Chapter 6

Magnetic Resonance Spectroscopy in Bipolar Disorder

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6.1 Background

Bipolar disorder (BD) is associated with cognitive impairment and mood dysregulation. It is clear that BD pathophysiology primarily affects the brain with implications in other areas, such as the gut microbiota, but is overwhelmingly a central nervous system (CNS) disorder (Scaini et al., 2021; Yildiz-Yesiloglu & Ankerst, 2006). However, the etiology of BD and the mechanism by which neural abnormalities translate in to clinical symptoms remain largely unknown. Neuroimaging is one tool that may bridge this knowledge gap. Neuroimaging studies of BD patients consistently show abnormalities related to structure (e.g., computed tomography or magnetic resonance imaging [MRI]) and function (e.g., positron emission tomography [PET], functional MRI, single-photon emission computed tomography, and ^{18}[F]fluorodeoxyglucose) of frontal and cortical areas (Strakowski, DelBello, Adler, Cecil, & Sax, 2000).

6.2 Proton magnetic resonance spectroscopy

Magnetic resonance spectroscopy (MRS) is a noninvasive, repeatable, and radiation-free neuroimaging technique that assesses the brain's metabolic profile by measuring energy metabolism and neurochemical composition of tissue

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in vivo. Using the same general technique as MRI, which provides structural information based on the spatial position of hydrogen nuclei in water-rich tissue, MRS provides compositional information by suppressing the abundant water signal and identifying additional molecular content in tissue (Buonocore & Maddock, 2015). The most widely used spectroscopy technique is proton MRS (^{1}H-MRS), but other techniques are available, such as ^{31}P-MRS, which focuses on phosphorous instead of hydrogen (as well as ^{7}Li, ^{13}C, ^{17}O, ^{19}F, ^{23}Na MRS) (Paslakis, Träber, Roberz, Block, & Jessen, 2014; Strakowski et al., 2000).

^{1}H-MRS detects and identifies distinct molecules based on the subtle difference in the frequency of resonance signals produced by different local molecular configurations, or "chemical shifts" (Paslakis et al., 2014). These signals, which correspond to various metabolites are displayed on a spectrum based on frequency and expressed in parts-per-million (ppm) (Buonocore & Maddock, 2015). ^{1}H-MRS quantifies the neurochemical profile of the brain by measuring metabolites like glutamate (Glu), glutamine (Gln), gamma-aminobutyric acid (GABA), *N*-acetyl-aspartate (NAA), choline (Cho), creatine (Cr), myo-inositol (mI), and lactate (Lac). To differentiate between metabolite signals that often overlap, a range of magnetic field strengths are used. Typically, the field strengths of clinical equipment range from 0.2 to 7 T (Tesla), while experimental magnets use up to about 12 T, which provides a higher resolution image with better spatial sensitivity. Magnetic field strengths of 1.5 or 2 T can detect Cho and NAA, but mI, GABA, Glu, and Gln resonate at lower intensities and require higher field strength. Chemical shift imaging methods also allow for a larger, higher resolution region of interest (ROI) in a shorter period of time (Ladd et al., 2018; Yildiz-Yesiloglu & Ankerst, 2006).

^{1}H-MRS is often performed using single-voxel spectroscopy, focusing on a specific brain ROI that is covered by one single voxel, such as the hippocampus. In contrast, MRS imaging provides a more complete "metabolic map" showing larger regional molecular concentrations (Paslakis et al., 2014). Internal/external concentration standards are used to calibrate resonance signals and quantify the MRS spectra of various metabolites. Some studies use absolute quantifications which contrast observed neurometabolite levels to those of other patients or populations, while others use ration quantification, comparing observed levels to a constant internal standard, such as Cr content (Wu et al., 2018). However, recent evidence indicates that Cr levels may not be constant in psychiatric disorders, despite longstanding assumptions to the contrary (Kraguljac et al., 2012; Yildiz-Yesiloglu & Ankerst, 2006). This finding will impact clinical and research MRS techniques, disrupting a frequently applied internal standard.

