Magnetic Resonance Spectroscopy Studies of Autistic Spectrum Disorders

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In this chapter, we review magnetic resonance spectroscopy (MRS) studies of Autism Spectrum Disorders (ASD). We present a brief clinical overview of autism and related pervasive developmental disorders, and then summarize the neuropathology findings in ASD and neuroimaging investigations of ASD using techniques other than MRS. We then review all published MRS studies of ASD known to us, with some emphasis upon the impact of varying spectroscopic imaging techniques. Finally, we suggest potential future MRS research applications in ASD.

Epidemiology and Diagnosis

Autism is a disorder of development encompassing three primary domains: communication, reciprocal social interactions, and restricted repetitive/stereotyped behaviors and interests [1]. The diagnosis of autism is made based upon symptoms in these domains, typically occurring prior to 3 years of age. Autistic spectrum disorder (ASD) is the broader term that includes autistic disorder, Asperger disorder, Childhood Disintegrative Disorder, atypical autism/pervasive developmental disorders not otherwise specified (PDD-NOS), and Rett syndrome (for review, see Filipek et al.) [2]. Reported prevalence rates vary from 10 [3] to 38.9 [4] per 10,000 for autism, and 60 [5] to 100 [6] per 10,000 for the broader phenotype. Many studies present evidence that prevalence rates have increased dramatically over several decades; however, it is unclear whether this is due to changes in diagnostic practices or an actual increase in the incidence of the disorder. For a review, see King and Bearman [7].

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Neuropathology

Despite numerous findings across a variety of investigational methodologies the pathophysiology of autism remains unclear. Neuropathology findings are relatively fewer than imaging, with early studies implicating cerebellar [8–12] and limbic forebrain [8, 13] abnormalities in this disorder of development. These include such findings as decreased numbers of Purkinje cells in the cerebellum [12, 14, 15] and smaller cell size and increased packing density in the hippocampus, amygdala, subiculum, entorhinal cortex, and mammillary bodies [14]. A recent quantitative investigation demonstrating decreased numbers of neurons in the amygdala [16] provides further support for abnormal development of this region in ASD.

Kemper and Bauman [14] demonstrated decreased size and increased packing density of neurons in the anterior cingulate gyrus, and later studies have described wider involvement of the cerebral cortex, with prominent abnormalities of neuronal density and organization, as well as white matter and brain stem irregularities [15]. Disturbance of the normal architecture of cortical minicolumns has been shown as well, with smaller, more compact and more numerous minicolumns in several areas [17].

Similarly, recent immunohistochemical investigations of autopsy subjects have shown variable findings including reductions in GABAa receptor binding in the hippocampus [18], nicotinic receptors in frontal and parietal lobes [19] and cerebellum [20], and increased brain-derived neurotrophic factor in the basal forebrain [19].

S. Blüml and A. Panigrahy (eds.), *MR Spectroscopy of Pediatric Brain Disorders*,
DOI 10.1007/978-1-4419-5864-8_17, © Springer Science+Business Media, LLC 2013

Structural Magnetic Resonance Imaging in ASD

It is thought that heterogeneity of the disorder has contributed to the disparity in neuropathology findings [11]. Not surprisingly, neuroimaging studies in autism have shown a wide variety of findings as well. Similar to the neuropathology literature, some volumetric studies of ASD support limbic [21–28] and cerebellar abnormalities [29–32] while others have failed to find significant differences from controls in these regions [33].

As noted above, Bailey also found postmortem evidence for neocortical involvement in ASD, including increased frontal cortical neuronal density and cortical dysgenetic lesions [15]. Such lesions may be associated with defective neuronal migration, proliferation, or pruning [34], and reflected in brain structure, such as abnormal organization of the cortical surface [15]. Although nonspecific to autism, qualitative neuroimaging evidence for such surface abnormalities has been demonstrated by Piven et al. [35]. Quantitative neuroimaging evidence for surface abnormalities comes from cortical mapping studies demonstrating irregularities of sulcal anatomy [36] and abnormal gyrification [37].

Volumetric and voxel-based morphometry (VBM) studies have shown abnormalities of both gray and white matter in autistic subjects in a variety of regions throughout the cerebrum, including parietal lobe, left occipito-temporal cortex, right inferior temporal gyrus, left middle temporal gyrus, and left inferior frontal sulcus [22, 38–45]. Reports vary as to direction (increased or decreased) and location of volumetric changes.

Cortical mapping studies have demonstrated displacement of cortical sulci [36], gyrification [36, 37, 46], and cortical thickness including cortical thinning in two studies [47, 48] and primarily increased cortical thickness in one other [49].

Increased head size or overall head circumference [50–52], as well as brain size/volume [26, 45, 53–57] are among the most replicated findings in ASD [39, 52, 55, 58]. The literature suggests that this brain overgrowth occurs in some subjects between 2 and 4 years of age [26, 59], with some cross-sectional studies demonstrating arrest or normalization of this growth in later childhood and adolescence [58, 60]. Other studies, however, have found enlarged brains in older subjects as well [54, 61, 62]. The extent to which gray and white matter contribute to this finding has not been clearly established. While diffusion tensor imaging studies have consistently demonstrated abnormalities of both fractional anisotropy (FA) [63–65] and elevated diffusivity [64, 66], other imaging modalities provide strong evidence for gray matter involvement as well [67, 68].

