MR Spectroscopic Studies of the Brain in Psychiatric Disorders

Richard J. Maddock and Michael H. Buonocore

Abstract The measurement of brain metabolites with magnetic resonance spectroscopy (MRS) provides a unique perspective on the brain bases of neuropsychiatric disorders. As a context for interpreting MRS studies of neuropsychiatric disorders, we review the characteristic MRS signals, the metabolic dynamics, and the neurobiological significance of the major brain metabolites that can be measured using clinical MRS systems. These metabolites include *N*-acetylaspartate (NAA), creatine, choline-containing compounds, myo-inositol, glutamate and glutamine, lactate, and gamma-amino butyric acid (GABA). For the major adult neuropsychiatric disorders (schizophrenia, bipolar disorder, major depression, and the anxiety disorders), we highlight the most consistent MRS findings, with an emphasis on those with potential clinical or translational significance. Reduced NAA in specific brain regions in schizophrenia, bipolar disorder, post-traumatic stress disorder, and obsessive–compulsive disorder corroborate findings of reduced brain volumes in the same regions. Future MRS studies may help determine the extent to which the neuronal dysfunction suggested by these findings is reversible in these disorders. Elevated glutamate and glutamine (Glx) in patients with bipolar disorder and reduced Glx in patients with unipolar major depression support models of increased and decreased glutamatergic function, respectively, in those conditions. Reduced phosphomonoesters and intracellular pH in bipolar disorder and elevated dynamic lactate responses in panic disorder are consistent with metabolic models of pathogenesis in those disorders. Preliminary findings of an increased glutamine/glutamate ratio and decreased GABA in patients with schizophrenia are consistent with a model of NMDA hypofunction in that disorder.

R. J. Maddock (✉) · M. H. Buonocore
University of California Davis Medical Center, Sacramento, CA, USA
e-mail: rjmaddock@ucdavis.edu

Curr Topics Behav Neurosci
DOI: 10.1007/7854_2011_197

As MRS methods continue to improve, future studies may further advance our understanding of the natural history of psychiatric illnesses, improve our ability to test translational models of pathogenesis, clarify therapeutic mechanisms of action, and allow clinical monitoring of the effects of interventions on brain metabolic markers.

Keywords Frontal · Limbic · Cortex · Neural · Glial · Metabolism

Abbreviations

1H-MRS	Proton magnetic resonance spectroscopy
2D	Two dimensional
31P-MRS	Phosphorous magnetic resonance spectroscopy
ADP	Adenosine diphosphate
AGAT	Arginine-glycine aminotransferase
ASICs	Acid sensing ion channels
ASPA	Aspartoacylase
Asp-NAT	Aspartate N-acetyltransferase
ATP	Adenosine triphosphate
CK	Creatine kinase
CNS	Central nervous system
CO2	Carbon dioxide
CSF	Cerebrospinal fluid
CSI	Chemical shift imaging
EAAT1	Excitatory amino acid transporter 1
EAAT2	Excitatory amino acid transporter 2
ECF	Extracellular fluid
EEG	Electroencephalogram
GAA	Guanidinoacetate
GABA	Gamma aminobutyric acid
GABA-T	Gamma aminobutyric acid transaminase
GAD	Glutamic acid decarboxylase
GAD65	65 kilodalton form of GAD
GAD67	67 kilodalton form of GAD
GAMT	Guanidinoacetate methyltransferase
GAT	GABA transporter
Glx	The combined signal from glutamate and glutamine
GPCho	Glycerophosphorylcholine
H+	Hydrogen ions
Hz	Hertz, or cycles per second
Km	Michaelis-Menten constant
MCT	Monocarboxylate transporter
MEGA	Mescher-Garwood
mM	Millimoles
MR	Magnetic resonance

MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
MRS	Magnetic resonance spectroscopy
MRSI	Magnetic resonance spectroscopic imaging
MRUI	Magnetic Resonance User Interface
ms	Milliseconds
NAA	N-acetylaspartate
NAAG	N-acetylaspartylglutamate
NMDA	N-methyl-D-aspartic acid
OCD	Obsessive compulsive disorder
PCho	Phosphorylcholine
PEPSI	Proton echoplanar spectroscopic imaging
pH	Negative logarithm of hydrogen ion concentration
PMEs	Phosphomonoesters
ppm	Parts per million
PRESS	Point resolved spectroscopic sequence
PTSD	Post traumatic stress disorder
SSRI	Selective serotonin reuptake inhibitor
TCA	Tricarboxylic acid
TE	Echo time
VGluT	Vesicular glutamate transporter

Contents

1 Introduction

Approximately 60% of the human body is water. Most clinical applications of magnetic resonance phenomena involve creating images based primarily on the magnetic properties of the nuclei of hydrogen atoms in water molecules. In contrast, magnetic resonance spectroscopy (MRS) provides information based on the magnetic properties of atomic nuclei present in other molecules in addition to water. Generally, this information is in the form of MR spectra, which display a series of resonance signals. The strength of each signal is proportional to the concentration of molecules containing nuclei that resonate at the indicated frequency. Although MR spectra from the atomic nuclei of several different elements in the body can be measured, most MRS studies using clinical MR systems measure spectra from the nucleus of the hydrogen atom. In this review, the MR spectra from hydrogen nuclei are referred to as 1H-MRS. MRS information can also be displayed as low-resolution images [chemical shift imaging (CSI) or magnetic resonance spectroscopic imaging (MRSI)], in which image contrast is based on regional differences in the concentration of a specific molecule.

The substance of this review is divided into two sections. The first section reviews the molecules most commonly studied with MRS in the human brain. It describes the pattern of MRS resonance peaks arising from each such molecule, the pathways for biosynthesis and degradation of each molecule, and reviews current understandings of the neurobiological function and the significance of abnormal concentrations of each molecule. This section is intended to provide the metabolic and neurobiologic background for interpreting MRS observations about each of the major metabolites studied with 1H-MRS in the human brain. In discussing each metabolite, special emphasis is given to metabolic and signaling functions that may be relevant to translational models of psychiatric disorders. The second section reviews and summarizes the scientific literature on brain MRS studies of major psychiatric disorders, including schizophrenia, bipolar disorder, unipolar major depression, and anxiety disorders. In order to provide a context for interpreting these MRS findings, this section also provides an overview of the literature on brain structure and function in each disorder and current concepts of the pathophysiology of each condition. While the MRS literature in psychiatric disorders has grown quite large, our review will attempt to identify the most consistently replicated experimental observations and will give priority to findings that address specific translational questions of theoretical or clinical importance. In addition, a discussion of the physics of MRS and a technical description of MRS methods commonly used in neuropsychiatric research today is provided as supplementary material (link below). The supplementary material assumes a basic familiarity with MR principles and concepts such as longitudinal and transverse magnetization, nutation of magnetization by radiofrequency pulses, and precession of transverse magnetization by the application of the main magnetic field and fields due to the gradient pulses. For the reader equipped with this background, this material offers an in-depth introduction to the unique physical principles

underlying MRS experiments. Supplement: http://ucdirc.ucdavis.edu/CLR327bgt/maddock-buonocore-CTBNsuppl.pdf.

2 Metabolites Observable in Normal Brain

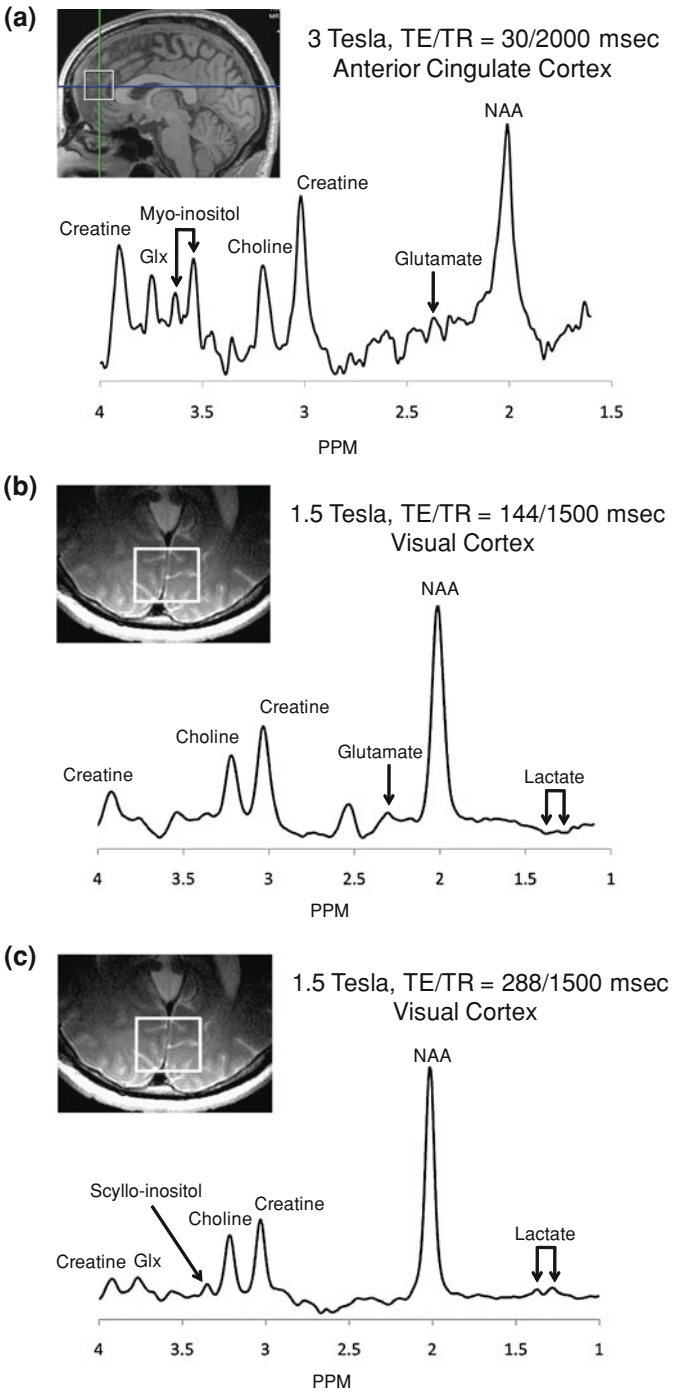
For a brain metabolite to be reliably measured with MRS methods currently available on clinical MRI systems, its concentration must be in the millimolar range and it must be in a freely mobile form (not anchored to a membrane or organelle). Molecules that are not free to rotate rapidly in solution generally do not generate a resonance that can be detected with clinical MRI systems. The brain is a densely cellular organ with a high rate of resting energy consumption. Its primary functions require complex signaling mechanisms for communication both within and between cells. Accordingly, many of the mobile molecules present in sufficiently high concentration to be reliably observed with MRS are involved in energy metabolism, signaling, and cell membrane metabolism. Figure 1 portrays examples of 1H-MRS data acquired from 3 and 1.5 T scanners using several different echo times (TEs). Each of the metabolites commonly studied with 1H-MRS in patients with neuropsychiatric disorders is discussed below in detail.

2.1 NAA

The molecular structure of *N*-acetylaspartate (NAA) is shown in Fig. 2. Other than water, the most prominent peak in the 1H-MRS spectrum of brain tissue is the singlet peak of NAA at about 2.01 ppm (Fig. 1). This large peak arises from the three hydrogen nuclei in the methyl group within the acetyl moiety of NAA. Hydrogen nuclei from the aspartate moiety of NAA give rise to several other much smaller peaks, but only the multiplet with peaks at about 2.49 and 2.67 ppm is generally visible in in vivo spectra (Govindaraju et al. 2000).

NAA is often considered to be a marker of the density of viable neuronal tissue in the brain region under study (Meyerhoff et al. 1993). However, there is accumulating evidence that NAA levels also reflect reversible changes in neuronal health (Clark 1998; Gasparovic et al. 2001; Demougeot et al. 2004). For example, reduced NAA levels are observed in the context of acute brain injury or illness, or chronic methamphetamine abuse. However, a normalization of NAA levels can be observed following a period of recovery, treatment, or extended abstinence from drug abuse (De Stefano et al. 1995; Kalra et al. 1998; Narayanan et al. 2001; Salo et al. 2010; Yoon et al. 2010b). Thus, reduced NAA is more accurately interpreted as reflecting *either* permanent loss *or* reversible dysfunction of neuronal tissue (Moffett et al. 2007).