6.3 Metabolite abnormalities in bipolar disorder

6.3.1 Glutamatergic hyperactivity

6.3.1.1 Glx (glutamate, glutamine, gamma aminobutyric acid)

Glu and GABA are, respectively, the CNS's primary excitatory and inhibitory neurotransmitters accounting for the overwhelming majority of all

neurotransmission in the brain (Duman, Sanacora, & Krystal, 2019; Stagg et al., 2011). Together, these neurotransmitters control the brain's overall levels of excitation and play a role in neuronal migration, differentiation, and synaptic plasticity (Eastwood & Harrison, 2010; Rossignol, 2011; Stagg et al., 2011). Increasing evidence suggests a neurobiological role for GABA−Glu imbalance in the pathophysiology and etiology of BD as well as other mood disorders (Brady et al., 2012; Duman et al., 2019; Machado-Vieira, Manji, & Zarate, 2009; Yüksel & Öngür, 2010).

The mood instability and cognitive impairments associated with BD may come from an imbalance between excitatory Glu and inhibitory GABA in key cortical areas responsible for affective regulation, such as the anterior cingulate cortex (ACC) (Krystal et al., 2002; Lener et al., 2017; Prevot & Sibille, 2021). This hypothesis is supported by evidence of Glu/GABA abnormalities in BD patient's cerebrospinal fluid (CSF), post-mortem brain tissue (PMBT), and various neuroimaging techniques (Gigante et al., 2012). Because Glu and Gln are very similar molecules, their ^{1}H-MRS signals, represented by wide peaks between 3.2 and 3.4 ppm, overlap significantly and can therefore appear indistinguishable (Buonocore & Maddock, 2015). Because it peaks in the same range, the same can be true for GABA, depending on the magnetic field strength of the MRS technique (Govindaraju, Young, & Maudsley, 2000). While it is possible to differentiate between these molecules using higher magnetic fields or specialized techniques, most studies refer to the collective Glu + Gln signals as "Glx," indicating overall glutamatergic activity (Yüksel & Öngür, 2010).

The aberrant increase in glutamatergic activity likely leads to excitotoxicity through overactivation of glutamatergic receptors and postsynaptic calcium influx, and ultimately results in neuronal damage and cell death. Unintuitively, there is not enough evidence to consider excess ACC Glx metabolites as a biomarker of BD, due to lack of clarity surrounding Glx concentrations. While Glx is generally considered indicative of glutamatergic neurotransmission, the concentration of Glu to Gln to other metabolites is unclear, and while studies generally corroborate increased Glx, increased ACC Glu is not robustly supported. However, increased ACC Gln is characteristic of euthymic and depressive BD mood states. Gln can be considered a nonexcitatory form of stored Glu; therefore some suggest that this cycle may function as a buffering mechanism to combat excitotoxicity. Another confounding factor is the Glu−Gln cycle which constantly shifts metabolite concentrations, represented by Glu/Gln ratios, which may be affected by anticonvulsants. Medications that act on GABA, such as benzodiazepines and anticonvulsants, may also confound results, which overwhelmingly show unaltered GABA levels in ^{1}H-MRS studies. However, if overactive glutamatergic signaling does play a substantial role of BD pathophysiology, it makes sense that concentrations/activity of GABA, the inhibitory mediator of glutamatergic activity, is unchanged even during periods of Glu overactivity. This lack of a reactionary mechanism to sufficiently combat glutamatergic overactivity may indirectly increase it.

Despite several lines of evidence showing GABA abnormalities in BD, reviews/*meta*-analyses of MRS studies in BD have not found any significant indications of GABA concentration abnormalities in the brains of BD patients compared to healthy controls. However, this is likely a product of the lack of comparable, high-quality studies and seemingly unavoidable confounds than true evidence of the state of GABA concentrations in the BD brain. One review, Chiapponi, Piras, Piras, Caltagirone, and Spalletta (2016) of five studies concluded that the heterogeneity of the studies' designs precluded and consensus of evidence. A different *meta*-analysis corroborated these findings, stating that there is need for GABA measurement in medication-free states, as medications such as anticonvulsants and benzodiazepines have been shown to affect GABA (Sanacora, Mason, Rothman, & Krystal, 2002; Scotti-Muzzi et al., 2021). See Fig. 6.1 for Glu−GABA interactions.