Functional Neuroimaging in ASD

Similarly, the functional imaging literature indicates varying regional involvement in ASD. Both ^{18}FDG-PET [69] and single photon emission correlated tomography (SPECT) [21, 70] studies provide evidence for abnormal metabolism or perfusion in subjects with ASD. fMRI studies at rest have shown bilateral hypoperfusion of temporal lobe areas [71] in autistic children. Activation studies demonstrate altered activity in cortical regions including the fusiform gyrus [72–74], left middle temporal gyrus [72], inferior temporal gyrus [73], inferior occipital gyrus, and superior temporal sulcus [74] in autistic subjects during face processing tasks; abnormal activation of the superior temporal gyrus (STG) bilaterally during auditory activation tasks [75], and aberrant activity in the right parietal lobe/temperoparietal junction during imitation tasks [76], which may be related to the development of communication skills in autistic children [77].

The above studies demonstrate abnormalities of brain function in regions that subserve language, facial/emotion recognition, and imitation, all of which have been implicated in the primary symptoms of autism [73, 76, 78]. In addition, investigations finding aberrant functional connectivity (FC) in ASD have led to hypotheses that hyper- or hypo-connectivity as a central cause of symptoms in this disorder [78–80].

Magnetic Resonance Spectroscopy in ASD

Magnetic resonance spectroscopy (MRS) provides information on the metabolic aspects of these anatomic and functional abnormalities. Similar to neuropathology, morphometric and fMRI findings, the magnetic resonance spectroscopy research literature in ASD presents a variety of conflicting findings. Some of this is due to heterogeneity of the disorder and some to differences in technique both in acquiring data and in postprocessing. Many of the early studies in the field used ratio evaluation of metabolite content. This approach assumes that the denominator, typically the creatine level, remains constant, which is an assumption that has been repeatedly challenged. In fact, there is evidence that in autism, creatine (Cr) and/or phosphocreatine (PCr) abnormalities may contribute to the disorder [36, 81].

Phosphorous Spectroscopy in ASD

The earliest MRS studies in autism include the only ^{31}P-MRS investigation in this disorder conducted by Minshew and colleagues [82]. ^{31}P MRS measures levels of energy metabolites such as PCr, adenosine di- and triphosphate (ADP, ATP), and

inorganic phosphate (Pi). Some membrane phospholipids are also "visible" with ^{31}P MRS. These include phosphomonoesters (PMEs) and phosphodiesters (PDEs) which are, respectively, precursors and breakdown products of membrane phospholipids and provide information about neuronal (and glial) membrane metabolism [83].

The authors examined prefrontal cortex functioning of 11 high-functioning males with autism, aged 12–40 years and controls matched for age, IQ, gender, race, and SES. They found a significant decrease in the content of PCr and esterified ends in the autistic group and an association between these findings and lower test performance on neuropsychological tests including the Wechsler Intelligence scales, Wisconsin Card Sort Test, California Verbal Learning Test, and the Token Test and Test of Language Competence. Minshew and colleagues [82] suggested that these results provide evidence for disturbances of membrane synthesis and metabolism in autism.

Proton Spectroscopy in ASD

Neocortical Spectroscopy Findings in Autism

Here we continue the discussion of neocortical spectroscopy literature in ASD. With the exception of one study finding no abnormalities in any region examined [84], and one finding increased metabolites in subjects with ASD [85], the majority of these investigations have demonstrated reductions of metabolites in the neocortical regions investigated. As we address the amygdala–hippocampus separately, we leave the discussion of the medial temporal lobe (MTL) for that section.

Most spectroscopy studies of ASD have used proton imaging, with early studies focusing on single voxel investigations. Table 17.1 lists MRS and MRSI studies of pediatric ASD in cortical regions. Hashimoto et al. [84] used single voxel proton spectroscopy in 28 subjects with autism (20 male, eight female; age range 2 year 8 months—12 year 2 months), 28 age-matched subjects with mental retardation (MR) (male 22, female 6; age range 2 year to 13 year 3 months), and 25 age-matched healthy children (male 16, female 9; age range from 2 years to 13 years 8 months). The diagnosis of autism was clinical and based on DSM-III-R criteria [86], and the diagnosis of MR was given for an IQ <80 on the Tsumori-Inage and Suzuku-Binet test. The autistic and MR children did not differ in IQ assessment; the control children were not tested. Six of the autistic children and nine of the MR children had epilepsy. Many of the MR and control children less than 6 years of age were administered triclofos sodium for sedation.

The investigators used the chemical shift selective excitation (CHESS) sequence for water suppression and the stimulated echo acquisition mode (STEAM) sequence at a long TE (270 ms). Volumes varied between 8 and 27 cm^3 and were placed in the right parietal region, overlapping both gray and white matter. Using metabolite ratios with either Cho or Cr as the denominator, this group found no differences in the *N*-acetyl-aspartate/choline (NAA/Cho), NAA/Cr+PCr) or Cho/Cr+PCr ratios between subjects with autism and controls in any age group (2 to <5 years of age; 5–<8 years of age, 8–13 years of age).