NAA is synthesized from aspartate and acetyl-coenzyme A in a reaction catalyzed by aspartate *N*-acetyltransferase (Asp-NAT) (Moffett et al. 2007;


(a)
3 Tesla, TE/TR = 30/2000 msec
Anterior Cingulate Cortex
NAA
Creatine
Myo-inositol
Creatine
Glx
Choline
Glutamate
4
3.5
3
2.5
2
1.5
PPM
(b)
1.5 Tesla, TE/TR = 144/1500 msec
Visual Cortex
NAA
Creatine
Choline
Creatine
Glutamate
Lactate
4
3.5
3
2.5
2
1.5
1
PPM
(c)
1.5 Tesla, TE/TR = 288/1500 msec
Visual Cortex
NAA
Scyllo-inositol
Choline
Creatine
Lactate
Creatine
Glx
4
3.5
3
2.5
2
1.5
1
PPM

◀**Fig. 1** Representative 1H-MRS spectra acquired from human brain using three different TEs are shown. The spectrum in (**a**) was acquired at TE = 30 ms from the anterior cingulate cortex at 3 Tesla. The spectra in (**b** and **c**) were acquired at TE = 144 and 288 ms respectively from the primary visual cortex at 1.5 Tesla. Selected metabolite peaks are indicated. Note that the ppm value on the horizontal axis increases to the left, not the right. Spectral peaks that appear on the *right side* of the graph arise from nuclei that are relatively more shielded from the main magnetic field by nearby electrons. Spectral peaks on the *left side* of the graph arise from relatively less shielded nuclei (discussed in Supplement Sect. 4.2)

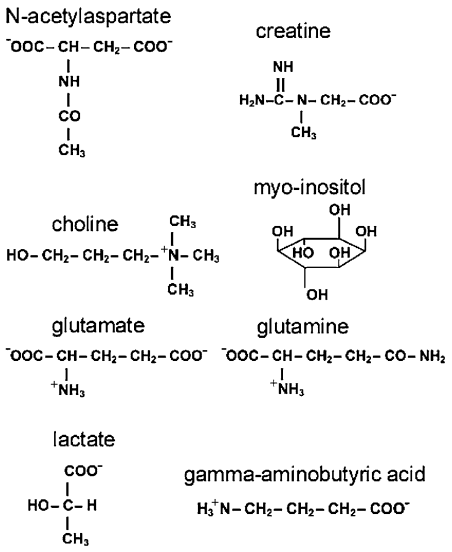


Fig. 2 The molecular structures of eight brain metabolites commonly studied with 1H-MRS are shown

Ariyannur et al. 2010). There is not yet a consensus about the subcellular localization of NAA synthesis or about the physiological functions of NAA. However, there is general agreement that NAA is synthesized predominantly in neurons, and that its substrates are found together primarily within mitochondria. Therefore, it is likely that most NAA is synthesized in neuronal mitochondria, although there may be some Asp-NAT and NAA synthesis in neuronal cytoplasm. Many investigations have shown that NAA synthesis is coupled to the capacity of neuronal mitochondria for oxidative metabolism and ATP synthesis (Bates et al. 1996; Clark 1998; Moffett et al. 2007). Animal studies of experimental brain trauma show that the acute decrease and later recovery of ATP and other indicators of mitochondrial energy metabolism were temporally correlated with changes in NAA levels (Gasparovic et al. 2001; Signoretti et al. 2010). This evidence supports the use of brain 1H-MRS NAA levels as a marker for the integrity and functional capacity of neuronal mitochondria.

Aspartoacylase (ASPA) is the enzyme that catalyzes the hydrolysis of NAA to aspartate and acetate in human brain (Bitto et al. 2007). ASPA is found predominantly in oligodendrocytes, the glial cells that constitute the myelin sheaths around axons. The important role of acetate in the synthesis of myelin and converging evidence from a wide range of studies support the hypothesis that one

important function of NAA is to transport acetate from neuronal mitochondria to oligodendrocytes for use in myelin synthesis (Moffett et al. 2007). NAA may also contribute to other aspects of oligodendrocyte lipid and energy metabolism. Several other proposed neurobiological functions of NAA have been the subject of experimental study, including participation in an alternate pathway of neuronal mitochondrial respiration in which glutamine substitutes for glucose, providing a reservoir for glutamate, functioning as an organic osmolyte for regulating cell volume, and serving as an anion to ameliorate the "anion deficit" within neurons (Clark et al. 2006; Moffett et al. 2007).

NAA is an immediate precursor for the biosynthesis of the neuronal dipeptide *N*-actelyaspartylglutamate (NAAG). NAAG is the most highly concentrated peptide in the human brain and may serve a cell-signaling function (Neale et al. 2000). It generates a small peak in the brain 1H-MRS spectrum that is difficult to distinguish from the NAA peak (Edden et al. 2007). Measures of the percent contribution of NAAG to the combined signal from NAA and NAAG range from about 9% in gray matter to about 30% in white matter (Pouwels and Frahm 1997; Edden et al. 2007). NAAG is synthesized in neurons from NAA and glutamate. It is stored in vesicles and released from neurons by a calcium-dependent mechanism, and it is hydrolyzed to glutamate and NAA by the enzyme NAAG peptidase, which resides on the extracellular surface of astrocytes (Baslow 2007; Chopra et al. 2009). Considerable evidence suggests that NAAG interacts with group II metabotropic glutamate receptors prior to hydrolysis. However, the nature and significance of this interaction is not yet clear (Neale et al. 2000; Chopra et al. 2009).

In summary, the NAA singlet at 2.02 ppm is the most prominent peak in normal brain 1H-MRS spectra. In most cases, this NAA signal represents "total NAA," as it includes the combined signals from both NAA and NAAG. The 1H-MRS signal arising from the total pool of NAA + NAAG can be interpreted as a marker for the health, viability and/or number of neurons, and it may more specifically reflect the functional capacity of neuronal mitochondria.

2.2 Creatine

Together, creatine and phosphocreatine give rise to a prominent singlet peak at approximately 3.03 ppm (Fig. 1). This peak arises from the three hydrogen nuclei in the methyl group of the creatine moiety (Fig. 2). Another smaller but distinct peak is evident at approximately 3.91 ppm. This singlet peak arises from the methylene hydrogen nuclei of the creatine moiety (Govindaraju et al. 2000). In general, creatine and phosphocreatine cannot be reliably distinguished by 1H-MRS. In this review, the term "creatine" used in the context of 1H-MRS measurements refers to the combined signal from creatine and phosphocreatine.

Creatine and phosphocreatine are present in both gray matter and white matter, and in all of the major cell types of brain parenchyma, including neurons, astrocytes, and oligodendrocytes. The pool of creatine in the body is maintained by a

combination of dietary uptake and endogenous synthesis. Although it was previously thought that the brain's supply of creatine was primarily maintained by uptake from the blood, it now appears that local synthesis within the brain may contribute substantially to its supply (Andres et al. 2008; Beard and Braissant 2010). Two enzymes are required for the synthesis of creatine. Arginine–glycine aminotransferase (AGAT) generates ornithine and guanidinoacetate (GAA), the immediate precursor of creatine. GAA is then methylated by guanidinoacetate methyltransferase (GAMT) to produce creatine. AGAT and GAMT are widely expressed throughout the brain, but it appears that they are not often co-expressed in the same cells. This suggests that the transporter for GAA and creatine is also required for the final synthesis and distribution of creatine throughout the brain (Braissant et al. 2010). Some studies have found high levels of GAMT in glial cells and suggest that the final step in creatine synthesis may occur mainly in glia. However, this and other questions regarding the precise compartmentation of creatine synthesis and transport remain unresolved (Andres et al. 2008; Beard and Braissant 2010).

Creatine has an essential role in CNS energy homeostasis. In the presence of ATP, creatine can be phosphorylated by the enzyme creatine kinase (CK). This reaction is reversible, so that ATP can be regenerated from phosphocreatine, in the presence of ADP. The creatine/phosphocreatine system has two essential functions in brain energetics. It provides a buffer, or storage mechanism, for high-energy phosphate bonds generated in subcellular regions where ATP production is high, and it provides a means for transport of high-energy phosphate bonds from subcellular regions of net energy production to subcellular regions of net energy consumption. Unlike ATP and ADP, phosphocreatine and creatine can diffuse rapidly across subcellular regions (Andres et al. 2008). This relatively rapid rate of diffusion makes the creatine/phosphocreatine system an efficient mechanism for shuttling high-energy phosphate bonds between subcellular compartments.

In addition to its central role in energetics, creatine appears to have important functions in other fundamental aspects of cellular metabolism in brain parenchyma. In combination with the CK isoform expressed in brain mitochondria, creatine has an important antiapoptotic effect by stabilizing mitochondrial membrane pores (Dolder et al. 2003). Creatine also helps suppress free radical (reactive oxygen species) formation within mitochondria by facilitating the recycling of ADP during periods of increased glucose utilization (Meyer et al. 2006). Furthermore, creatine appears to be released from neurons by a depolarization-induced, calcium-dependent mechanism (Almeida et al. 2006) suggesting that it functions as a neuromodulator. In this regard, there have been reports that creatine may act as a partial agonist at the GABA-A receptor (Koga et al. 2005; Almeida et al. 2006) and may interact with the NMDA receptor (Royes et al. 2008).

The 1H-MRS signal attributable to creatine and phosphocreatine (total creatine) is generally interpreted as a measure of the global health of brain parenchyma, with reductions indicative of impairment of function or integrity. While a measurement of the ratio of phosphocreatine to creatine would provide information about the current status of energy metabolism and high-energy phosphate bonds in the brain, this ratio generally cannot be reliably measured by 1H-MRS alone, but

requires additional measurements with phosphorous MRS (31P-MRS). In studies of patients with multiple sclerosis, increased creatine (as observed, for example, in normal-appearing white matter) has been interpreted as an indication of the proliferation of astrocytes (Caramanos et al. 2005). This interpretation is supported, in part, by in vitro studies of cultured neuronal and glial cells suggesting that the concentration of creatine in astrocytes is higher than in neurons (Urenjak et al. 1993; Bhakoo et al. 1996). However, a subsequent in vitro study did not confirm this (Griffin et al. 2002) and uncertainty remains about the relative concentration of creatine in different brain cell types.

In general, the concentration of total creatine is relatively similar throughout the brain and tends to be stable over time in the absence of major pathology. For these reasons, the 1H-MRS signal from creatine is commonly used as an "internal standard" to normalize the signals from other metabolites measured within the same voxel. There are several advantages of this approach. It partially corrects for some of the variation in metabolite signal intensity that is due to the location of the voxel, such as the proportion of cerebrospinal fluid (CSF) within the voxel and the sensitivity of the coil to signal from a specific location within the brain. The main disadvantage of this approach is that the creatine signal may increase or decrease in association with a pathologic condition, as has been demonstrated for ischemic stroke and brain trauma (Lei et al. 2009; Signoretti et al. 2010).

In summary, the combined signals from creatine and phosphocreatine give rise to singlet peaks at 3.03 and 3.91 in 1H-MRS spectra. Creatine and phosphocreatine are present in all types of brain cells. The total creatine signal is relatively similar across brain regions and reflects the global health of the underlying tissue. Creatine signal intensity is often used for within-voxel normalization of the signals arising from other metabolites of interest.

2.3 Choline-Containing Compounds

Many molecular compounds in the brain contain a choline moiety. The nine hydrogen nuclei associated with the trimethylammonium group within the choline moiety of choline-containing compounds (Fig. 2) give rise to a prominent singlet peak at about 3.21 ppm (Fig. 1) (Govindaraju et al. 2000). In brain, phosphorylcholine (PCho) and glycerophosphorylcholine (GPCho) are the primary sources of this resonance peak. Choline-containing phospholipids in myelin and cell membranes (primarily phosphotidylcholine) are present in brain parenchyma in higher concentration than PCho and GPCho (Boulanger et al. 2000). However, these compounds are not freely mobile and therefore cannot generate a measurable magnetic resonance signal during a 1H-MRS acquisition. Thus, these choline-containing phospholipids do not directly contribute to the choline resonance at 3.21 ppm. Free choline, acetylcholine, and cytidine diphosphate choline are mobile choline-containing compounds present at much lower concentrations than PCho and GPCho (Boulanger et al. 2000). They contribute directly, but to a

minor degree, to the choline peak at about 3.21 ppm. Betaine is produced by the oxidation of choline. Like choline, betaine contains nine hydrogen nuclei within a trimethylammonium group. Betaine makes a minor contribution to the total choline signal. Phosphorylethanolamine, another precursor of membrane phospholipids, also contributes in a minor way to the choline signal at 3.21 ppm.

Although 1H-MRS does not directly measure the concentration of membrane phospholipids, the observed choline peak is influenced by both the density of cell membranes and the rate of cell membrane and myelin turnover. PCho is a precursor of the synthesis of membrane phospholipids. Both GPCho and, to a lesser extent, PCho are generated during the breakdown of membrane phospholipids. Thus, an increase in either the synthesis or the breakdown of membrane phospholipids can be associated with an increase in the concentrations of PCho and/or GPCho (Geddes et al. 1997; Boulanger et al. 2000). For this reason, increases in the breakdown or turnover rate of membrane or myelin phospholipids are believed to be associated with increases in the 1H-MRS choline signal. Furthermore, at a constant rate of turnover of phospholipids, the concentrations of PCho and GPCho vary in proportion to the density of cell membranes within the voxel (Yue et al. 2009). Thus, the 1H-MRS choline signal is often interpreted as a measure of overall cell density and/or the rate of membrane turnover. Increased choline signal can also result from the accumulation of myelin breakdown products, as occurs during active demyelination.

2.4 Myo-Inositol

Inositol is a six-carbon ring sugar with an alcohol group attached to each carbon (a six-fold alcohol of cyclohexane) (Fig. 2). Myo-inositol is the most abundant stereoisomer of inositol in mammalian systems. In the brain, about 90% of the inositol is myo-inositol, less than 10% is scyllo-inositol, and trace amounts of other stereoisomers are also present (Govindaraju et al. 2000; Fisher et al. 2002). The most prominent 1H-MRS signal from myo-inositol is a pair of multiplet peaks arising at about 3.52 and 3.61 ppm (Fig. 1a). The myo-inositol peaks are generally not observable in long TE 1H-MRS acquisitions (Fig. 1b, c). The scyllo-inositol singlet peak is variably present at about 3.3 ppm. It can often be observed when using a long TE (Fig. 1c).

The myo-inositol content of brain cells is governed by several physiological mechanisms, including the recycling of inositol phosphate second messengers, de novo synthesis of inositol from glucose, carrier-mediated energy-coupled transport of inositol into cells against a concentration gradient, and efflux of inositol out of cells during hypotonic stress as part of cell volume regulation (Fisher et al. 2002). In healthy brain tissue under normal osmotic conditions, the former two mechanisms predominate (Williams et al. 2002). Myo-inositol is synthesized from glucose-6-phosphate in two steps. The final step is catalyzed by inositol monophosphatase. This same enzyme is responsible for generating free myo-inositol during the recycling of

inositol phosphate second messengers. Free inositol is required to regenerate phosphotidylinositol, a key component of the second messenger system. Interestingly, inositol monophosphatase is inhibited by lithium. Indeed lithium, valproate and carbamazepine all alter inositol phosphate metabolism to cause a reduction in intraneuronal free inositol levels (Williams et al. 2002).