6.3.2 Mitochondrial dysfunction and neuronal alterations

6.3.2.1 N-*acetyl-aspartate*

The most prominent MRS signal is NAA, which peaks at about 2.0 ppm (Paslakis et al., 2014). NAA is synthesized in neuronal mitochondria and therefore associated with the functional integrity of neuronal energy consumption (Arun, Moffett, & Namboodiri, 2009; Clark, 1998; Moffett, Ross, Arun, Madhavarao, & Namboodiri, 2007). Because of its sensitivity to mitochondrial oxidative phosphorylation, NAA can be applied as a marker of neuronal density, damage, and overall integrity (Birur, Kraguljac, Shelton, & Lahti, 2017; Cheng et al., 1997; Lentz et al., 2005; Paslakis et al., 2014). Although its specific function is not fully understood, NAA is found highly concentrated in healthy neurons and plays a putative role in osmoregulation, Glu modulation, myelin synthesis, and neuron−glia signaling (Baslow, 2003; Moffett et al., 2007). Decreased NAA concentrations in gray matter (Paslakis et al., 2014), particularly frontal cortical areas like the prefrontal cortex (PFC) and basal ganglia (BG) are a consistent finding among *meta*-analyses of proton MRS studies in BD (Birur et al., 2017; Kraguljac et al., 2012).

Across psychiatric disorders, NAA levels are sensitive to treatment and increase even following nonpharmacological therapies such as electroconvulsive therapy (Michael et al., 2003), cognitive behavioral therapy (Premkumar et al., 2010), and physical exercise (Pajonk et al., 2010). In BD, short-course (weeks to months) lithium and valproate therapy result in widespread increases in NAA levels not observed in association with long-term treatment (>9 months), suggesting that NAA concentrations reflect short-term neuronal functioning, and more specifically, the functional status of neuronal mitochondria (Manji et al., 2012; Paslakis et al., 2014). In animal models, NAA reductions follow the administration of mitochondrial toxins even outside of

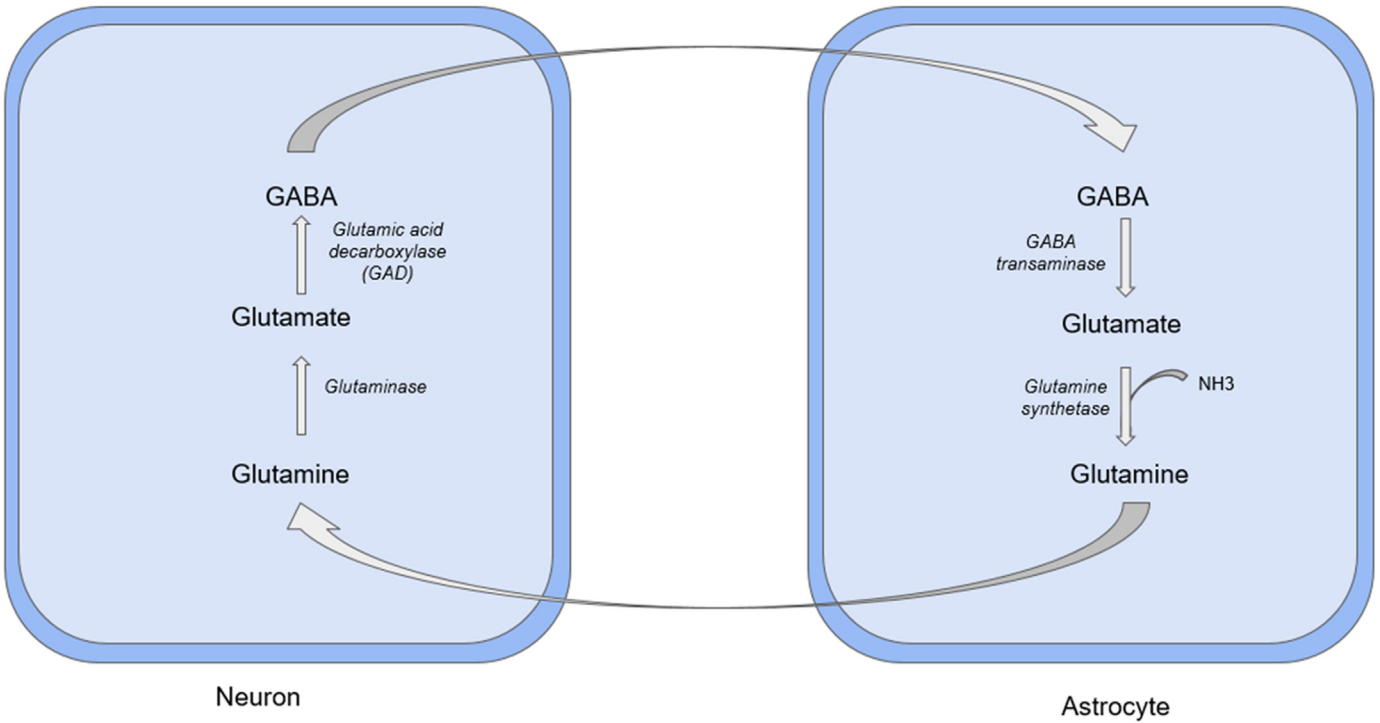

FIGURE 6.1 The glutamine−GABA pathway cycling between a neuron and astrocyte. The neuron begins by receiving glutamine from astrocyte cells and is then metabolized to glutamate via the enzyme glutaminase. Glutamate then becomes GABA via the enzyme glutamic acid decarboxylase. GABA then leaves the neuron and enters the astrocyte cell where it is transformed to glutamate by the enzyme GABA transaminase. Glutamate then combines with NH_3 and becomes glutamine by the enzyme glutamine synthetase.