Although no differences were found between autistic and controls subjects, the groups were well matched and it is possible that the use of ratios to assess outcome negatively affected the investigators' ability to detect differences between subject groups.

However, in another single voxel proton spectroscopy investigation, Hisaoka et al. [87] found significant differences in autistic subjects and controls in the lateral temporal lobes. This was a relatively large study of 55 autistic subjects (ages 2–21 years; 47 male and eight female) and 51 control children (ages 3 months–15 years, 26 boys and 25 girls). Using a point-resolved spectroscopic sequence (PRESS), and a long TE of 135 ms, these investigators found significant reductions of NAA bilaterally in the temporal lobe (presumptive Brodman's areas 41 and 42) ($p < 0.05$)—but no differences in frontal or parietal regions, or brain stem. All were single voxels quantified using the water reference method and corrected for T1 and T2 relaxation (although no differences were found in relaxation times between groups).

Murphy et al. [85] also used TE 136 with single voxels to investigate the right frontal and medial parietal lobes in a group of subjects with Asperger's syndrome (AS). Voxels included both gray and white matter, and in this case, as opposed to those previously mentioned studies, the content of gray matter, white matter, and CSF was calculated for each voxel of interest. Data were analyzed both as metabolite concentration based on water reference and also as ratios NAA/Cr+PCr, NAA/Cho, and Cho/Cr+PCr. There were no significant differences in the parietal lobe, but in the frontal lobe NAA, Cr+PCr, and Cho were increased in AS subjects compared to controls, although gray and white matter volumes did not differ between groups. Moreover, prefrontal NAA levels in the AS subjects were positively correlated with scores on the Yale–Brown Obsessive Compulsive Scale [88], and Cho was significantly correlated with the communication domain on the Autism Diagnostic Interview-Revised [89].

Magnetic resonance spectroscopic imaging (MRSI) techniques have further advanced the field, allowing for sampling of multiple brain regions in a single session. Such studies have produced somewhat similar results, although there are differences regarding specific metabolites per region [36, 67, 68, 90]. Figures 17.1 and 17.2 illustrate voxel size and placement in the cingulate gyrus.

Table 17.1 Magnetic resonance spectroscopy (MRS) and magnetic resonance spectroscopic imaging (MRSI) studies of pediatric autism spectrum disorder (ASD) in cortical regions

Reference	MRS technique	Brain regions	Key findings
Hashimoto et al. 1997 [84]	Single Voxel STEAM TR-1500, TE 270	–Right Parietal gray and white	No significant Differences—reported as ratios to Cho and Cr
Hisaoka et al. 2001 [87]	Single Voxel PRESS TR 1300,TE 135	–Frontal, –Parietal –Temporal –Brain Stem	Reduced NAA Temporal lobe
Murphy et al. 2002 [85]	Single Voxel PRESS TR 2000,TE 136 gray/white/CSF segmentation	–Right Frontal –Medial Parietal	– Increased NAA, Cr, Cho Frontal lobe – NAA correlation with Y-BOCS – Cho correlation with ADI-R communication scores
Friedman et al. 2003 [90]	MRSI TR 2,000 TE 20/272 ms Quantitation	Slices placed at the level of: –Temporal lobe –Basal Ganglia	Decreased metabolites throughout See Table 17.2
Levitt et al. 2003 [36]	MRSI TR 2300,TE 272 gray/white/CSF segmentation	Slices placed at the level of: –Supraventricular –Ventricular –Basal Ganglia	– Decreased Cr + PCr –R occipital – Decreased NAA left caudate; left frontal and left parietal white matter; left parietal white matter – Increased Cr + PCr –Caudate – Decreased Cho –Left ACC
Friedman et al. 2006 [67]	MRSI, Gray/white/CSF segmentation	see Friedman et al. 2003	Attributed decreased metabolites in 2003 study primarily to gray
Devito et al. 2007 [68]	3 T MRSI TR 100 TE 135	Slices placed at the level of: –Occipital lobe– Corpus Callosum –Cerebellum–Thalamus	– Decreased NAA frontal and occipital lobes gray – Decreased Glx frontal and occipital gray, and cerebellum – Decreased Cr + PCr left temporal and left occipital gray matter.
Harada et al. 2010 [96]	3 T single voxel –PRESS-TE 68 for GABA –STEAM TE 15 for conventional metabolites	–Frontal lobe –Lenticular Nucleus	Decreased GABA in frontal lobe Decreased GABA/NAA and GABA/Glu in frontal lobe
Bernardi et al. 2011 [95]	3 TMRSI TR 2000 TE 30	–Anterior Cingulate/Thalamus –Temperoparietal	Reduced Glx right anterior cingulate Reduced mI temperoparietal junction
Vasconcelos et al., 2008 [119]	Single Voxel PRESS TR 1500 TE 30	–Cingulate –Left Striatum –Left Frontal lobe –Left cerebellum	Increased mI and Cho anterior cingulate Increased mI/Cr in cingulate and striatum
Oner et al. 2007 [121]	2D-CSI PRESS TR 1500 TE 270	–Right Anterior Cingulate –Right Dorsolateral Prefrontal Cortex	– Increased NAA/Cho ($p = 0.028$) in ACC; – Correlation to Y-BOCS ($p = 0.047$); – Neg correlation Y = BOCS and DLPFC NAA/Cho ($p = 0.015$)
Endo et al. 2007 [148]	Single Voxel PRESS TR 2000 TE 35	–Prefrontal Cortex –Amygdala–hippocampus	Decreased NAA/Cr ASD vs control Decreased NAA/Cr Autism vs PDD-NOS
Kleinhans et al. 2007 [106]	Single Voxel PRESS TR 2000,TE 30 CSF but not gray/white assessed	–Left middle frontal –Left parietal –Occipital cortex –Right cerebellum –Cerebellar vermis	Decreased NAA left frontal lobe middle gyrus.