In addition to its key role as a precursor for the regeneration of phosphotidylinositol in the inositol phosphate second messenger system, myo-inositol has other important functions in the brain. Free myo-inositol serves as a "non-perturbing" osmolyte that is normally maintained at a manyfold higher concentration within brain cells than in CSF (>25:1) or blood (>50:1). In response to hypotonic stress (e.g. hyponatremia), myo-inositol can efflux from brain cells (or enter brain cells in the case of hypertonic stress) to preserve cell volume without altering the function of intracellular processes (Fisher et al. 2002). Additionally, myo-inositol, similar to choline, is an intermediate in the metabolism of membrane and myelin phospholipids.

Although the myo-inositol signal in brain 1H-MRS is often considered to be a glial marker, its distribution across brain cell types is more complex than is suggested by that characterization. Currently, the extent to which myo-inositol may be preferentially concentrated within neuronal or glial cell types remains uncertain (Fisher et al. 2002). One of the strongest assertions of an exclusively glial source for the 1H-MRS myo-inositol signal comes from a 1H-MRS study of cultured brain cells that showed a high concentration of myo-inositol in astrocytes and negligible myo-inositol in neurons (Brand et al. 1993). The conclusions of this study are widely cited in support of the characterization of myo-inositol as a glial marker. Thus, it is worthwhile to examine their limitations. The cultured neurons studied were in an embryonic stage of development, as evidenced by the observation they contained only trace amounts of NAA. In contrast, the cultured astrocytes studied were in a more mature stage of development and exhibited a spectral pattern more similar to in vivo brain 1H-MRS studies (more prominent Cr and Choline peaks than observed in the embryonic neurons). Neither type of cultured cell (neurons or astrocytes) were able to synthesize myo-inositol from glucose (Brand et al. 1993), although this is known to occur in mature neurons (Schmidt et al. 2005). Since the cultured cells could not synthesize it, myo-inositol was added to the culture medium. Thus, the Brand et al. results reflect the relative uptake of myo-inositol into mature astrocytes compared to its uptake into embryonic neurons in a cell culture environment. Mature neurons and glia are both known to express myo-inositol transport proteins. Two such transporters have been described. One is present in both cell types and the other is observed only in astrocytes. Under acidic conditions, the former is less active while the exclusively astrocytic transporter is more active (Fisher et al. 2002). Acidic conditions (10% CO_2) in the culture media may have favored preferential uptake of myo-inositol by the cultured astrocytes in the Brand et al. experiment. The comparison of relatively immature neurons to relatively mature astrocytes, the absence of normal neuronal myo-inositol synthesis, and cell culture conditions favoring selective myo-inositol uptake by astrocytes limit the generalizability of their findings. In their systematic

review, Fisher et al. (2002) summarized findings from seven prior experiments on neuronal cells and five prior experiments on glial cells. There was no significant difference in the estimated myo-inositol concentrations in glia compared to neurons, but the median estimated concentration was 38% lower in the neuronal cells than in the glial cells.

Although myo-inositol may not be a specific glial marker, clinical observations often support an association between elevated 1H-MRS myo-inositol signal and gliosis in neurodegenerative disorders (e.g. multiple sclerosis and Alzheimer's disease) (Bitsch et al. 1999; Yang et al. 2010). However, elevated inositol is found in a range of pathological conditions not involving gliosis, including Down's syndrome, increased myelin breakdown, and hypertonic stress (Fisher et al. 2002). It is important to note that high concentrations of myo-inositol are observed in some types of cultured neurons, and that myo-inositol is actively taken up into most types of mature brain cells, including neurons and glia (Fisher et al. 2002). Furthermore, neurons can both synthesize inositol from glucose and regenerate it during the recycling of inositol phosphates (Schmidt et al. 2005), Thus, there is little evidence to support the characterization of myo-inositol as a specific glial marker, and increases or decreases in the brain inositol 1H-MRS signal must be interpreted in the context of the specific condition under study.

2.5 Glutamate and Glutamine

The amino acid neurotransmitter glutamate is one of the most abundant mobile metabolites present in the brain, being second only to NAA in concentration (Govindaraju et al. 2000). However, it lacks methyl groups, and the J-coupled signals from its methylene and methine groups (Fig. 2) produce broad complex peaks. For these reasons, glutamate does not generate a prominent single peak in the 1H-MRS spectrum of the brain. A multiplet peak centered at about 2.34 ppm arises from the methylene protons near the carboxy terminal of glutamate and is often the most readily recognized glutamate peak in brain 1H-MRS spectra (Fig. 1). A second methylene multiplet centered at about 2.08 ppm is typically obscured by the large NAA peak at 2.01 ppm. A third complex glutamate peak arises from its methine proton at about 3.74 ppm (Fig. 1) (Govindaraju et al. 2000).

These signals from glutamate are difficult to distinguish from the analogous peaks arising from glutamine at about 2.44, 2.12, and 3.75 ppm. The concentration of brain glutamine is estimated to be about 40% to 60% of the concentration of glutamate (Govindaraju et al. 2000; Jensen et al. 2009), thus signal arising from glutamine often confounds measures of glutamate. Hancu recently compared a range of specialized 1H-MRS methods for measuring brain glutamate on a 3 T scanner. A conventional short TE point resolved spectroscopic sequence (PRESS) and the specialized Carr-Purcell PRESS sequence provided measurements with the best repeatability. J-resolved PRESS was the most accurate for measuring absolute values of glutamate, but at the cost of reduced repeatability (Hancu 2009)

(see Sects. 4.3.1, and 4.5.3 of the Supplement for discussions of PRESS and J-resolved MRS techniques). Unless optimized 1H-MRS methods are used (e.g. a high-field scanner with a short echo time and long acquisition time, or a specialized J-editing or J-resolved sequence), the measurements obtained are generally considered to reflect the combined signal from glutamate and glutamine, with minor contributions from glutathione and GABA. This combined signal measurement is often abbreviated as "Glx."

In the resting awake state, up to 20% of brain glucose metabolism is directed toward the de novo synthesis of glutamate, which occurs primarily in astrocytes (Hertz 2006). Pyruvate carboxylase, which is located exclusively in glial cells (probably within their mitochondria), has a key role in directing pyruvate toward de novo glutamate synthesis. Thus astrocytes, unlike glutamatergic neurons, are capable of net synthesis of glutamate without depletion of tricarboxylic acid (TCA) cycle intermediates (Hertz 2004; Waagepetersen et al. 2007). The TCA cycle intermediate, alpha ketoglutarate, is the immediate precursor of glutamate via exchange reactions such as transamination (by aspartate aminotransferase) and possibly by reductive amination (by glutamate dehydrogenase). Once synthesized in astrocytes, some glutamate are used as a metabolic intermediate and some are directed toward the synthesis of glutathione, a major intracellular antioxidant in the brain that is present in much higher concentrations in glia than in neurons (Janaky et al. 2007). However, most astrocytic glutamate is converted to glutamine by the astrocyte-specific enzyme, glutamine synthase, and released for uptake into glutamatergic neurons. These neurons then convert glutamine back to glutamate (via phosphate-activated glutaminase) (Waagepetersen et al. 2007). In neurons, glutamate has both metabolic and neurotransmitter functions. Glutamate can reenter the TCA cycle for oxidative energy production or be used in the synthesis of other amino acids, including GABA. Glutamate is the most abundant excitatory neurotransmitter in the brain. For use in neurotransmission, it is first transported into synaptic vesicles, where concentrations are about 10-fold higher than whole-brain glutamate concentrations. Vesicular glutamate can then be exocytotically released into the synaptic cleft during neurotransmission. The neurotransmitter action of glutamate is quickly terminated by its rapid uptake from the synaptic zone into astrocytes. Most of the glutamate taken up by astrocytes reenters the glutamate–glutamine cycle to be returned to neurons and reused in neurotransmission (Waagepetersen et al. 2007). However, some glutamate is directed toward other metabolic fates and is lost from this cycle, necessitating the continuous de novo synthesis of glutamate in astrocytes. Possible additional components of the cycling of glutamate and glutamine between neurons and astrocytes are under investigation (Maciejewski and Rothman 2008). Recent studies suggest that astrocytes also store glutamate in vesicles for exocytotic release in the service of intercellular communication (Hertz 2006; Waagepetersen et al. 2007).

Current models of the compartmentation of brain glutamate metabolism suggest a time-limited segregation into two cellular pools: a smaller astrocytic pool (comprising about 20% of total glutamate), in which glutamate is rapidly converted to glutamine, and a larger neuronal pool (about 80% of total glutamate),

which has a slower turnover time (Waagepetersen et al. 2007). Glutamate is further compartmentalized into cytosolic, mitochondrial, and vesicular subcellular compartments. It is important to note that only about 80% of glutamate in brain tissue appears to be observable by 1H-MRS. It is possible that low MRS visibility of glutamate in the vesicular compartment accounts for this finding (Kauppinen and Williams 1991). A small amount of glutamate is present in the extracellular fluid (ECF) of the brain. However, elevated ECF concentrations of glutamate can have excitotoxic effects. Because of the rapid clearance of glutamate from the ECF, primarily by astrocytes, ECF glutamate concentration in healthy brain is maintained three to four orders of magnitude less than whole-brain concentrations (Waagepetersen et al. 2007). Some studies suggest that most glutamate observable by MRS is in rapid exchange across compartments on a timescale of seconds to minutes (Rothman et al. 2003; Hertz 2004). If this is so, then glutamate as measured over several minutes by MRS may represent a single, integrated pool of the metabolite in ongoing exchange between neuronal and glial cytoplasm.

Glutamine's primary role in the brain is as a non-neuroactive intermediate in the recycling of amino acid neurotransmitters, most abundantly glutamate and GABA. In addition, it has an important role in the regulation of brain ammonia metabolism (Waagepetersen et al. 2007). However, the synthesis and catabolism of brain glutamine are strictly yoked to glutamate metabolism. All brain glutamine synthesis is via glutamate and takes place within astrocytes. Brain glutamine participates in no metabolic pathways other than via its initial conversion back to glutamate. Thus, the 1H-MRS measure of Glx represents a good approximation of the total glutamate–glutamine pool available for the integrated metabolic and neurotransmitter functions of glutamate in the brain (Rothman et al. 2003; Yuksel and Ongur 2010).

Glutamate is one of several brain metabolites that exhibit acute changes in MRS signal strength in response to sensory, cognitive, or pharmacological manipulations. The general paradigm of measuring dynamic changes in brain metabolites in response to behavioral or drug conditions is known as dynamic MRS or functional MRS. An extensive animal literature demonstrates that changes in local cortical glutamate and glutamine concentrations are activity dependent, meaning that they increase or decrease according to the degree of local neural activity (Carder and Hendry 1994; Arckens et al. 2000; Qu et al. 2003; Hertz 2004). Dynamic 1H-MRS studies in normal human volunteers have similarly found local activity-dependent increases in cortical glutamate. Mullins et al. (2005) observed a 9% increase in glutamate in the anterior cingulate cortex during cold pressor pain. Gussaw et al. (2010) subsequently showed an 18% increase in anterior insular cortex glutamate during thermal pain. Using a 7 T system, Mangia et al. (2007) reported a small but statistically significant increase in glutamate in the visual cortex while subjects viewed a flickering checkerboard stimulus. Our laboratory has observed a similar significant 5% increase in visual cortex Glx during visual stimulation (Maddock et al., unpublished data). We recently found that vigorous aerobic exercise, which is known to cause a widespread brain metabolic activation (Fukuyama et al. 1997; Delp et al. 2001), leads to an 18% increase in Glx in the visual cortex (Maddock et al. 2011).

1H-MRS measures of glutamate or Glx arise from both neuronal and glial cells and primarily reflect cytoplasmic concentrations. Measures of glutamate or Glx can provide information about both activity-dependent changes in the size of the MRS-visible metabolite pool and about the enduring integrity of glutaminergic neurons and astrocytes that sustain this pool of glutamate and glutamine. Brain MRS measures of glutamate, glutamine, and Glx may have particular value in testing translational hypotheses about dysfunction of glutamatergic systems in neuropsychiatric disorders.

2.6 GABA

Gamma aminobutyric acid (GABA) is the most abundant inhibitory neurotransmitter in the brain. It is present in brain parenchyma at about 15% to 20% of the concentration of glutamate (Govindaraju et al. 2000). GABA contains three methylene groups (Fig. 2), each of which gives rise to a complex signal in 1H-MRS spectra. A GABA multiplet peak at about 3.01 ppm is normally obscured by the creatine singlet at 3.03 ppm. A GABA triplet at about 2.28 ppm is partially overlapped by the glutamate multiplet centered at about 2.34 ppm. A GABA multiplet peak at 1.89 ppm is obscured by the large NAA singlet centered at 2.01 ppm. Because of their extensive overlap with larger signals from other metabolites, none of the three GABA peaks can be reliably distinguished or quantified with conventional brain 1H-MRS acquisitions at 1.5 or 3.0 T field strengths. The GABA resonance at 2.28 may contribute in a small way to the total Glx signal measured with conventional acquisitions. However, specialized pulse sequences including J-resolved and J-difference editing sequences can render some or all of the GABA peaks visible and isolate them from larger overlapping signals, even when used on clinical MRI systems. Perhaps the most commonly used sequence for measuring GABA is the MEGA-PRESS J-difference editing sequence (Mescher et al. 1998). Figure 3 shows the broad GABA peak at about 3.01 ppm after the creatine resonance has been removed by the MEGA-PRESS J-difference editing method.