the context of neuronal death, suggesting an intrinsic link between NAA levels and mitochondrial function that cannot be explained by overall cellular health and function (Bates et al., 1996; Dautry et al., 2000).

Overall, decreased NAA levels in key cortical areas associated with cognitive and affective mediation suggest that mitochondrial dysfunction is involved in the pathophysiology of BD, while findings of NAA increases following treatment may reflect mitochondrial restoration as well as improved neuronal and synaptic plasticity (Anglin, Mazurek, Tarnopolsky, & Rosebush, 2012; Manji et al., 2012). These findings also implicate NAA concentrations as a potential disease nonspecific treatment response biomarker (Birur et al., 2017; Paslakis et al., 2014), though only in the short term.

6.3.2.2 Choline

Cho and choline-containing compounds show peaks at approximately 3.2 ppm. Cho is a marker of cellular turnover and plays an important role in cell membrane integrity (Birur et al., 2017), memory and mood regulation, DNA synthesis (Ueland, 2011), and has neuroprotective properties (Skripuletz et al., 2015). Cho is an essential precursor to production of neurotransmitter acetylcholine and plays a vital role in cellular and organelle phospholipid membrane integrity, and therefore signal transduction. It also acts as a source of methyl groups necessary for proper cellular metabolism processes (Zeisel & Blusztajn, 1994). Cho resonance has been considered a possible biomarker of the status of membrane phospholipid metabolism based on its primary composition of phosphorylcholine and glycerophosphorylcholine (Birur et al., 2017).

Abnormalities in Cho resonance have been linked to neurodegeneration (Birur et al., 2017). According to MRS studies and *meta*-analyses from the last two decades, ACC Cho levels may be a trait marker of BD (Monkul, Yildiz, & C Soares, 2004; Scotti-Muzzi et al., 2021). In ^{1}H-MRS studies, increased ACC Cho levels are shown in medication-free BD patients as well as during euthymic and depressive mood states. Elevated Cho levels in the ACC and BG have also been correlated with depressive severity (Moore et al., 2000; Wu et al., 2018). Cecil, DelBello, Morey, and Strakowski (2002) reported elevated ACC Cho concentrations in manic BD patients, but *meta*-analyses have not established a robust connection between mania and cortical Cho concentrations, likely due to a lack of data since few neuroimaging studies focus on manic patients (Scotti-Muzzi et al., 2021).

Cho plays a role in BG myelin formation and maintenance, which are implicated in the pathophysiology of BD (Olvera, Glahn, Caetano, Pliszka, & Soares, 2004). Phospholipid cycling and neuronal membrane metabolism, commonly associated with neurodegenerative and demyelination processes, release membrane Cho compounds, suggesting that increased MRS Cho levels act as a chemical marker of increased phospholipid turnover and

neuromorphometric losses (Stork & Renshaw, 2005). Therefore observations of elevated ACC Cho levels may be associated with cortical thinning, a consistent neuroanatomical finding that is particularly robust in the ACC of BD patients (Hibar et al., 2018).

6.3.2.3 Creatine

Cr resonance (3.0 ppm peak) appears at higher levels in gray matter compared to white matter, and reflects both Cr and phosphocreatine content, with this equilibrium dependent on cellular energy demands (Yildiz-Yesiloglu & Ankerst, 2006). During periods of intense neuronal activity and high energy demand, phosphocreatine functions as a secondary energy source for ATP production and is rapidly metabolized, leading to an acute drop in total Cr levels, which normally remain stable (Kato, Murashita, Shioiri, Hamakawa, & Inubushi, 1996). This suggests that Cr can be a marker of neuronal energy production (Öngür, Prescot, Jensen, Cohen, & Renshaw, 2009). Indeed, persistent phosphocreatine (PCr) reductions may disrupt energy production and lead to a perpetual state of ATP deficit in the neuron (Stork & Renshaw, 2005). Therefore decreased Cr levels may indicate long-term deficits in energy production and metabolic abnormalities consistent with the growing body of evidence implicating mitochondrial dysfunction in BD pathophysiology (Fries et al., 2020; Manji et al., 2012).