N-Acetyl (NAA) Compounds, Choline-Containing Compounds (Cho), Creatine + Phosphocreatine (Cr), Myoinositol (MI), Glutamate-glutamine (Glx), Chemical Shift Imaging (CSI)

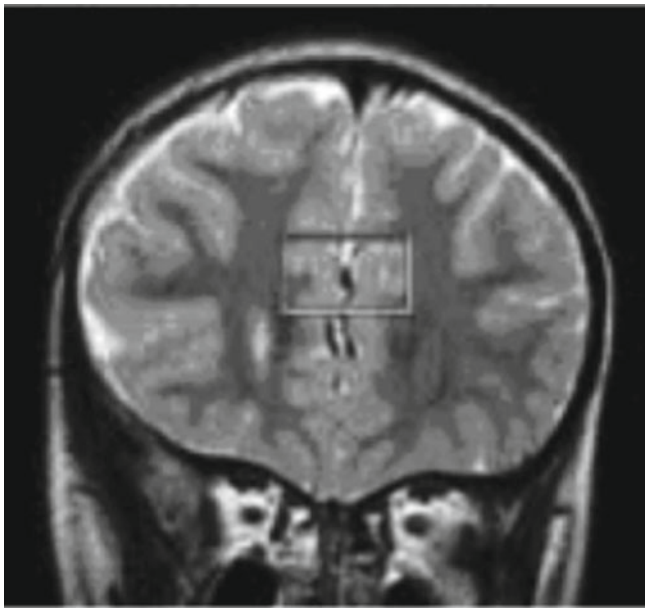

Fig. 17.1 Single voxel study by Hisaoke et al. demonstrating placement bilaterally in the anterior cingulate gyrus. (From Hisaoka S, Harada M, Nishitani H, Mori K. Regional magnetic resonance spectroscopy of the brain in autistic individuals. Neuroradiology 2001;43(6):496–8, with permission.)

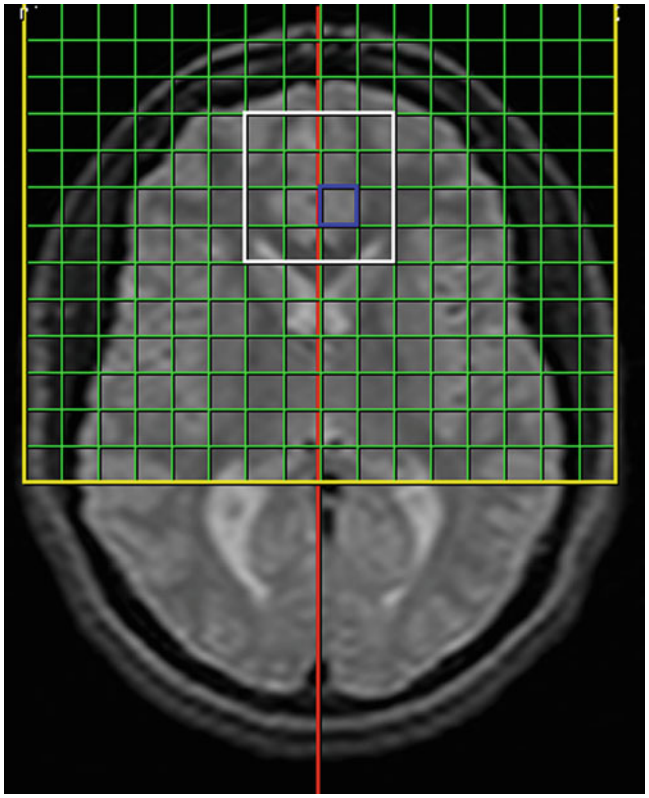

Fig. 17.2 The excited volume of the spectroscopic imaging study area is outlined in white, whereas the smaller voxels within the volume indicate the ROIs for individual voxels. Outlined in blue voxel is a representative ACC voxel. (From Levitt J, O'Neill J, Blanton RE, et al. Proton magnetic resonance spectroscopic imaging of the brain in childhood autism. Biol Psych 54:1355–1366, 2003; with permission.)