GABA is synthesized from glutamate by the enzyme glutamic acid decarboxylase (GAD), a reaction that occurs almost exclusively in GABAergic neurons. After it is released during neurotransmission, GABA is taken up by both GABAergic neurons and by astrocytes. Current evidence suggests that neuronal reuptake of GABA predominates and that it occurs primarily in the nerve terminal region (Waagepetersen et al. 2007). After reuptake into neurons, GABA either reenters synaptic vesicles for reuse in neurotransmission, or it is degraded by the mitochondrial enzyme GABA transaminase (GABA-T) and enters the TCA cycle, from which it can be recycled to glutamate and then GABA again. This latter cycle is known as the GABA shunt. The fraction of GABA that is taken up by astrocytes is also metabolized via the GABA shunt, but the resulting glutamate is converted to glutamine and released into the ECF. The glutamine is taken up by either

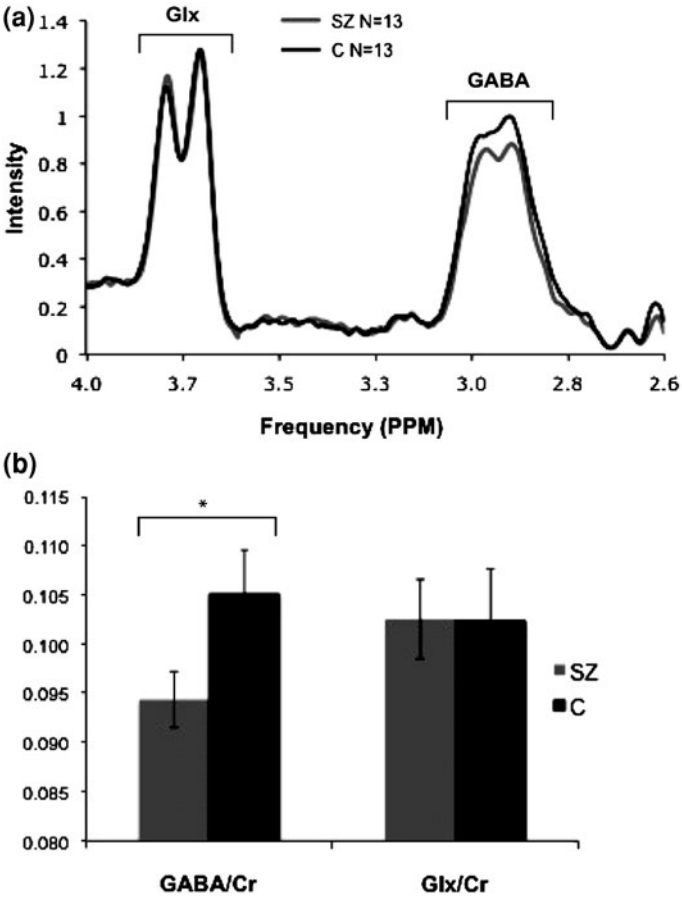


Fig. 3 **a** shows peaks for GABA and Glx from 1H-MRS difference spectra acquired using the MEGA-PRESS pulse sequence for GABA editing (TE = 68 ms) on a 3 Tesla system. The mean difference spectra are shown for 13 schizophrenia patients and 13 healthy comparison subjects. **b** illustrates the finding of significantly lower GABA signal in the patient group ($p<.05$ two-tailed), but no group difference in the Glx signal

glutamatergic or GABAergic neurons, where it either enters energy metabolism or serves as the substrate for neurotransmitter synthesis (Waagepetersen et al. 2007). De novo synthesis of GABA depends on both the anaplerotic production of glutamate by astrocytes, and the conversion of glutamate to GABA by GABAergic neurons (Hertz 2004).

There appear to be at least two distinct pools of GABA in GABAergic neurons, a large cytoplasmic pool and a smaller vesicular pool. Furthermore, two forms of the GABA synthetic enzyme GAD are known, GAD67 and GAD65. GAD67 is widely distributed throughout the cytoplasm and nerve terminals of GABAergic

neurons, and it contributes to the generation of both the cytoplasmic and the vesicular pools of GABA. In contrast, GAD65 is localized to nerve terminals, and it contributes only to the vesicular pool of GABA. Under basal conditions, most GABA are synthesized by GAD67. However, the activity of GAD65 can be upregulated on demand to increase GABA in the vesicular pool (Waagepetersen et al. 2007; Dericioglu et al. 2008).

While it appears that vesicular glutamate may not be detectable by MRS (Kauppinen and Williams 1991), whether or to what extent the vesicular pool of GABA can be detected by MRS is not known. Thus, the 1H-MRS GABA signal arises either mostly or almost entirely from the large cytoplasmic GABA pool in GABAergic neurons under basal conditions. The functional significance of the considerable cytoplasmic store of GABA is not known. It may have metabolic functions or it may act as a reservoir from which to replenish vesicular stores of GABA. However, some evidence suggests that cytoplasmic GABA serves as an important source for "extrasynaptic" GABA release via the neuronal GABA transporter (GAT) from cell membrane regions not associated with synaptic structures or vesicles (Wu et al. 2007; Dericioglu et al. 2008). Extrasynaptic GABA mediates a tonic inhibitory process and plays a key role in regulating both tonic and phasic excitability in GABAergic circuits (Farrant and Nusser 2005; Wu et al. 2007).

Neurophysiological, behavioral, and pharmacological studies indicate that cortical GABA content as measured in human volunteers by 1H-MRS is predictive of the functional status of GABA-mediated processes. It is generally agreed that oscillations in the EEG gamma band (30–90 Hz) depend on the rhythmic activity of local networks of GABAergic interneurons via their synchronizing effects on the output of glutamatergic excitatory neurons (Mann and Mody 2010). Three recent human studies of visual and motor cortices have reported a significant positive correlation between GABA content as measured by 1H-MRS using a MEGA-PRESS sequence and the frequency of evoked activity in the EEG gamma band (Edden et al. 2009; Muthukumaraswamy et al. 2009; Gaetz et al. 2011). Two psychophysical studies have shown that performance on visual tasks mediated by the activity of GABAergic interneurons is significantly correlated with GABA content in the primary visual cortex as measured by 1H-MRS using a MEGA-PRESS sequence (Edden et al. 2009; Yoon et al. 2010a). In addition, several studies have shown that anticonvulsant medications that appear to increase GABAergic tone cause an increase in brain GABA as measured with 1H-MRS (Weber et al. 1999; Petroff et al. 2001). It is worth noting that several studies have found evidence that the 1H-MRS GABA signal varies over the course of the menstrual cycle in women, with GABA signal reduced during the luteal phase (Epperson et al. 2002; Harada et al. 2010). Overall, it appears that 1H-MRS measures of GABA acquired with specialized pulse sequences can provide information about a pool of cortical GABA with a predictive relationship to GABA-mediated responses. It also appears that such measures reflect the functional integrity and capacity of the underlying GABAergic neurons.

2.7 Lactate

Lactate is a three-carbon product of the glycolytic metabolism of glucose (Fig. 2). Its methyl hydrogens give rise to a doublet signal at about 1.32 ppm (Fig. 1b, c). A smaller complex peak from its methine hydrogen arises at about 4.10 ppm but cannot be detected in brain with conventional 1H-MRS methods. Lactate detected at 1.32 ppm in a clinical 1H-MRS acquisition is widely assumed to indicate brain pathology. Indeed, the concentration of lactate in normal brain is rarely greater than 1 mM. The appearance of an obvious lactate signal when no special attempt has been made to optimize its detection strongly suggests that ischemia, tumor, trauma, infection, mitochondrial disease, or other pathological process is present.

Although a high concentration of lactate is a sign of pathology, lactate is a normal and essential component of brain energy metabolism. When measures of brain lactate are of interest in studies of neuropsychiatric disorders, slight modifications to conventional procedures are recommended for its detection with clinical MRI systems. The lactate peak at 1.32 ppm overlaps and is often obscured by the methylene resonances of lipids centered at about 1.30 ppm. Several adjustments to conventional procedures can reduce or eliminate this potentially obscuring lipid signal. Since the relaxation time for the lipid methylene protons is much shorter than for the methyl protons of lactate, much of the lactate signal will be retained while most of the lipid signal will be lost by using a long TE acquisition (such as 144 or 288 ms). Although the inversion of the lactate doublet (due to J-coupling, see Supplement Sect. 4.2.2) at TE = 144 ms can be an aid to the visual identification of the lactate signal, elimination of lipid is more complete and lactate quantification appears to be more reliable when spectra are acquired with TE = 288 ms (Fig. 1b, c) (Roelants-Van Rijn et al. 2001; Maddock and Buonocore 2008). Tissues of the scalp and skull contain high concentrations of lipid. Lipid signal from these and other tissues outside of the voxel of interest can contaminate 1H-MRS data. Use of specialized lipid suppression pulses and attention to optimizing the gradient order can minimize lipid signal originating from outside of the prescribed voxel (Maddock et al. 2006). Because the concentration of lactate in the brain is normally near the low end of the sensitivity range of clinical MRI systems, increasing the signal-to-noise ratio will improve detection of the lactate signal. Thus, 1H-MRS studies of brain lactate often use large voxel sizes and long acquisition times. The use of surface or phased array coils can also improve signal-to-noise ratio from voxels close to the coil (Maddock and Buonocore 2008). Specialized pulse sequences, such as the J-difference editing approach described in Supplement Sect. 4.5.1, can provide even more sensitive and specific measures of brain lactate (Star-Lack et al. 1998).

Although once considered a “dead end” metabolite produced only under anaerobic conditions (e.g. hypoxia), lactate is now recognized as being an essential intermediate in the energy metabolism of organs with high-energy requirements, including muscle, heart, and brain (Brooks 2002; Gladden 2004). In all brain cells,

the first sequence of steps in the generation of ATP from glucose occurs in cytoplasm and proceeds without a requirement for oxygen (glycolysis). The end products of glycolysis are lactate and pyruvate, which are in equilibrium with respect to the reaction catalyzed by lactate dehydrogenase. This equilibrium strongly favors the production of lactate under basal conditions. However, pyruvate is the primary substrate for the oxidative generation of ATP in mitochondria via the TCA cycle and oxidative phosphorylation. The aerobic consumption of pyruvate as part of the mitochondrial TCA cycle promotes the conversion of lactate to pyruvate.

One of the most energy-intensive components of neurotransmission is the clearance of glutamate from the synaptic cleft by astrocytes and the subsequent conversion of glutamate to glutamine for release back into the ECF. This process occurs, in part, in the thread-like filopodia of astrocytes that surround synapses. The filopodia of astrocytes are too narrow to accommodate mitochondria, but they are highly enriched in glycogen granules (a storage form of glucose). Thus, a significant fraction of the ATP required for the astrocytic recycling of glutamate during neural activation is derived from the glycolytic conversion of glucose (and glycogen during strong activation) to lactate (Brown 2004; Pellerin et al. 2007). During neural activation, lactate levels increase and lactate is released into the ECF for uptake into intracellular compartments containing mitochondria, where it can be converted to pyruvate for subsequent metabolism and ATP generation (Hu and Wilson 1997). Although specific details regarding the production and consumption of lactate during neural activity remain to be clarified, it is clear that lactate levels increase during and after neural activation, and that lactate constitutes an important energy source for neuronal oxidative metabolism. It is also clear that astrocytes are the major cell type in the brain for storage of carbohydrate energy as glycogen and that the abundance of lactate transporters in astrocytic and neuronal cell membranes makes lactate a likely vehicle by which carbohydrate energy can be shuttled from cell to cell during times of high-energy demand. 1H-MRS studies in humans using appropriate methods have consistently observed increases in cortical lactate during neural activation (e.g. visual stimulation by a pattern reversal checkerboard) (Prichard et al. 1991; Sappey-Marinier et al. 1992; Maddock et al. 2006; Maddock and Buonocore 2008).

A 1H-MRS finding of substantially elevated brain lactate in the absence of an activation condition is most likely a sign of major pathology. However, small increases in basal lactate may reflect subclinical inflammation, impairment of oxidative metabolism, or increased neural activity. Converging evidence suggests that brain lactate levels increase acutely (over a period of several minutes) in proportion to the degree of glutamatergic activity (Hu and Wilson 1997; Pellerin et al. 2007). Thus, dynamic 1H-MRS studies of the brain lactate response to an experimental activation paradigm can provide insight into the functional state of basic neural and metabolic processes.

2.8 31Phosphorous-MRS

With suitable equipment, clinical scanners can be modified to collect brain MRS data from metabolites containing the 31Phosphorous nucleus (31P-MRS) including phosphocreatine, ATP, phosphomonoesters (mainly phosphorylethanolamine and phosphorylcholine) that are precursors for membrane phospholipid synthesis, phosphodiesters that are breakdown products of membrane phospholipids, and inorganic phosphate. When available, these measurements can provide insight into the status of high-energy phosphates and membrane turnover. The resonance frequency of inorganic phosphate is sensitive to the pH of its microenvironment. Thus, accurate measures of the resonance frequency of inorganic phosphate can be used to estimate the pH of the intracellular compartment in brain tissue (Petroff et al. 1985).

3 MRS Findings in Major Psychiatric Disorders

Since the early 1990s, the non-invasive measurement of brain metabolite concentrations with MRS has provided a unique avenue for extending our understanding of the pathogenesis of neuropsychiatric disorders. There is now a large literature describing the findings of brain MRS studies in the major psychiatric disorders. In this section, we provide an overview of this literature and summarize the most consistent findings in patients with schizophrenia, bipolar disorder, major depression, and anxiety disorders, with an emphasis on findings with potential translational significance.