Several ^{1}H-MRS studies demonstrate Cr abnormalities in the PFC and BG in association with mood phase and medication status (Birur et al., 2017; Wu et al., 2018). Interestingly, Öngür et al. (2009) reported age-related Cr abnormalities in HC, but not psychiatric patients. Specifically, Cr levels declined with age in HC, while BD and Schizophrenic (SZ) patients demonstrated reduced Cr levels at young ages. This finding is consistent with evidence of premature aging and altered metabolic function in BD pathophysiology (Fries et al., 2020; Scaini et al., 2021).

6.3.2.4 Lactate

Lac (1.3 ppm peak) is an important component linking astroglial glucose uptake and metabolism with neurotransmitter cycling and mitochondrial function (de Graaf, 2019; Dogan, Yuksel, Du, Chouinard, & Öngür, 2018). Lac is a product of glycolysis, the pathway used when the brain is unable to carry out its preferred method of energy production, oxidative phosphorylation. Oxidative phosphorylation occurs in the mitochondria, but increasing evidence suggests that mitochondrial dysfunction associated with BD may shunt cells toward anaerobic metabolism, thereby increasing Lac production (Scaini et al., 2021). Studies showing increased Lac in the CSF of patients with BD support this theory, but the mechanism linking BD to mitochondrial dysfunction remains largely unknown (Dager et al., 2004; Dogan et al., 2018; Regenold et al., 2009; Xu et al., 2013; Yoshimi et al., 2016). Despite

the relatively small number of ^{1}H-MRS studies investigating Lac levels in BD, a recent systematic review showed the cortical concentrations are elevated in the ACC, BG, and other key frontal areas, regardless of medication status and mood state (Dogan et al., 2018). Machado-Vieira and collaborators found increased Lac levels in the cingulate cortices of chronically ill, medication-free patients during depressed/mixed mood states, which decreased following short course lithium monotherapy. These findings shed light on a possible mechanism by which lithium is used to alter mitochondrial function in patients with BD (Soeiro-de-Souza et al., 2016).

In contrast, Brady and colleagues found no difference in Lac levels between manic BD patients and controls (Brady et al., 2012). During a follow-up, significantly lower Lac levels were observed in euthymia compared to the same patients during manic state and healthy controls, suggesting oxidative phosphorylation dysfunction in BD regardless of mood state or clinical presentation (Brady et al., 2012). Studies in this area are heterogenous in their methods and patient criteria but demonstrate a pattern of Lac overactivity suggestive of Lac abnormalities as a trait marker for BD (Dogan et al., 2018). Overall, these findings may contribute to the convergent bolstering of the mitochondrial hypothesis in the etiology of BD, and further inquiry is being conducted. Lac is just one of the mitochondrial metabolites that has been associated with BD, as other markers include decreased ATP, ADP, and NAA (Kato, Takahashi, Shioiri, & Inubushi, 1992; Scaini et al., 2016; Scaini et al., 2021). Dogan and colleague's systemic review emphasizes the utility of other MRS techniques in refining Lac measurements, such as ^{31}P-MRS, which indirectly measures pH through corollary quantification (Dogan et al., 2018; Santos-Díaz & Michael, 2020). See Fig. 6.2 for an explanation of the relationship between NAA, Cho, Lac, and Cr.

6.3.3 Intracellular signaling abnormalities

6.3.3.1 Myo-Inositol

mI is abundant in CNS tissue and acts as a precursor molecule for inositol lipid synthesis, which mediates cellular signaling and membrane homeostasis. (Fisher, Novak, & Agranoff, 2002). mI (3.56 ppm peak) is a sugar involved in a variety of neuronal functions relevant to BD and other psychopathologies, including signal transduction, calcium homeostasis, and a possible prophylactic mechanism of lithium (Fisher et al., 2002; Yildiz-Yesiloglu & Ankerst, 2006). mI concentration alterations may indicate abnormal intracellular signaling patterns in BD based on its pervasive role in intracellular signaling pathways, modulating Ca^{2+} homeostasis, signal transduction, and overall neuronal function (Fisher et al., 2002). A *meta*-analysis of mI levels in mood disorders showed significant abnormalities in the frontal regions, including BG and cingulate gyrus, in patients during manic and depressive mood states, but not euthymia,