Friedman et al. [90] utilized proton echoplanar spectroscopic imaging (PEPSI), two echo times (TE 20/272 ms), and also measured relaxation times in children 3–4 years of age with ASD (38 boys, 7 girls), developmental delay (DD) (6 boys, 9 girls), and typical development (TD) (11 boys, 2 girls). Groups were age matched, but differed in gender distribution, although no covariates were used for this as the authors cited lack of evidence for sex effects on spectroscopy. All autistic and DD children were administered propofol for sedation, while TD children were imaged during sleep and/or after administration of diphenhydramine. Two slices were acquired—one placed atop the temporal lobes and one placed through the basal ganglia. Data was analyzed using the LCModel commercial package [91] for automated fitting and water referencing for metabolite content.

Initial data analysis of averaged metabolite content throughout the slices demonstrated reduced NAA in both autistic and DD children as compared to TD children. The autistic children alone had decreased Cho, Cr+PCr, and myo-inositol (mI) compared to TD subjects. There were no differences in glutamate+glutamine (Glx) between groups. While averaged NAA T2 relaxation time (T2r) was prolonged in the ASD subjects compared to both TD and DD controls, Cr+PCr and Cho T2r were prolonged in ASD subjects compared to DD subjects. The authors suggest, given their findings of prolonged T2r, that proton spectroscopy studies in autism should employ short TE ($\leq$ 30 ms) as the differences in T2r at longer TEs may affect results. Post hoc analysis directed to regional sites demonstrated multiple reductions in proton metabolites, some of which are outlined here and in Table 17.2.

Metabolite differences in the ASD group, not replicated in the DD group, were widespread and affected the thalamus, basal ganglia, cingulate/callosum, and temporal and parietal regions. Metabolite differences that may be attributed to developmental delay in both ASD and DD subjects include the left frontal white matter reduction in NAA and Cr+PCr, and the parietal white matter reduction in NAA.

In an effort to better understand these data, Friedman et al. [67] applied linear regression techniques to analyze the relative contributions of gray and white matter to their findings. In addition, cerebral volume was included as a covariate in these analyses. Their results demonstrated that findings unique to the autistic subjects occurred primarily in gray matter (decreased NAA, Cr, Cho, and mI and prolonged Cho T2r compared to controls), while both AD and DD had reduced white matter NAA and mI (mI at the trend level only in the DD group however) relative to the control subjects. Cho and mI were reduced in AD compared to DD as well.

Table 17.2 Spectroscopic imaging results, Friedman et al. [90]

	Decreased NAA	Decreased Cr + PCr	Decreased Cho	Decreased mI
ASD vs TD	– Right thalamus – Bilateral cingulate	– Left thalamus Anterior Callosum – Left parietal white – Left insula	– Left thalamus – Right medial temporal lobe – Right superior temporal gyrus	– Bilateral caudate – Anterior callosum – Left parietal white – Right insula
ASD and DD vs TD	Left frontal white Right parietal white	Left frontal white		
ASD vs DD	Occipital cortex			

The authors suggest that these findings may provide evidence for a common metabolic abnormality in white matter of both ASD and DD children. However, Levitt et al. [36] also found significant reductions of NAA in left frontal and left parietal white matter in older children with ASD, most of whom had IQ ≥ 70.

In this study, Levitt et al. [36] also used multislice MRSI (TE = 272 ms, Fig. 17.3) to investigate proton metabolites in 22 subjects with autism (4 girls, 18 boys aged 5.4–15.7 years) and 20 age-matched healthy controls (10 girls, 10 boys aged 6.8–16.3 years). Only three of these subjects had IQ < 70, two with full scale IQ scores of 61 and 64, and one scoring 33 verbal and 59 performance on the Mullens Scale of Early Learning [92]. Three 12-mm axial slices were proscribed through (1) the supraventricular region, (2) the ventricles, and (3) the dorsoventral midplane of the basal ganglia. Slices were co-registered to segmented tissue maps, and voxels were selected within manually delineated regions of interest including: the cingulate gyrus, caudate, putamen, and thalamus. Only voxels containing ≥ 75 % gray or white matter were retained in cortical, respectively, regions. Voxels were CSF corrected and absolute quantitation of MRSI metabolite levels was expressed in terms of institutional units (IU), rather than mmol concentrations, because no correction was made for T1 and T2 relaxation effects. Gender was included as a covariate in Levitt et al. [36], but not in Friedman et al. [90].

The findings included decreased Cr + PCr in right occipital cortex ($p = 0.043$), decreased Cho in left anterior cingulate gyrus ($p = 0.003$), and increased Cr + PCr in the left ($p = .0068$) and right ($p = 0.03$) caudate nucleus. Post hoc analyses revealed significantly decreased NAA in autistic subjects in left parietal white matter ($p = 0.019$), left frontal white matter ($p = 0.029$), and left caudate ($p = 0.04$).

