino acids has in some cases been used successfully as a mood stabilizer (Sapolsky, 2000).

4.9. Is neurochemical profile of the brain in BD different than unipolar depressive disorder?

Brambilla et al. (2004) found significant reductions in the total callosal area of BD patients compared to NC suggesting disruption of inter-hemispheric communications in the FL in BD, something not identified in unipolar depressive disorder–MDD. In keeping with this, the metabolic profile of brain as detected by ^{1}H MRS seems to be different in BD than MDD. Available literature suggests increased Cho/Cr levels in the BG while NAA seems to be unaltered in the FL and BG of MDD patients. This may suggest increased membrane turnover in MDD without a neurodegenerative outcome. While a hyperglutamatergic state in BD is plausible a hypoglutamatergic state in MDD seems more likely (Yildiz-Yesiloglu and Ankerst, in press). These findings may suggest that distinct pathophysiological mechanisms are involved in these mood disorders.

4.10. What are the technical implications for future studies?

1.5 or 2 T magnetic field strengths, which are mostly available in clinical settings, seem sufficient to detect alterations of the metabolites NAA and Cho. However, newly available higher field magnets including 3, 4.7, 8 and even 9.4 T, will be more beneficial for the metabolites with overlapping lower resonance intensities, such as mI, Glu, Gln, GABA. Besides, optimization of pulse sequences specifically targeting individual metabolites of interest will provide better spatio-temporal resolution and higher sensitivity. Both 1D and 2D multi-slice chemical shift imaging (CSI) methods provide a larger ROI to be assessed during a shorter period with greater spatial resolution. Although most ^{1}H MRS studies reported no difference, there are some reports suggesting altered Cr levels by disease or medication effects. Thus the Cr ratio method used for spectral quantification needs validation in well-designed studies. Until then, it may be judicious to use absolute concentrations in ROIs suitable for this approach or an external standard of known concentration as the reference peak.

4.11. Limitations

Because of the heterogeneity of the MRS methods utilized, variability of ROI studied, and the heterogeneity of the bipolar samples in terms of the diagnostic and medication status we could not perform meta-analyses of the available data. Yet in spite of the heterogeneous methodologies, the data reviewed here still show a significant degree of consistency. Medication is an obvious source of concern, primarily because relevant data are now just emerging. Another potential limitation may be the Cr ratio method rendered for spectral quantification in most of the studies. Absolute metabolite concentrations may represent a potential advantage over ratios in terms of sensitivity, especially if the reference compound itself is subject to alterations. However, absolute concentrations are also referenced to brain water and can be significantly influenced by the cerebrospinal fluid (CSF) content of the ROI. In addition, the Cr referencing approach helps to control for variance associated with assay irregularities across regions and subjects, such as magnetic field inhomogeneities, and for partial volume effects (Bertolino et al., 2003). Most of the studies, especially in adult BD subjects, indicate no significant difference in Cr resonance. Nevertheless, the reports suggesting some alteration of this metabolite either by disease or medication effects necessitate cautious evaluation of the present findings.

5. Conclusion

The studies reviewed in this paper suggest regional abnormalities of the brain biochemistry in BD, with the DLPFC, prefrontal and AC cortices, hippocampus, and BG being specifically implicated. Some common themes of alteration in brain biochemistry, in particular with NAA, Cho and Glx, as just reviewed, have emerged from studies done so far. Given the fact that both in the developing and mature brain neuronal activity is dependent upon properly functioning glia and a specific pattern of glial loss is detected in BD, we postulate a glial defect as being pivotal in the pathophysiology of BD. As technological advances occur, MRS will continue to be used as a research tool to understand the neurochemical effects of pharmacologic agents and in the future, also may be used as a clinical tool to create targeted treatment strategies for patients with BD.

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