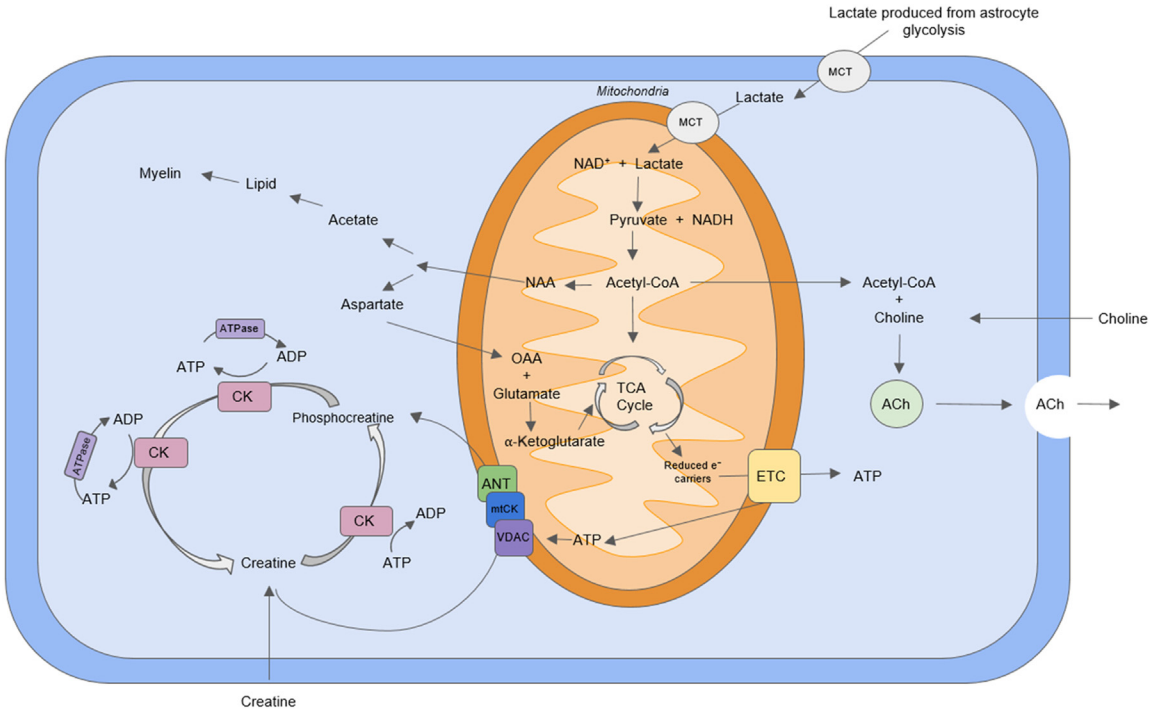

FIGURE 6.2 Pathways of NAA, choline, lactate, and creatine. NAA is produced from acetyl-CoA, which then goes on to produce aspartate and acetate. Aspartate is then metabolized into oxaloacetate (OAA), which then combines with glutamate to generate alpha-ketoglutarate that enters the TCA cycle in order to generate ATP. Choline enters the cell and combines with acetyl-CoA to produce acetylcholine, which then leaves the cell via a vesicular transport mechanism. Lactate, a product of glycolysis, can enter the cell and mitochondria through monocarboxylate transporters (MCTs). It then combines with NAD + to produce pyruvate and NADH via the mitochondrial lactate oxidation complex. The produced pyruvate can go on to generate acetyl-CoA and enter the TCA cycle. Creatine enters the cell and is phosphorylated by creatine kinase, generating ADP and phosphocreatine. An alternate pathway to generating phosphocreatine is through the use of a mitochondrial creatine kinase that utilizes ATP from the TCA cycle to phosphorylate creatine. Phosphocreatine is then phosphorylated, creating ATP and regenerating creatine.

suggesting mI could be a treatment response biomarker (Silverstone, McGrath, & Kim, 2005). This is supported by evidence of an association between lithium's mechanism of prophylactic action and mI activity.