As noted above, Friedman et al. [67] suggest that findings of decreased NAA in frontal and parietal white matter may represent a phenomenon common to both subjects with ASD and with DD. However, Levitt et al. [36] found that NAA levels remained significantly reduced in the autistic subjects compared to controls when the analysis was restricted to subjects with full-scale IQ of 83–127. Moreover, a separate single voxel study in 18 month to 7-year-old boys [93] found no significant difference between 25 male subjects with ASD and 12 male subjects with MR or language disorder but not ASD.

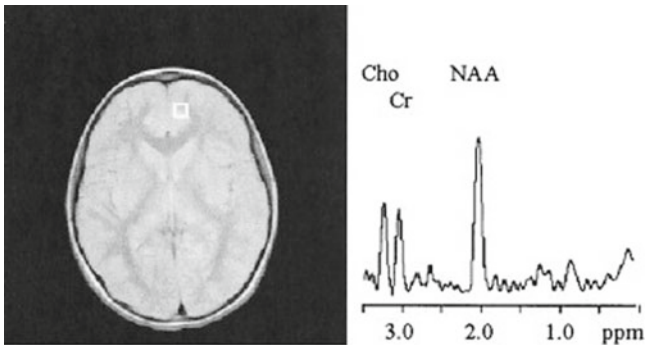

Fig. 17.3 A representative spectrum obtained with MRSI. (From Levitt J, O'Neill J, Blanton RE, et al. Proton magnetic resonance spectroscopic imaging of the brain in childhood autism. Biol Psych 54:1355–1366, 2003; with permission.)

Possible confounds in these studies include the effect of medications in some subjects in both Friedman et al. and Levitt et al., as well as the administration of propofol sedation to some subjects in Levitt et al. [36] and all ASD and DD subjects in Friedman et al. [90]. Levitt et al. [36] examined these potential confounds by excluding medicated and or sedated subjects from the analyses, although this reduced power to detect changes. Significant differences from initial results were found (1) eliminating sedated subjects from the analysis resulted in a loss of Cho findings in the caudate and (2) further analysis of the effect of medication revealed a "normalization" of Cr + PCr content in the right caudate in the medicated subjects. Of note, a proton spectroscopy investigation of obsessive compulsive disorder (OCD) demonstrated a similar effect of selective serotonin inhibitors, producing a normalization of the Glx peak in the caudate of OCD subjects compared to controls [94].

While none of the aforementioned studies detected Glx differences in ASD, all were performed at 1.5 T. De Vito et al. [68] performed the first 3 T study in subjects with ASD, which greatly improves the ability to characterize the Glx peak. Using spectroscopic imaging (TE 135 ms), 2 slices were placed at (1) the lower at the level of the superior

cerebellum and thalamus; and (2) through the occipital lobe and splenium of the corpus callosum. This allowed for a sampling of cortical regions except the parietal lobe, in 26 male subjects with autism (6–17 years of age) and 29 controls (6–16 years of age). Eighteen subjects required midazolam for sedation, and 12 were on psychotropic medications. There were no significant group differences in age or nonverbal IQ, although verbal IQ was lower in the subjects with autism.

Voxel gray/white/CSF proportions were calculated based on T1-weighted segmentation data, and metabolites were quantified using phantom metabolite solutions of known concentration. All cortical voxels were pooled for metabolite assessment and, in addition, manually segmented regions were assessed. Based on content of gray and white matter, the regions assessed included: left and right frontal, temporal and occipital gray matter; left and right cerebral white matter; and left and right cerebellum.

Averaged results showed significantly decreased NAA in the autistic subjects, primarily in gray matter ($p=0.006$); regional analysis attributed this to both frontal and occipital lobes and at a trend level, the temporal lobes. NAA was also reduced in white matter in the autistic subjects, but only at the trend level (0.06), and was reduced at the trend level in the ASD group in the cerebellum ($p=0.06$). Glx was significantly decreased in gray matter autistic subjects ($p=0.0007$) in frontal ($p=0.02$) and occipital ($p=0.002$) lobes and in the cerebellum ($p=0.003$), but not in white matter. Cr+PCr was reduced in gray matter in the left temporal ($p=0.04$) and left occipital ($p=0.05$) lobes.

Furthermore, there was a negative correlation found between age and cerebral gray matter NAA ($p=0.002$) and Glx ($p=0.00002$) in frontal, temporal, and occipital gray matter of control subjects, but not in autistic subjects. This negative correlation was found for both groups for NAA in the cerebellum. Analyses of the effects of medication or sedation upon the results did not reveal any significant differences in findings between medicated and unmedicated subjects.

Bernardi et al. [95] also used a 3 T magnet to investigate proton metabolites in the cerebral cortex of 14 adults with ASD and 14 healthy controls matched for age and nonverbal IQ. Using a PRESS sequence (TE = 30 ms) in two slices placed as (1) an axial slice through the anterior cingulate gyrus (ACC) and thalamus and (2) a coronal slice placed approximately along the intraparietal sulcus (IPS) and the temperoparietal junction (TPJ), proton metabolite data was quantified and reported in IU. The investigators found significant reductions in Glx in the right ACC ($p<.006$) and decreased mI in the left temperoparietal junction ($p<.03$). These results are consistent with the previous findings of decreased frontal Glx by DeVito et al. [68]; and as the authors point out, indicate that these changes may be stable into adulthood.