3.1 Schizophrenia

Schizophrenia is a mental disorder characterized by disordered thinking, perceptual disturbances, and impairment of affect, cognition, and cognitive control. The disorder typically begins in late adolescence or early adulthood and is most often chronic. Of all psychiatric disorders, schizophrenia has been the most extensively studied with MRS methods. Anatomical brain imaging studies and postmortem neuropathological studies of brain tissue provide clear evidence for structural and neuropathological abnormalities in patients with schizophrenia. Recent progress in identifying the neuropathological abnormalities associated with schizophrenia suggests that brain MRS may be a particularly valuable tool for in vivo studies of pathophysiology and treatment effects in this disorder.

The most consistent findings from structural brain imaging studies in schizophrenia include an overall reduction in brain volume, enlarged cerebral ventricles, and regional gray and white matter volume reductions, primarily in medial temporal structures, but also in the lateral temporal lobes, thalamus, and parts of the frontal

lobes (Wright et al. 2000; Ellison-Wright et al. 2008; Jaaro-Peled et al. 2010). Reliable evidence also shows that the reduction in hippocampal volume occurs early in the illness and is also observed in the relatives of patients with schizophrenia, implicating a genetic vulnerability to this phenotypic feature (Jaaro-Peled et al. 2010; Meyer-Lindenberg 2010). Although statistically significant in large samples of patients, these volume reductions are small, and there is extensive overlap between patient and control groups. Several consistent neuropathological findings may account for some of these macroscopic structural observations in schizophrenia. The pyramidal neurons of the frontal cortex, which are the main source of excitatory neurotransmission between cortical regions, are reduced in size and packed more densely without any change in the total number of such neurons (Selemon and Goldman-Rakic 1999). There is similar evidence for reduced size of the pyramidal neurons in the hippocampus. These findings suggest a reduction in neuronal tissue in schizophrenic patients, which would be expected to be associated with a reduced concentration of NAA. Consistent neuropathological abnormalities have also been observed in the GABAergic interneurons of the cerebral cortex in schizophrenia. These observations are discussed in Sect. 3.1.2.

3.1.1 NAA

Steen et al. (2005) conducted an extensive review and meta-analysis of published 1H-MRS data on brain NAA content that spanned over 1,250 patients with schizophrenia and over 1,200 control subjects. They found consistent evidence that NAA is reduced in many brain regions in schizophrenia patients compared to control subjects. In general, the extent of reduction of NAA appeared to be similar in gray matter and white matter. However, they found evidence that the degree of schizophrenia-related NAA reductions varied across brain regions. Specifically, NAA levels did not appear to be reduced in the basal ganglia, occipital cortex, or posterior cingulate cortex. In contrast, NAA levels were consistently and substantially reduced (>5% reduction compared to control subjects) in temporal gray and white matter, hippocampus, frontal gray and white matter, and cerebellum, with the largest reductions (>10%) in temporal white matter and the hippocampus. Smaller, but consistent, reductions were also seen in the anterior cingulate cortex and thalamus. The authors reported no compelling evidence to suggest that NAA is significantly elevated in any brain region in schizophrenia. Although most patients in the studies they reviewed had chronic schizophrenia, over 200 of the patients had been studied while in their first episode of the illness. There was no robust evidence for a difference between first episode and chronic patients. However, in a comparison of 74 first episode and 171 chronic schizophrenia patients in whom frontal cortex NAA levels were measured, the authors noted a trend toward lower NAA in the first-episode patients.

The 1H-MRS studies of NAA compliment the findings of structural imaging and neuropathological studies and offer further evidence of reduced neuronal tissue in schizophrenia, especially in the temporal lobes, frontal lobes, hippocampus, and

cerebellum. The reduction in NAA is present from the onset of clinically overt illness and there is little evidence to suggest that it is attributable to treatment with antipsychotic medications (Steen et al. 2005).

MRS studies showing that reductions in NAA levels are reversible in some disorders (Sect. 2.1) and neuropathological findings of reduced size but not number of pyramidal neurons in schizophrenia leaves open the possibility that reduced NAA in specific brain regions in schizophrenia may represent a neurotrophic change rather than an irreversible loss of viable neurons. If correct, it is conceivable that NAA levels could increase toward normal with effective treatments for schizophrenia. However, longitudinal studies of treatment effects on NAA levels in schizophrenia have yielded mixed results. A few small longitudinal studies of treatment with antipsychotic medications have found increased NAA in selected brain regions, but the studies with larger samples and longer treatment intervals have generally found no effect (Bertolino et al. 2001; Pae et al. 2004; Bustillo et al. 2008, 2010). Only a few small studies have looked at the effect of non-pharmacological treatments on brain NAA in schizophrenia. Premkumar et al. (2010) examined the effects of adding cognitive-behavioral therapy to ongoing treatment with antipsychotic medication in outpatients with schizophrenia. Following 8 months of add-on psychotherapy, they observed a decrease in positive symptoms and an 8% increase in anterior cingulate cortex NAA (the only region they studied). Also in a small sample, Pajonk et al. (2010) observed a 35% increase in hippocampal NAA in schizophrenia patients following three months of aerobic exercise training. No change was seen in a control group of patients who did not participate in exercise training. No randomized, controlled studies have compared the effects of different treatments on brain NAA in schizophrenia, although naturalistic cross-sectional studies suggest NAA levels may be higher in patients taking atypical compared to typical antipsychotic medications (Fannon et al. 2003; Braus et al. 2002; Bustillo et al. 2001). Further studies will be necessary to determine whether NAA levels can be reliably increased by treatment in schizophrenia, and whether such increases are associated with clinically meaningful improvement.

3.1.2 GABA

In a development that has stimulated much theoretical and translational work, postmortem studies on brain tissue have consistently demonstrated a reduction in the GABAergic potential of specific interneurons in many cortical regions, including the frontal cortex and hippocampus in patients with schizophrenia. In particular, the concentration of cortical GABA and the activity of the 67 kDa form of glutamic acid decarboxylase (GAD67, the enzyme responsible for most GABA synthesis in the brain) are reduced in postmortem cortical tissue from patients with schizophrenia (Lisman et al. 2008). Low GABA activity is most consistently observed in the fast-spiking, parvalbumin-positive interneurons. These interneurons are functionally coupled to excitatory pyramidal neurons and

regulate their activity (Lisman et al. 2008). The coordinated activity of these two types of neurons gives rise to EEG activity in the gamma band (30–80 Hz), which appears to be essential for communication and processing of information across cortical regions. Thus, gamma band activity is critically dependent on GABAergic inhibition mediated by the fast-spiking interneurons that are deficient in schizophrenia. Accordingly, gamma band activity is consistently found to be abnormal in patients with schizophrenia (Uhlhaas and Singer 2010).

Several 1H-MRS studies have examined the relationship between cortical GABA and measures of brain function believed to depend on the fast-spiking GABAergic interneurons that are deficient in schizophrenic patients. Muthukumaraswamy et al. (2009) used the MEGA-PRESS method to measure GABA concentration in the visual cortex in normal subjects. They demonstrated a significant positive correlation between resting GABA concentration and the frequency of stimulus-induced visual gamma band EEG oscillations. A second study used the same 1H-MRS method to measure GABA concentration in the visual cortex in normal volunteers who also underwent psychophysical testing on a visual orientation discrimination task. GABAergic inhibition appears to play a key role in visual orientation discrimination. The investigators reported significant positive correlations between oblique orientation discrimination and both visual cortex GABA and the frequency of visual stimulus-induced gamma oscillations in the visual cortex. GABA concentration was also correlated with gamma frequency (Edden et al. 2009). In a psychophysical study of patients with schizophrenia, Yoon et al. (2009) demonstrated a deficiency in visual orientation processing using an orientation-specific surround suppression task. In a subsequent study, Yoon et al. (2010a) measured visual cortex GABA with 1H-MRS using the MEGA-PRESS method and demonstrated significantly lower GABA levels in the schizophrenic patients compared to healthy comparison subjects (Fig. 3). They also found a significant positive correlation between orientation-specific surround suppression and visual cortex GABA levels. These studies suggest that 1H-MRS can be used to measure a pool of cortical GABA that has a direct, functional relationship with GABA-mediated behavioral and physiological responses, at least in the visual cortex, and that these measurements can be used in patient populations to test translational models of schizophrenia. It must be noted that other recent 1H-MRS studies have not observed significantly reduced cortical GABA levels in patients with schizophrenia (Goto et al. 2009; Ongur et al. 2010; Tayoshi et al. 2011). A variety of different MRS acquisition and post-processing procedures were used in these studies, which may account for the differing results. However, only the Yoon et al. study measured GABA in the primary visual cortex and included a parallel behavioral measure to validate the GABA measurements (Yoon et al. 2010a). Although 1H-MRS measures of cortical GABA in schizophrenia appear to have great potential, it is clear that further work is needed to provide more definitive answers to critical translational research questions, such as (1) Does 1H-MRS reliably demonstrate a cortical GABA deficiency in patients with schizophrenia in vivo as has been observed in postmortem brain tissue? (2) If so, do in vivo cortical GABA deficits vary by brain region? (3) Do cortical GABA

deficits predict clinical symptoms or information processing deficits? (4) Do treatment-related changes in cortical GABA predict treatment response in schizophrenia? (5) Can 1H-MRS measures of cortical GABA be used to test GABA-related predictions of the NMDA hypofunction model of schizophrenia? Future studies will clarify the value of 1H-MRS measures of brain GABA in translational studies of schizophrenia.

3.1.3 Glutamate and Glutamine

1H-MRS studies have reported decreased, increased, or no difference in observable brain glutamate or Glx levels in schizophrenia patients compared to healthy comparison subjects (Abbott and Bustillo 2006; Stone 2009; Yoon et al. 2010a). At present, there is no consistent 1H-MRS evidence implicating a specific pattern of abnormal brain glutamate or Glx in schizophrenia. However, models of the neuropathology of schizophrenia suggest that an underlying disturbance of glutamatergic function may be present. Basic studies in animals and 1H-MRS studies in normal volunteers have demonstrated activity-dependent increases in MRS-visible cortical glutamate (Carder and Hendry 1994; Arckens et al. 2000; Qu et al. 2003; Hertz 2004; Mullins et al. 2005; Mangia et al. 2007; Gussew et al. 2010). That is, regional cortical glutamate (or Glx) is observed to increase during neuronal activation. In the NMDA receptor hypofunction model of schizophrenia, NMDA receptor hypofunction leads to both a reduced output from GABAergic interneurons and a downstream hyperglutamatergic state (Lisman et al. 2008). The associated increase in flux through the glutamate/glutamine cycle might be expected to lead to a measurable increase in the levels of these amino acids in the brain. On the other hand, glutamate levels, like NAA levels, may vary with the functional integrity of neurons, most of which are glutamatergic. Neuronal integrity appears to be compromised in many cortical regions in schizophrenia. Impaired functional integrity of glutamatergic neurons could reduce Glx levels in schizophrenia patients. Thus, a combination of factors may predispose to both increased and decreased brain Glx levels in schizophrenia patients. Such counterbalancing effects would make it difficult to detect Glx abnormalities with conventional 1H-MRS approaches.

Glutamate release during neurotransmission leads to astrocytic uptake and conversion of glutamate to glutamine by the enzyme glutamine synthase. NMDA receptor hypofunction appears to increase the activity of glutamine synthase, and thus to increase glutamine levels (Rodrigo and Felipo 2007). Pharmacological blockade of NMDA receptors in animals leads to an increase in cortical glutamine (Kosenko et al. 2003; Rodrigo and Felipo 2007) and in the glutamine/glutamate ratio (Brenner et al. 2005; Iltis et al. 2009). High-field 1H-MRS studies suggest that NMDA receptor blockade has similar effects in the anterior cingulate cortex of human volunteers (Rowland et al. 2005). There have been mixed results from 1H-MRS studies of glutamine measured in patients with schizophrenia. The 1H-MRS signals from glutamate and glutamine partially overlap, and it is difficult to reliably quantify brain glutamine as distinct from glutamate. However, it may be

achievable with higher field scanners, short echo times, and long acquisition times. In this regard, one study using a high-field scanner observed elevated glutamine in the anterior cingulate cortex in treatment naïve patients with schizophrenia (Theberge et al. 2002). However, a second study by the same group found lower glutamine levels in the anterior cingulate cortex in chronic schizophrenia patients (Theberge et al. 2003). Two recent studies (Bustillo et al. 2010; Shirayama et al. 2010) specifically measured the glutamine/glutamate ratio with high-field scanners and both found an elevated glutamine/glutamate ratio in the medial prefrontal cortex or anterior cingulate cortex of the patients with schizophrenia. Both studies also reported a significantly reduced NAA/Cr ratio. In addition, a study of CSF in first episode, drug-naïve patients with schizophrenia also found an increase in the glutamine/glutamate ratio in CSF in the patient group (Hashimoto et al. 2005). The glutamine/glutamate ratio may provide a more useful reflection of the functional status of the glutamine/glutamate cycle in astrocytes and neurons in the context of compromised neuronal integrity in patients with schizophrenia. Similarly, repeated measures, dynamic 1H-MRS studies of activity-dependent increases in glutamate or Glx during an activation paradigm may also offer a useful means of testing hypotheses about NMDA receptor hypofunction and hyperglutamatergic states in the context of compromised neural integrity in patients with schizophrenia.

3.1.4 Other Metabolites

Early 31P-MRS studies suggested that phosphomonoesters were low and phosphodiesters were high in the frontal lobes of patients with schizophrenia, a pattern consistent with increased membrane breakdown in this brain region (Fukuzako 2001). However, more recent studies have not found this to be a consistent finding (Yacubian et al. 2002; Jensen et al. 2006; Smesny et al. 2007). No consistent patterns of abnormalities in brain creatine, choline, or myo-inositol have been observed in schizophrenia (Deicken et al. 2000; Kim et al. 2005; Steen et al. 2005).