However, there are still inconsistencies in mI MRS evidence. mI levels decrease with lithium treatment in patients experiencing acute mood episodes (Monkul et al., 2004), but not in euthymic patients regardless of medication status (Silverstone et al., 2005). The mI/Cr ratio in the ACC was found to be significantly higher in unmedicated bipolar depressed patients compared to HC, and, after 6 weeks of lithium monotherapy, subjects who had achieved euthymia had mI/Cr levels that no longer differed from those of HC (Soeiro-de-Souza et al., 2021). This effect highlights lithium's inhibition of inositol monophosphatase in the phosphatidylinositol pathway, thus decreasing mI levels (Harwood, 2005). However, baseline mI levels among BD patients compared to HC remain unclear, as a recent *meta*-analysis focused on mI levels in the ACC using ^{1}H-MRS found no significant differences between BD subjects and HC (Scotti-Muzzi, Umla-Runge, & Soeiro-de-Souza, 2021). See Fig. 6.3 for more on the inositol pathway in BD.

6.4 Brain regions involved in cognitive and affective regulation

In neuroimaging studies of affective disorders, the ACC has been the most well-studied brain region due to its unique integration of cognitive and affective neuronal connections, as well as its connection to key frontolimbic structures (Bush, Luu, & Posner, 2000; Strakowski, Adler, et al., 2012). As such, many studies show morphological and functional abnormalities in the ACC associated with BD and other mood disorders. Indeed, decades of research support reduced ACC gray matter in BD patients compared to healthy controls (Drevets, Price, et al., 1997; Drevets, Savitz, & Trimble, 2008; Haldane & Frangou, 2004; Hibar et al., 2018; Savitz, Price, & Drevets, 2014). *Meta*-analyses consistently support ACC glutamatergic abnormalities in the pathophysiology of BD (Fusar-Poli, Howes, Bechdolf, & Borgwardt, 2012; Gigante et al., 2012; Scotti-Muzzi et al., 2021), which coincides with findings from functional and morphological studies. Several key neurometabolic alterations in BD appear mood state dependent (Scotti-Muzzi et al., 2021). However, ^{1}H-MRS studies in BD are uniquely challenging due to the heterogenous presentation of BD symptoms and presence of at least three mood states (manic, depressed, euthymic), which can cooccur in a significant portion of patients (i.e., mixed states). So, although ^{1}H-MRS studies consistently show altered neurometabolite levels in cortical regions, such as the ACC and frontal lobe, any assigned relationship between findings and clinical presentation is tenuous. This challenge is further exacerbated by the relatively few meta-analyses/systematic reviews accounting for mood states or medication status in subjects. Mood state appears associated with distinct neurochemical profiles in the BG. Mood state is associated with significant abnormalities in the