In an investigation designed to examine GABA in ASD, Harada et al. [96] used a 3 T magnet to examine proton metabolites in 12 children with ASD (2–11 years of age) and 10 control subjects (3–12 years of age). Ten of the autistic subjects and nine of the control subjects required sedation with triclofos sodium. The investigators incorporated the MEGA-editing J difference technique [97] into a PRESS sequence (TE = 68 ms) to improve the GABA signal, as well as a STEAM sequence (TE = 15 ms) for the conventional proton metabolites. Single voxels were placed in the frontal lobe and in the lenticular nucleus and were segmented into gray/white/CSF fractions; LCModel [98] was used for metabolite analysis.

Data analysis demonstrated a significant reduction in GABA in the frontal lobe region of the ASD subjects compared to the control subjects ($p<0.01$), and reduced GABA/NAA ($p<0.01$) and GABA/Glu ($p<0.05$). There were no other statistically significant differences. Noting recent research demonstrating irregularities of the $GABA_A$ and $GABA_B$ receptors in subjects with ASD [99, 100], the authors hypothesize that these findings implicate suppression of the GABAergic system and subsequent hyperfunction of glutamate (Glu) during brain development in ASD.

In summary, several proton spectroscopy studies in ASD have found decreased NAA in regions throughout the neocortex in subject groups including very young children [90], children and adolescents [36, 68], and subjects spanning both of these age groups [87]. NAA may be a marker of either neuronal numbers/density, or integrity/function [101, 102], and/or more specifically, of mitochondrial function [103]. Given the evidence outlined above for increased brain volume [58], numbers/density of neurons in the cortex of subjects with autism [15, 17], and cortical thickness [49], these findings seem more consistent with an abnormality of function in the neurons or glia in these regions, and less an indication of reduced neuronal numbers.

Findings of other proton metabolite irregularities in these same cortical regions support this notion. There is evidence for decreased Cr+PCr in occipital gray matter [36, 68], as well as frontal and parietal white matter [90]. The Cr+PCr peak is a marker of cellular energetics that may be driven in part by cytosolic glycolysis [104] and are consistent with earlier fMRI studies demonstrating diminished functional activity in autistic subjects [71, 76, 78] and Harris et al. [105].

Support for a relationship between such abnormalities and the symptom profile of ASD comes from several studies, including a single voxel investigation by Kleinhans et al. [106]. Using short TE (35 ms) PRESS 1 H-MRS in 13 males with ASD (7 autistic, 3 Asperger disorder, and 3 PDD-NOS) and 13 age- and gender-matched controls, these

investigators found that reduction of NAA in the left frontal lobe middle gyrus of the subjects with ASD ($p=0.043$) was correlated with the percent of frontal lobe activation on an fMRI test of verbal fluency.

In the temporal lobes, there is also evidence for reduced Cr+Pcr [68] as well as for decreased Cho in the right superior temporal gyrus and reduced mI in the temperoparietal junction [95]. Cho is attributed primarily to membrane constituents, and therefore abnormalities of this metabolite in the STG, a node in the language comprehension network [107], suggest disruption of normal membrane synthesis or degradation [108, 109] in this region. mI is considered to be primarily a marker of glia [101]. Findings of decreased mI in the left temperoparietal junction ($p<.03$) may be evidence of glial abnormalities in this region subserving attention and empathy (see Bernardi et al. for review [95]), and are consistent with Williams et al.'s [76] findings of abnormal metabolic activity in the temperoparietal region during imitation tasks.

In addition, findings of reduced Glx (including both glutamine and glutamate) in frontal, temporal, and occipital lobes [68], as well as decreased GABA in the frontal lobe [96] support hypotheses of disturbed excitation/inhibition in ASD [110]. Taken together, these metabolic changes support and extend neuropathology, morphometric and functional imaging studies outlined above that demonstrate widespread neocortical involvement in the brain in ASD. Similar metabolic abnormalities have been found in many other brain regions in autism, which we discuss below.

The Cingulate Gyrus in Autism

In addition to its well-known role in cognition and attention [111], the anterior cingulate gyrus is centrally involved in processing both cognitive and emotional stimuli [112, 113], and motor responses to these stimuli [114]. Studies implicate this region, as well as the prefrontal cortex, in theory of mind and empathy, which are hypothesized to be central to ASD symptomatology [115, 116]. The ACC is implicated as well in the pathophysiology of obsessive compulsive symptoms [117], which may in some cases be related to the repetitive-stereotyped behaviors symptom domain seen in autism [85, 118].