3.2 Bipolar Disorder

Bipolar disorder is characterized by episodes of manic and depressed moods interspersed with periods of relatively normal mood. There is strong evidence for a genetic vulnerability to this disorder, which typically follows a relapsing and remitting course in the absence of treatment with lithium or other mood stabilizing medication. High-resolution brain imaging studies demonstrate both global and regional structural abnormalities in bipolar disorder. A recent meta-analysis found evidence for a small but reliable reduction in whole-brain volume (effect size $= -0.15$) and in volume of the frontal cortex (effect size $= -0.42$) in bipolar patients (Arnone et al. 2009). The patient group also showed an increase in the size of the lateral ventricles (effect size $= +0.27$), although lateral ventricle size was

significantly smaller than in patients with schizophrenia across studies directly comparing the two diagnostic groups (Arnone et al. 2009). The bilateral volume of the globus pallidus was found to be significantly larger in bipolar patients across 5 studies, and this effect was associated with the use of mood stabilizer medications (Arnone et al. 2009). A meta-analysis of voxel-based morphometry studies of gray matter observed reduced volume of anterior cingulate and fronto-insular cortex in bipolar disorder (Bora et al. 2010), along with increased basal ganglia volume associated with duration of illness. Mood stabilizers in general, and lithium in particular, have been shown to have neurotrophic effects and to promote neuroplasticity (Manji et al. 2000; Quiroz et al. 2010). The use of lithium by bipolar patients has consistently been associated with increased volume of the anterior cingulate cortex and the hippocampus (Emsell and McDonald 2009). These brain morphometry differences and the neurotrophic effects of mood stabilizing medications should be kept in mind when interpreting the 1H-MRS findings in bipolar disorder.

3.2.1 NAA

There have been many 1H-MRS studies of bipolar patients and, in general, this literature supports the conclusion that NAA levels are reduced in some brain regions. However, variations in MRS acquisition methods, brain regions investigated, metabolite quantification and normalization strategies, sample characteristics, and medication status make it difficult to interpret conflicting findings. Medication status is a particularly important source of variance in studies of NAA, since considerable evidence suggests that lithium and other mood stabilizers may increase brain levels of NAA. We found five published 1H-MRS studies reporting on NAA levels in adult bipolar patients free of recent medication use and matched control subjects. Four of the five studies demonstrated significantly reduced NAA levels in their patient groups. These studies included a total of 53 patients and 65 healthy comparison subjects and observed reduced NAA levels in regions including the hippocampus (2 studies), the dorsolateral prefrontal cortex, and the occipital cortex (Winsberg et al. 2000; Bertolino et al. 2003; Atmaca et al. 2007; Bhagwagar et al. 2007). One study, including 29 patients and 26 healthy comparison subjects, observed no significant difference in NAA levels in composite gray matter and white matter regions obtained from an axial 1H-MRSI slab acquired at the level of the corpus callosum (Dager et al. 2004). Many studies of bipolar patients taking mood stabilizers also show a decrement in NAA levels in frontal and hippocampal regions (Yildiz-Yesiloglu and Ankerst 2006a). In general, these findings are consistent with the meta-analytic evidence for a reduction in global brain and frontal lobe volume in this condition.

The neurotrophic effects of mood stabilizers may include increasing levels of NAA in brain regions where NAA and gray matter volume are reduced in bipolar disorder (Manji et al. 2000). Many cross-sectional studies comparing unmedicated bipolar patients to patients taking lithium have found that NAA levels are higher in the lithium-treated patients (Yildiz-Yesiloglu and Ankerst 2006a). However,

longitudinal studies of the same individuals before and during lithium treatment can provide a more conclusive test of the effects of lithium on regional brain NAA content. One study of 12 adult bipolar patients and 9 healthy volunteers found that 4 weeks of treatment with lithium led to an increase in NAA levels in all regions studied (frontal, temporal, parietal, and occipital lobes) (Moore et al. 2000). However, this effect was not observed in studies of children or adolescents with bipolar disorder (Patel et al. 2008; Dickstein et al. 2009) or in a group of healthy volunteers (Brambilla et al. 2004). There is less consistent evidence for increased NAA with other mood stabilizers (Yildiz-Yesiloglu and Ankerst 2006a).

3.2.2 Glutamate and Glutamine

Elevated gray matter Glx has been consistently observed across a range of brain regions and clinical conditions in patients with bipolar disorder. Yuksel and Ongur recently reviewed the published literature on Glx in bipolar adults through 2009 (Yuksel and Ongur 2010). They found nine 1H-MRS studies that measured Glx in various brain regions, medication conditions, and mood states (depressed, manic, and euthymic) in bipolar patients. Six of the nine studies observed significantly elevated Glx (in cingulate, prefrontal, insular, parietal, occipital, and hippocampal gray matter) in the bipolar patients (Michael et al. 2003b; Dager et al. 2004; Bhagwagar et al. 2007; Frye et al. 2007; Ongur et al. 2008; Senaratne et al. 2009). A seventh study examined Glx in the left dorsolateral PFC in both rapid cycling and non-rapid cycling bipolar II patients. They found elevated Glx in the rapid cycling but not in the non-rapid cycling patients. However, they did not report on the results across all of the bipolar patients (Michael et al. 2009). An eighth study examined only the left amygdala, and found no difference in Glx in the bipolar patients (Michael et al. 2003a). The ninth study found reduced Glx in the right lentiform nucleus in the bipolar patients (Port et al. 2008). Four other studies reported results for glutamate, but not for the combined Glx signal. Two of these reported elevated glutamate in bipolar patients (Colla et al. 2009; Lan et al. 2009). One additional study examined Glx in older adolescents and young adults (mean age = 22) and found elevated Glx in the bipolar patients (Cecil et al. 2002). Considering the variation in technical and quantitative methods used, brain regions examined, and clinical mood state of the patients, these studies provide compelling evidence for a consistent pattern of elevated brain Glx in adult patients with bipolar disorder. Fewer studies have examined Glx in pediatric bipolar patients, and the results are inconsistent (Yildiz-Yesiloglu and Ankerst 2006a; Capizzano et al. 2007). 1H-MRS studies of brain GABA in bipolar patients have produced inconsistent results.

There have been only a few studies examining the effects of medication treatments for bipolar disorder on 1H-MRS measures of Glx. Longitudinal studies in bipolar patients (Friedman et al. 2004), normal volunteers (Shibuya-Tayoshi et al. 2008), and rats (O'Donnell et al. 2003) found evidence for a reduction in brain Glx following lithium treatment. A longitudinal study of lamotrigine

observed no effect on Glx levels in bipolar patients (Frye et al. 2007). A cross-sectional study found no differences in Glx levels attributable to treatment with lithium, anticonvulsants, or benzodiazepines (Ongur et al. 2008). In six cross-sectional 1H-MRS studies, at least 75% of the bipolar patients studied were medication free. Three of these studies observed significantly elevated Glx levels in the bipolar patients compared to the healthy comparison subjects (Michael et al. 2003b; Dager et al. 2004; Bhagwagar et al. 2007). It remains to be determined whether mood stabilizers reduce brain Glx in bipolar patients. However, it appears unlikely that the reliable elevation of brain Glx seen in bipolar disorder is an artifact of medication treatment.

The singular importance of glutamate in neurotransmission, the evidence that some mood stabilizers act, in part, by reducing glutamatergic activity, and the contrasting finding that brain Glx is consistently reduced during episodes of unipolar depression (reviewed below) all support the hypothesis that elevated brain Glx has pathophysiological significance in bipolar disorder. Glutamate and glutamine have important functions in both metabolism and neurotransmission. However, some evidence suggests that 1H-MRS measures a single, integrated pool of cytoplasmic Glx in neurons and glia participating in both metabolic and cell-signaling processes (Hertz 2004). This consideration further supports the possibility that elevated Glx in bipolar disorder may reflect a pathophysiologically significant abnormality. Eastwood and Harrison recently found that bipolar patients have elevated levels of vesicular glutamate transporter 1 (VGluT1) mRNA in the anterior cingulate cortex compared to healthy comparison subjects and schizophrenia patients (Eastwood and Harrison 2010). Their finding reinforces the idea that elevated Glx in bipolar patients reflects an increase in glutamatergic neurotransmission, at least in the anterior cingulate cortex. Assessing the utility of 1H-MRS measures of Glx or glutamate in interrogating pathophysiological models of bipolar disorder or in aiding the diagnostic discrimination between bipolar disorder and other mood disorders will be important objectives of future studies (Yuksel and Ongur 2010).

3.2.3 Choline

There have been consistent demonstrations of elevated choline signal in the basal ganglia of patients with bipolar disorder (Kato et al. 1996; Hamakawa et al. 1998; Dager et al. 2004; Yildiz-Yesiloglu and Ankerst 2006a). Although most evidence suggests that lithium does not change the brain 1H-MRS choline signal (Stork and Renshaw 2005), it is possible that other medications in common use could have such an effect. Thus, studies in unmedicated patients are of particular value. In the only study that reported choline data from the basal ganglia in unmedicated bipolar patients, Dager et al. (2004) found significantly increased choline in the patient group. The 1H-MRS evidence of an increase in mobile choline-containing compounds in the basal ganglia of bipolar patients is consistent with the results of the meta-analysis by Bora et al. (2010) showing that a longer duration of illness is

associated with a larger gray matter volume in the basal ganglia of bipolar patients. Altered metabolism or increased cell density in this region could lead to an increase in the choline signal. Further studies will be necessary to clarify the significance of basal ganglia changes in bipolar disorder. In other brain regions, there is no consistent evidence for an alteration in choline levels in bipolar disorder (Stork and Renshaw 2005; Yildiz-Yesiloglu and Ankerst 2006a).

3.2.4 Myo-Inositol

Lithium can acutely reduce myo-inositol levels by inhibiting the enzyme inositol monophosphatase, which regenerates myo-inositol from inositol monophosphates as part of the phosphoinositol second messenger cycle (Hallcher and Sherman 1980). Recognition of this effect of lithium suggested two related hypotheses: (1) that bipolar disorder may be characterized by elevated levels of myo-inositol; and (2) that depletion of myo-inositol may be an important component of the therapeutic effect of lithium and other mood stabilizers (Berridge 1989). If lithium and other mood stabilizers decrease myo-inositol levels, then the hypothesized elevation of myo-inositol levels may be obscured in studies of medicated patients. However, 1H-MRS studies of sustained lithium administration have not found that it decreases brain myo-inositol (Brambilla et al. 2004; Patel et al. 2006; Silverstone and McGrath 2009) and myo-inositol levels are not consistently lower in untreated than treated bipolar patients (Yildiz-Yesiloglu and Ankerst 2006a; Silverstone and McGrath 2009). This suggests that sustained treatment may not be a significant confound in studies of myo-inositol levels. Generally, neither unmedicated nor medicated bipolar patients show consistent abnormalities of brain myo-inositol levels (Yildiz-Yesiloglu and Ankerst 2006a; Silverstone and McGrath 2009).

3.2.5 Other Metabolites

Two publications have systematically reviewed brain 31P-MRS studies in bipolar patients. From these meta-analyses, the most consistent finding is a decrease in phosphomonoesters (PMEs) in euthymic bipolar patients, which has been observed in four of six studies of the frontal lobe and in one temporal lobe study (Yildiz et al. 2001; Stork and Renshaw 2005). This effect appears to be mood state specific, as frontal lobe PMEs are frequently observed to be higher in currently depressed or manic patients than in currently euthymic bipolar patients. The apparent, state-specific alterations of brain PMEs may reflect an underlying abnormality affecting membrane metabolism in bipolar disorder. 31P-MRS can also be used to measure intracellular pH in the brain. This derives from the effect of pH on the chemical shift of inorganic phosphate, which has a primarily intracellular localization. Five out of five studies (albeit from the same group) have observed lower intracellular pH in euthymic bipolar patients. Most of these studies

examined whole-brain pH, but one study also found lower pH in the basal ganglia region (Stork and Renshaw 2005). There is preliminary evidence that low intracellular pH may be specific to the euthymic state, as pH has been observed to be higher in currently depressed or manic patients than in currently euthymic patients. Both the PME and pH abnormalities may be evidence of mitochondrial dysfunction in bipolar disorder (Stork and Renshaw 2005). The relative normalization of PMEs and pH during periods of active mood disturbance could reflect dysregulatory processes triggered by homeostatic mechanisms attempting to compensate for the mitochondrial deficiency. The 1H-MRS finding that brain lactate is elevated in bipolar patients is also consistent with a mitochondrial deficiency and compensation model (Dager et al. 2004).

3.3 Unipolar Major Depression

Unipolar major depressive disorder is characterized by episodes of sustained depressed mood, loss of motivation, and the associated somatic, emotional, and cognitive symptoms of depression. There is clear evidence for a genetic vulnerability to this condition, and most patients have recurrent episodes of illness. Brain morphometric studies have found no reliable evidence for a global reduction in brain volume in major depression (Konarski et al. 2008). However, there is consistent evidence for a volume reduction in prefrontal regions, especially the orbital frontal cortex, the anterior cingulate cortex, and its rostroventral terminus, the subgenual cingulate cortex, in patients with major depression (Hajek et al. 2008; Konarski et al. 2008; Savitz and Drevets 2009). Volume reduction in the hippocampus also appears to be a consistent pattern in major depression, although this finding may be most marked in older or chronically depressed patients (Konarski et al. 2008; Savitz and Drevets 2009). There is some evidence for volume loss as well as consistently reduced metabolic activity in the dorsolateral prefrontal cortex and for volume loss in the basal ganglia in major depression (Konarski et al. 2008; Savitz and Drevets 2009). Neuropathological studies in postmortem brain tissue from patients with major depression report generally consistent evidence for reduced glial cell number and/or density in frontal and limbic regions, including orbital, anterior cingulate, subgenual and dorsolateral prefrontal cortices, and the amygdala (Hercher et al. 2009; Yuksel and Ongur 2010). Molecular neurobiology studies have found evidence consistent with reduced neuroplasticity in frontal and limbic regions in major depression (Krishnan and Nestler 2008). Together, the findings from structural neuroimaging, neuropathological, and molecular studies suggest that frontal and limbic regions, including the hippocampus and basal ganglia, may be specifically implicated in the pathophysiology of major depression and that impairments in glial functions and neuroplasticity may be involved.