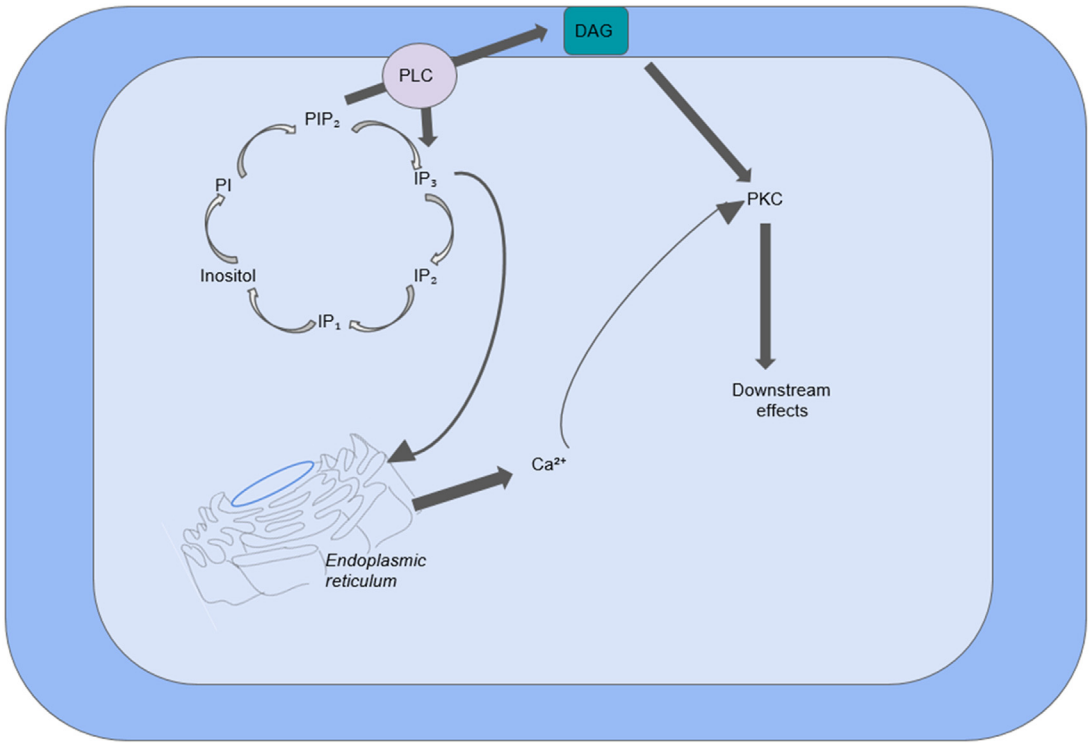

FIGURE 6.3 The myo-inositol signaling pathway. Upstream regulators activate phospholipase C (PLC), triggering the generation of IP3 and activating diacylglycerol (DAG). IP3 then goes on to activate the endoplasmic reticulum, triggering release of calcium stores which activate protein kinase C (PKC). IP3 continues to cycle, creating IP2 and eventually creating inositol. Inositol continues the cycle, generating PI and PIP2. PIP2 creates additional IP3 and further activates DAG. DAG then goes on to further activate PKC, setting off downstream pathways.

TABLE 6.1 Matrix of neurometabolite abnormalities by brain region and clinical characteristics.

	Frontal areas	PFC	ACC	BG
BD	↑Glx[a] ↓NAA[a] ↓ mI ↑Lac ↓Cho	↓NAA[a]	↑Glx ↑Gln ↓Glu ↑Lac ↑Cho	↑Cho[a] ↓NAA ↑Lac
Mania				↓Cho ↓NAA ↓Cr
Depression	↓mI ↓NAA		↑Cho	↑Cr ↑Cho*
Euthymia	↓NAA	↓NAA	↑Glx ↑Gln ↑Cho	↑Cho
Medication free	↑Glx		↑Cho	
Medicated	↑NAA ↑Glx	↑NAA	↑Cho ↑Gln ↑Glx	↓Cho

Abbreviations: *BD,* bipolar disorder; *PFC,* prefrontal cortex; *ACC,* anterior cingulate cortex; *BG,* basal ganglia; *Glx* combined glutamatergic metabolites; *NAA, N*-acetyl-aspartate; *mI,* myo-inositol; *Lac,* lactate; *Cho,* choline; *Gln,* glutamine; *Glu,* glutamate; *Cr,* creatine. *References (systemic reviews/meta-analyses):* Birur et al., 2017; Cecil et al., 2002; Chitty, Lagopoulos, Lee, Hickie, & Hermens, 2013; Dogan et al., 2018; Fusar-Poli et al., 2012; Gigante et al., 2012; Kraguljac et al., 2012; Monkul et al., 2004; Paslakis et al., 2014; Schür et al., 2016; Scotti-Muzzi et al., 2021; Silverstone et al., 2005; Yildiz-Yesiloglu et al., 2006; Wu et al., 2018.
[a]*Indicates a strong finding from more than one systematic review/*meta-*analysis.*

BG of BD patients, implicating Cho, NAA, and Cr in particular (Wu et al., 2018). This corroborates other lines of evidence linking the BG to BD pathophysiology, such as volumetric abnormalities (Strakowski et al., 2002). PET scanning has demonstrated low glucose metabolism in the BG associated with BD, suggestive of energy metabolism abnormalities (Buchsbaum et al., 1986). See Table 6.1 for an overview of MRS neurometabolite findings in BD based on clinical presentation and brain area.

6.5 Conclusion and future directions

Few ^{1}H-MRS studies investigate neurometabolite concentration differences between BD subtypes, and of those that do, most report no significant differences. However, neurometabolic profiles between BD and MDD show

inconsistencies that may reflect distinctions in pathophysiologic mechanisms. In MDD, NAA levels appear unaltered in the frontal lobe compared to HC, while in BD, frontal NAA abnormalities are shown across mood states and may be a disease marker (Yildiz-Yesiloglu & Ankerst, 2006). Few ^{1}H-MRS studies have investigated these neurometabolites in manic and medication-free BD patients as well as children with BD, hindering our ability to identify biomarkers with clinical applicability. However, conducting neuroimaging investigations on patients experiencing mania is uniquely difficult since manic episodes are difficult to predict. In addition, neuroimaging requires a patient to lie still for 15−90 minutes, which may be difficult for manic patients or children. Future ^{1}H-MRS investigations should consider less heterogeneity in study design and make careful considerations of the patient population, including subtype, mood state, and other clinical features. MrRS in BD is a burgeoning field that may be able to identify biomarkers to help identify the disease and judge treatment efficacy.

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