3.3.1 NAA

Reviews and meta-analyses of the 1H-MRS literature on major depression through 2006 found no consistent evidence that NAA was either increased or decreased in adult or pediatric patients with major depression (Yildiz-Yesiloglu and Ankerst 2006b; Capizzano et al. 2007; Kondo et al. 2011). Most of the studies reviewed examined the frontal lobes and most included only medication-free patients. Few studies have examined the medial temporal region, but preliminary evidence suggests it may be characterized by reduced NAA levels in major depression (MacMaster et al. 2008; Reynolds and Reynolds 2011). There is little evidence that antidepressant medications alter NAA in frontal regions (Capizzano et al. 2007). The observations of volume loss in prefrontal regions without a corresponding loss of NAA signal are consistent with the hypothesis that the pathophysiology of major depression involves an impairment of prefrontal glial integrity.

3.3.2 Glutamate and Glutamine

The most frequently replicated brain 1H-MRS finding in major depression is reduced glutamate and Glx in prefrontal and limbic regions when patients are currently in a depressive episode. In their 2010 comprehensive review, Yuksel and Ongur (2010) identified 9 studies that measured Glx levels in prefrontal or limbic regions in currently depressed adult patients with major depression. Although there was substantial variation in the 1H-MRS methods used and the specific brain regions examined, 6 of the 9 studies reported significantly reduced Glx in prefrontal regions, the hippocampus and the amygdala. A similar consistent reduction in prefrontal Glx was recently described by Kondo and colleagues in their review of 1H-MRS studies of major depression in children and adolescents (Kondo et al. 2011). A recent study found that diabetic patients with major depression also showed a significant reduction in basal ganglia Glx compared to non-depressed diabetic control patients and compared to healthy volunteers (Ajilore et al. 2007). Another recent study reported a specific decrease in glutamine in the anterior cingulate cortex of highly anhedonic patients with major depression, but this finding was based on only five patients (Walter et al. 2009).

The reduction in Glx in prefrontal and limbic regions appears to be a state-specific characteristic of major depression. Two studies reviewed by Yuksel and Ongur and an additional more recent study scanned euthymic patients subsequent to the remission of their major depressive episode. Two reported normal Glx levels in prefrontal regions, while one observed elevated Glx in the occipital cortex (Taylor et al. 2009; Yuksel and Ongur 2010). Two additional studies showed a normalization of prefrontal Glx levels following successful treatment with electroconvulsive therapy (Yuksel and Ongur 2010). A more recent study examined 22 depressed patients with varying degrees of response to antidepressant medication and found that Glx levels in the pregenual cingulate cortex, but not in the anterior

insula, demonstrated a significant negative correlation with Hamilton depression rating scores (Horn et al. 2010).

Converging observations support the hypothesis that reduced prefrontal and limbic Glx has pathophysiological importance during active episodes of major depression. Glx levels appear to normalize during clinical remission, and the apparently state-dependent reduction of prefrontal and limbic Glx in unipolar depression contrasts sharply with the state-independent elevation of Glx seen in bipolar disorder. Furthermore, blockade of the NMDA receptor by ketamine leads to a hyperglutamatergic state, and also leads to rapid improvement of symptoms in patients with major depression (Zarate et al. 2006). The apparent anatomical specificity of reduced Glx for frontal and limbic regions in major depression is concordant with the selective volume loss seen in these brain regions with structural MRI studies (Hajek et al. 2008; Konarski et al. 2008; Savitz and Drevets 2009). MRS-visible Glx largely reflects the sum of glutamate and glutamine in neuronal and astrocytic cytoplasm. Brain glutamine participates in no metabolic reactions other than those involving its initial conversion to glutamate, primarily within glutamatergic neurons (Albrecht et al. 2007). Thus, the reduced prefrontal and limbic Glx seen during major depressive episodes suggest a pathological process occurring within glutamatergic neurons or their associated glia. Normal levels of prefrontal NAA combined with MRI evidence for prefrontal volume loss suggest an impairment of glial integrity in major depression. Postmortem studies of brain tissue from patients who suffered from major depression have found consistent evidence for reduced number and/or density of glia in prefrontal and limbic regions. Two of the major functions of astrocytes are the de novo synthesis of glutamate from glucose (via the anaplerotic reaction catalyzed by pyruvate carboxylase) to replenish the glutamate–glutamine pool and the uptake and conversion of neurotransmitter glutamate to glutamine (via glutamine synthase) for recycling glutamate back to neurons (Hertz 2004). A deficit in these astrocyte-specific processes would be expected to compromise glutamatergic activity and lead to a reduction in the pool of glutamate and glutamine. Recent gene expression studies in postmortem brain tissue have found consistent evidence for a decrease in the expression of the astrocyte-specific enzyme glutamine synthase in patients with major depression (Choudary et al. 2005; Klempan et al. 2009; Sequeira et al. 2009). Similarly, expression of the glial excitatory amino acid transporters, EAAT1 and EAAT2, which are responsible for most glial glutamate uptake, has been found to be reduced in patients with major depression (Choudary et al. 2005; Miguel-Hidalgo et al. 2010) and in an animal model of depression (Zink et al. 2010). A reduced capacity of the astrocytic components of the glutamate–glutamine cycle could either cause, or be a trophic consequence of, reduced glutamatergic activity. In either case, the consistent 1H-MRS finding of low prefrontal and limbic Glx along with postmortem evidence for a loss of prefrontal glial integrity and deficits in the molecular mechanisms required for glutamate recycling support the hypothesis that glial dysfunction and dysregulation of glutamatergic function are important factors in the pathophysiology of major depression (Hercher et al. 2009; Valentine and Sanacora 2009; Yuksel and Ongur 2010). Continued MRS studies

of prefrontal and limbic glutamatergic function are likely to further advance understanding of the role of this system in the mechanisms of pathogenesis and treatment response in major depression.

3.3.3 GABA

Although the published 1H-MRS literature on GABA in major depression is not extensive, it suggests that cortical GABA is reduced during episodes of depression and normalized following successful somatic treatment. Two studies have examined occipital cortex GABA levels in drug-free depressed patients, and both observed decreased GABA levels (Sanacora et al. 1999; Sanacora et al. 2004). A subsequent study examined dorsal and ventral regions of the prefrontal cortex in drug-free depressed patients, and found decreased GABA only in the dorsal prefrontal voxel (Hasler et al. 2007). A recent study of occipital and anterior cingulate cortical GABA in treatment-resistant MDD, non-treatment resistant MDD, and control subjects found reduced GABA only in the treatment-resistant patients (Price et al. 2009). One study examined GABA levels only in frontal white matter in drug-free elderly depressed patients (ages 61–91), but found no difference between the patient and control groups (Binesh et al. 2004). Four studies have examined the effect of treatment on cortical GABA in patients with major depression. Two studies found that SSRI's increased occipital GABA (Sanacora et al. 2002; Bhagwagar et al. 2004) and one found that electroconvulsive therapy increased occipital GABA (Sanacora et al. 2003). In contrast, depressed patients showed a trend toward decreased occipital GABA following effective treatment with cognitive-behavioral therapy (Sanacora et al. 2006). In unmedicated, remitted patients, one study noted a normal level of GABA in the prefrontal cortex (Hasler et al. 2005) and one study found significantly reduced GABA in the occipital cortex (Bhagwagar et al. 2007) compared to healthy controls. In general, the evidence suggests that cortical GABA is reduced during episodes of major depression and that effective somatic treatment of depression is associated with a normalization of cortical GABA. This pattern of 1H-MRS findings is congruent with evidence from postmortem studies showing reduced size and density of calbindin-positive, GABAergic interneurons (Rajkowska et al. 2007) and reduced levels of GAD67 (Karolewicz et al. 2010) in prefrontal cortex, as well as reduced density of calbindin-positive, GABAergic interneurons in occipital cortex (Maciag et al. 2010) from patients with major depression. Given the evidence for glial dysfunction in major depression, it is important to note that GABA recycling and metabolism rely on the functional integrity of astrocytes, although to a lesser extent than glutamate recycling, This promising literature suggests that dysfunction of GABAergic systems may have an important role in the pathophysiology of major depression. If this work is substantiated and extended by further research, it may provide a translational rationale for studies of treatments targeting GABAergic systems.

3.3.4 Other Metabolites

Although not quite as consistent a finding as in bipolar disorder, a number of studies have observed elevated choline-containing compounds in the basal ganglia of patients with major depression (Yildiz-Yesiloglu and Ankerst 2006b). In light of the basal ganglia volume loss observed in major depression, choline elevation suggests increased membrane metabolism is occurring in this region. It is unclear to what extent this effect is influenced by medication use. Of three 31P-MRS studies of patients with major depression, two have found evidence for reduced ATP levels in the basal ganglia of unmedicated patients (Moore et al. 1997) and in the frontal lobes of medicated patients (Volz et al. 1998). A third study found no evidence for a group difference in ATP levels in medicated depressed patients and control subjects (Iosifescu et al. 2008). If consistent, low ATP levels would suggest a brain bioenergetic deficit is present in untreated major depression. There is no consistent evidence for alterations in brain creatine or myo-inositol in major depression (Yildiz-Yesiloglu and Ankerst 2006b).

3.4 Anxiety Disorders

The anxiety disorders that have been investigated by MRS experiments include panic disorder, posttraumatic stress disorder (PTSD), obsessive–compulsive disorder (OCD), social phobia, and generalized anxiety disorder. Of these, OCD, PTSD, and panic disorder have been the most extensively studied, and some consistent findings with translational implications have emerged from MRS studies of these disorders. However, none of the anxiety disorders have been studied as extensively with MRS as schizophrenia, bipolar disorder, or major depression. Brain MRI morphometry studies of patients with anxiety disorders have often grouped together patients with different anxiety disorders. Across anxiety disorders, the most consistent morphometric finding has been reduced gray matter volume in the anterior cingulate cortex and dorsomedial prefrontal cortex (Radua et al. 2010; van Tol et al. 2010).

3.4.1 Panic Disorder

Panic disorder is a condition characterized by the repeated occurrence of panic attacks, at least some of which are spontaneous (unprovoked). Panic disorder is often accompanied by agoraphobia—the fear and avoidance of situations that would be difficult to escape from or in which it would be difficult to get help in case of sudden incapacitation. There is strong evidence that the vulnerability to panic disorder is partly genetic, with heritability estimated to be about 48% (Hettema et al. 2001). In addition to the gray matter reduction in medial prefrontal regions seen across anxiety disorders, replicated brain morphometric findings in panic disorder include reduced volume of lateral and medial temporal lobe regions

(Ferrari et al. 2008) and increased gray matter volume of the midbrain and pons (Protopopescu et al. 2006; Uchida et al. 2008). We could find no published studies of postmortem brain tissue from patients with panic disorder. Neurobiological models of panic disorder often propose a role for increased reactivity of amygdala, hypothalamic, midbrain, or brainstem regions in the generation of panic attacks and a role for reduced function of orbital and medial prefrontal regions in the relative inability to regulate the anxiety originating in lower regions (Coplan and Lydiard 1998; Gorman et al. 2000). Patients with panic disorder are unusually sensitive to the panic-inducing effects of agents that increase brain acidity or respiratory drive, including CO_2 inhalation and intravenous sodium lactate infusion (Esquivel et al. 2010). Several models have specifically posited an important role for increased reactivity of acid-sensitive chemoreceptor systems in subcortical and brainstem nuclei in the generation of panic attacks (Klein 1993; Coplan and Lydiard 1998; Maddock 2001; Ziemann et al. 2009; Esquivel et al. 2010).

The most consistently replicated MRS finding in studies of patients with panic disorder has been an elevated brain lactate response to metabolic challenges. Prior to the first MRS studies in panic disorder patients, several investigators had demonstrated exaggerated systemic lactate responses to metabolic challenges in panic disorder (Maddock 2001). Dager and colleagues were the first to use 1H-MRS to examine brain lactate responses in panic disorder. In a series of studies examining the brain lactate response during an intravenous lactate infusion, the panic patients were consistently observed to have significantly greater increases in brain lactate in spite of receiving the same dose of intravenous sodium lactate. This effect was observed in both symptomatic, unmedicated patients (Dager et al. 1997, 1999), and asymptomatic medicated patients (Dager et al. 1997; Layton et al. 2001). While several of these studies examined a single voxel placed in the insular cortex, one study used the PEPSI sequence (discussed in Supplement Sect. 4.3.3) to obtain a 2D multivoxel axial slab of spectral data and concluded that the exaggerated increase in lactate in the panic patients was generalized across all brain regions studied (Dager et al. 1999). Hyperventilation is a metabolic challenge that leads to increases in brain lactate in normal volunteers. Panic patients demonstrate a significantly greater brain lactate response to hyperventilation than healthy comparison subjects, despite similar degrees of hypocapnia in the two groups (Dager et al. 1995). It was initially suggested that these findings of elevated brain lactate may have resulted from ischemic cerebral hypoxia due to excessive vasoconstriction triggered by the metabolic disturbance and anxiety induced by the lactate infusion and hyperventilation procedures. However, more recent studies have demonstrated significantly increased brain lactate responses in the visual cortex during visual stimulation in patients with panic disorder, a paradigm in which hyperemia, rather than ischemic vasoconstriction, is known to occur. Maddock and colleagues demonstrated significantly greater increases in visual cortex lactate during a 10 min period of viewing a flashing checkerboard pattern in a group of symptomatic, unmedicated panic patients compared to matched control subjects (Maddock et al. 2009). The visual stimulation procedure did not provoke more anxiety in the patient group than the control group. A second study showed

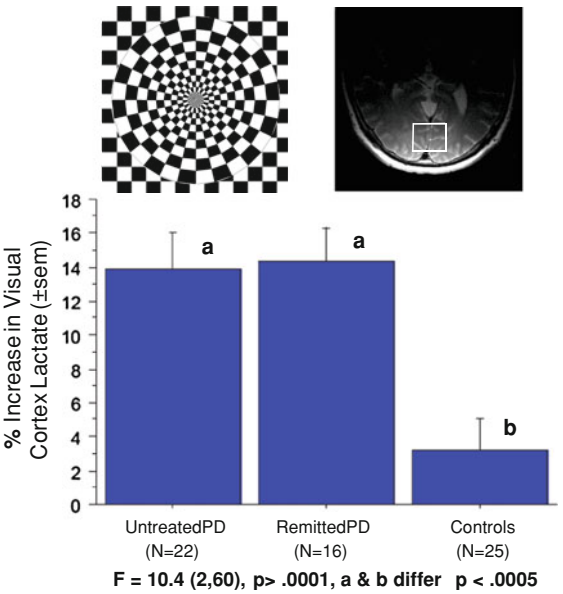


Fig. 4 An 8 Hz pattern reversal checkerboard stimulus was used to stimulate visual cortex lactate production in 22 symptomatic, untreated panic disorder patients, 16 remitted panic disorder patients, and 25 healthy comparison subjects. Percent change in lactate/creatine ratio averaged across 10 min of visual stimulation and 12 min of post-stimulation eyes-closed rest was calculated relative to a pre-stimulation eyes-closed resting baseline. Lactate accumulation was significantly greater in both patient groups compared to control subjects

that remitted panic patients (medicated and unmedicated) demonstrated the same significantly exaggerated visual cortex lactate response to visual stimulation (Maddock and Buonocore 2010). Figure 4 summarizes the visual cortex lactate responses in 22 symptomatic panic patients, 16 remitted panic patients, and 25 matched control subjects. Increased visual cortex lactate accumulation during visual stimulation in panic patients suggests that this metabolic abnormality is evident even during ordinary neural activity. The observation that exaggerated brain lactate responses are seen in both symptomatic and remitted panic patients suggests that it is an enduring or "trait" feature of the disorder and is consistent with metabolic models of the vulnerability to panic disorder.

As discussed in Sect. 2.5, glutamatergic neurotransmission triggers the glycolytic production of lactate from glucose and glycogen, most likely by astrocytes. The lactate is subsequently taken up by neurons for oxidative metabolism. A family of monocarboxylate transporters (MCTs) mediates the co-transport of lactate and hydrogen ions (H+) across glial and neuronal cell membranes. MCT-1 and MCT-4 are expressed in astrocytes, while MCT-2 is the primary form expressed in neurons (Pierre and Pellerin 2005; Bergersen 2007; Hashimoto et al. 2008). MCT-2 has a higher affinity for lactate (Km $\sim$ 0.7 mM) than MCT-1 (Km $\sim$ 4-6 mM) or MCT-4 (Km $\sim$ 32 mM) (reviewed in (Erlichman et al. 2008). When astrocytic production of lactate is stimulated, the relative affinities of these cell-specific subtypes of MCTs favors the rapid movement of lactate and H+ out of astrocytes into the ECF and then more slowly into neurons (Bergersen 2007; Erlichman et al. 2008; Hashimoto et al. 2008). Thus, lactate and H+ accumulate temporarily in the ECF of the synaptic zone, with the magnitude and duration of

the pH change determined by the amount of lactate transported and the buffering characteristics of the ECF. Acid-sensing ion channels (ASICs) respond to ECF pH changes associated with neural activity and are widely distributed in brainstem and hypothalamic regions and in the amygdala (Coryell et al. 2007). ASICs have been demonstrated to mediate fear responses in mice, including the fear response to CO_2 inhalation (Ziemann et al. 2009). Similarly, acid-sensing chemoreceptor systems in the brainstem have been shown to increase their activity in response to increased lactate accumulation (Erlichman et al. 2008). If increased accumulation of lactate during neural activation in panic disorder patients occurs in brain regions mediating fear and arousal responses and is accompanied by a temporary acidification of brain ECF, then the resulting stimulation of acid-sensing chemoreceptor systems might have an important role in triggering "spontaneous" panic attacks, as posited in some models (Klein 1993; Esquivel et al. 2010). In this regard, it is of interest that a recent 31P-MRS study examined the pH-related resonance shift of inorganic phosphate during hyperventilation and found suggestive evidence for altered acid–base regulation in the direction of increased brain acidity in patients with panic disorder (Friedman et al. 2006). 1H-MRS and 31P-MRS are likely to have an important role in future studies testing models of metabolic and acid/base mechanisms in the pathophysiology of panic disorder.

Brain GABA levels have been studied in two samples of unmedicated patients with panic disorder using validated GABA-editing 1H-MRS methods. In the first study, Goddard and colleagues demonstrated significantly lower GABA concentrations in the occipital cortex in panic patients (Goddard et al. 2001). In the second study, Hasler and colleagues found no difference in GABA levels in dorsal prefrontal or ventrolateral prefrontal regions (Hasler et al. 2009). In an extension of their original study and using the same patients, Goddard and colleagues reported that occipital cortex GABA in panic patients did not change following an acute oral dose of clonazepam, while GABA levels decreased significantly in the control group (Goddard et al. 2004). Some pharmacodynamic and PET studies have implicated reduced sensitivity of the GABA-A linked benzodiazepine receptor system in patients with panic disorder (Hasler et al. 2008). However, this abnormality may not involve a reduced concentration of cytoplasmic GABA, as measured by 1H-MRS. Future studies will be needed to establish whether and in which brain regions reduced GABA is a consistent finding in patients with panic disorder.

3.4.2 Post-Traumatic Stress Disorder

Post-traumatic stress disorder (PTSD) is a condition that develops in some individuals following exposure to a traumatic event that threatens a person's life or personal integrity. It is characterized by specific symptom patterns, including intrusive re-experiencing of the event, emotional blunting or avoidance, and generalized hyperarousal. In addition to the bilateral reduction in gray matter volume in medial prefrontal regions observed in common with other anxiety disorders, patients with PTSD also consistently demonstrate reduced volume of the hippocampus compared

to both trauma exposed controls without PTSD and healthy controls (Karl et al. 2006). Based on existing evidence, it appears that antidepressant medication ameliorates the reduction in hippocampal volume in PTSD patients compared to trauma exposed control subjects (Karl et al. 2006). Consistent volume reduction is also seen in the left amygdala in adults and in the corpus callosum in children with PTSD (Karl et al. 2006). Very few postmortem brain studies have been conducted in patients with PTSD, and none have examined hippocampal or amygdala tissue. However, studies showing dysregulation of the hippocampal–hypothalamic–pituitary–adrenal axis and impairments in declarative memory, along with brain volumetric studies, support the basic hypothesis that impairment in hippocampal function has a key role in the pathophysiology of PTSD (Bremner 2006). Functional imaging and lesion studies also support central roles for the amygdala and medial prefrontal cortex in PTSD (Etkin and Wager 2007; Koenigs et al. 2008; Liberzon and Sripada 2008).

In agreement with the results of other neurobiological studies, the most consistent 1H-MRS finding in patients with PTSD has been a reduction in NAA levels in the hippocampus. This effect has been reported as significant in nine of the 10 published 1H-MRS studies that have investigated the hippocampus in patients with PTSD (Schuff et al. 2008; Trzesniak et al. 2008). A recent 1H-MRS study in a mouse model of PTSD found that low NAA in the left dorsal hippocampus prior to electrical footshock trauma predicted the development of persistent PTSD-like symptoms (Siegmund et al. 2009). It is not yet clear whether antidepressant treatment influences hippocampal NAA in PTSD patients. A consistent finding of reduced NAA in the anterior cingulate cortex has also been observed in PTSD patients. This effect has been reported as significant in 4 of the 5 published PTSD studies that have investigated the anterior cingulate cortex (Schuff et al. 2008; Trzesniak et al. 2008). An episode of single, prolonged stress in a rat model of PTSD was recently shown to cause a reduction of glutamate and glutamine in medial prefrontal cortex (Knox et al. 2010). Overall, the 1H-MRS studies of patients with PTSD provide strong support for models of pathogenesis in which dysfunction of the hippocampus and anterior cingulate cortex play central roles. Notable gaps in the current literature include the absence of postmortem tissue studies of the hippocampus, amygdala, or medial prefrontal cortex in PTSD and no 1H-MRS studies of Glx or GABA in any brain regions in PTSD. Because of the unambiguous role of trauma in the pathogenesis of PTSD, it is a psychiatric disorder for which the use of animal models may be particularly fruitful. MRS studies in animals may have an increasingly valuable role in advancing our understanding of PTSD.

3.4.3 Obsessive Compulsive Disorder

Obsessive compulsive disorder (OCD) is a condition characterized by the persistent recurrence of obsessions (intrusive, unwanted thoughts, or images), compulsions (ritualized, repetitive behaviors), or both. The vulnerability to OCD is strongly genetic (Pauls 2010). In addition to bilateral gray matter volume reduction in the medial prefrontal and anterior cingulate cortices, as seen in other anxiety

disorders, patients with OCD also show decreased volume of the orbital frontal cortex and increased volume of the thalami and basal ganglia (lenticular and caudate nuclei) bilaterally (Rotge et al. 2009; Radua et al. 2010). Many of these morphometric findings appear to be independent of the use of antidepressant medications (Radua and Mataix-Cols 2009). Neuroimaging and neurosurgical studies support a general model of involvement of prefrontal cortex–basal ganglia–thalamic–prefrontal cortex circuits in the pathogenesis of OCD (Huey et al. 2008).

Although over 20 1H-MRS studies of pediatric and adult patients with OCD have been published, only a few findings have been consistently replicated. Four studies have demonstrated reduced NAA in the anterior cingulate cortex in adult patients with OCD (Yucel et al. 2007; Trzesniak et al. 2008). One of these studies showed that anterior cingulate NAA normalized after 12 weeks of treatment with citalopram (Jang et al. 2006). However, a recent study reported that NAA levels are increased in this region in OCD (Fan et al. 2010). A relatively large series ($N = 27$) of pediatric OCD patients demonstrated increased choline-containing compounds in the medial thalamus (Smith et al. 2003). A small group of adult SSRI non-responders with OCD showed increased thalamic choline compared to responders (Mohamed et al. 2007). Consistent 1H-MRS abnormalities have not been reported in the basal ganglia in OCD (Trzesniak et al. 2008). Further study will be needed to establish whether abnormalities in MRS-measurable brain metabolites are consistently observed in specific brain regions in OCD patients.

3.5 Summary

This review of the brain MRS literature highlights a number of frequently replicated findings in patients with psychiatric disorders. Some of these consistent findings are convergent with other neurobiological observations. For example, NAA is reduced in many but not all brain regions in patients with schizophrenia, in frontal and hippocampal regions in patients with bipolar disorder, in the hippocampus in patients with PTSD, and in the anterior cingulate cortex in patients with OCD. In each disorder, the reduction in NAA is congruent with evidence for reduced brain volume in similar regions. While irreversible neuronal damage is an important cause of reduced NAA, consistent evidence indicates that reversible reductions in neuronal function can also lead to reduced NAA. Serial 1H-MRS measures of NAA may have value in discerning whether or not specific interventions have remediating effects on an underlying, reversible neuronal dysfunction in psychiatric disorders. Preliminary evidence suggests that this may be the case for the effect of cognitive-behavioral treatment on the anterior cingulate cortex (Premkumar et al. 2010) and exercise on the hippocampus (Pajonk et al. 2010) in schizophrenia, lithium treatment on many brain regions in bipolar disorder (Moore et al. 2000), and SSRI treatment on anterior cingulate cortex in OCD (Jang et al. 2006). However, larger controlled longitudinal studies will be needed to confirm these preliminary findings.

Some of the MRS findings reviewed here provide support for specific models of pathogenesis. Elevated Glx in patients with bipolar disorder and reduced Glx in patients with unipolar major depression accord with models of increased and decreased glutamatergic function, respectively, in those conditions. Reduced phosphomonoesters and intracellular pH in euthymic bipolar patients and elevated dynamic lactate responses in panic disorder patients are consistent with metabolic models of pathogenesis in those conditions. Preliminary findings of an increased glutamine/glutamate ratio and decreased GABA in patients with schizophrenia are consistent with a model of NMDA hypofunction in that disorder. Additional studies are needed to fill in important gaps in this literature. As the sensitivity and specificity of methods continue to improve, MRS studies can be expected to play an important role in the testing of translational models of the pathogenesis of psychiatric disorders.

4 Conclusions

MRS provides a unique, non-invasive method for assessing the metabolic state of the living human brain. Steady growth of the technical capabilities of MRS systems is increasing the range of metabolites that can be measured and the sensitivity and reliability of these measurements. A growing understanding of the pathophysiological significance of abnormalities of the observable metabolite signals, especially with regard to those arising from amino acid neurotransmitter pools, is increasing the value of MRS experiments in neuropsychiatric research. The information gained from MRS studies can be used in conjunction with other non-invasive clinical imaging methods, neuropathological studies, and animal studies to achieve more complete understandings of the natural history of psychiatric illnesses and to test translational models of their pathogenesis. In addition, MRS has the potential to increase understanding of the therapeutic mechanisms of action of effective treatments and to allow clinical monitoring of the neurobiological effects of interventions on brain metabolic markers of psychiatric illnesses.

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