The findings in the spectroscopy literature regarding the anterior cingulate gyrus in autism are similar to those in the neocortex in that while several investigations provide evidence for metabolic abnormalities in this region, there is variability in the specific metabolic abnormalities found. The spectroscopic imaging investigations outlined above produced evidence for decreased NAA bilaterally in the ACC [90] and decreased Cho in the left ACC [36]. However, Vasconcelos et al. [119] found increased Cho ($p=0.04$) and increased mI ($p=0.02$) in the anterior cingulate using short TE (30 ms) single voxel PRESS in ten boys with autism (median age 9.5 =/−1.8 year) and ten control boys (median age 8.5±1.4 years). Finally, in their 3 T study described above, Bernardi et al. [95] demonstrated decreased Glx in the right ACC.

Decreased levels of Glx in the ACC may be related to receptor abnormalities in this region recently demonstrated by Oblak et al. [120] demonstrating significantly reduced numbers of $GABA_A$ receptors in the ACC in postmortem tissue from subjects with ASD. Corresponding abnormalities of glutamate and/or glutamine may ultimately manifest in aberrant connectivity and function, resulting in disruption of normal ACC function that may lead, at least in part, to the symptomatology of ASD.

Further evidence for the relationship between proton metabolites, functional abnormalities, and symptomatology comes from a study by Oner et al. [121], demonstrating significant correlations between proton metabolites in adult subjects with autism and scores on the Yale–Brown Obsessive Compulsive Scale (Y-BOCS) [88]—a measure of severity of obsessive compulsive symptoms. These investigators used 2D-CSI (Press, TE 270 ms) in both the right ACC and right DLPFC in 14 male patients with AS (17–38 years of age) and in 21 age-, IQ-, and gender-matched control subjects. They found significantly decreased NAA/Cho in the ACC of subjects with autism, as well as a positive correlation between this measure and scores on the Y-BOCS, used as a measure of repetitive and stereotyped behaviors, a cardinal symptom in ASD.

Proton Spectroscopy and the Caudate in ASD

The caudate is also a well-known node in the pathways involved in obsessive compulsive disorder [122–125]; for review, see Maia et al. [126]. Both spectroscopic imaging and single voxel studies describe significant abnormalities in the caudate in subjects with ASD (Table 17.3). Using spectroscopic imaging, Levitt et al. [36] found increased Cr+PCr bilaterally, and decreased NAA (left hemisphere), while Friedman et al. [90] demonstrated decreased mI bilaterally in the caudate. In their single voxel study, Vasconcelos et al. [119] found increased mI/Cr in the striatum.

Between these three studies investigating very young children (3–4 years of age), Friedman et al. [90], as well as older children and adolescents [36, 119], there is a pattern consistent with aberrant Cr+PCr (energy/metabolics) and mI (glial cell) abnormalities in the caudate in ASD. These findings are consistent with PET [127] and fMRI investigations demonstrating abnormalities of functional activation [128, 129] and functional connectivity [130] in this region.

Table 17.3 Proton spectroscopy in anterior cingulate gyrus, caudate, and thalamus in ASD

Reference	MRS technique	Brain regions	Key findings
Friedman et al. 2003 [90]	MRSI TR 2,000 TE 20/272 ms, Quantitation	–Temporal lobe –Basal ganglia	Decreased metabolites throughout See Table 17.2
Levitt et al. 2003 [36]	MRSI TR 2300 TE 272 gray/white/CSF segmentation	–Supraventricular –Ventricular –Basal Ganglia	Increased Cr+PCr–Caudate bilateral Decreased Cho–Left Anterior cingulate Decreased Cr+PCr -R occipital cortex Decreased NAA left caudate; left frontal white matter; left parietal white matter
Bernardi et al. 2011 [95]	3 T MRSI TR 2000 TE 30	–Anterior Cingulate/ Thalamus –Temperoparietal	Reduced Glx right anterior cingulate Reduced mI temperoparietal junction
Vasconcelos et al., 2008 [119]	Single Voxel PRESS TR 1500 TE 30	–Cingulate –Left Striatum –Left Frontal lobe –Left cerebellum	– Increased mI and Cho anterior cingulate – Increased mI/Cr in cingulate and striatum
Oner et al. 2007 [121]	2D-CSI PRESS TR 1500 TE 270	–Right anterior cingulate –Right dorsolateral prefrontal cortex	– Increased NAA/Cho ($p=0.028$) in ACC; – Correlation to Y-BOCS ($p=0.047$); – Neg correlation Y=BOCS and DLPFC NAA/Cho ($p=0.015$)
Hardan et al. 2008 [131]	STEAM CSI TR 1600 TE 20	–Thalamus—bilateral	Decreased NAA right thalamus Left thalamus trend

Proton Spectroscopy and the Thalamus in ASD

Hardan and colleagues [131], interested in investigating the neurophysiology of sensory abnormalities in subjects with autism, examined the thalamus using both morphometry and proton spectroscopy, and correlated their results with scores on the sensory profile questionnaire (SPQ) [132]—a parent report measure of sensory abnormalities.

Using a 2D multivoxel ^{1}H spectroscopy STEAM sequence [133] and chemical shift imaging (TE 20 ms), this group tested 18 boys with ASD and 16 controls boys 8–15 years of age. Significant findings were all in the left hemisphere and included decreased NAA ($p=.006$); PCr+Cr (.022); Cho (expressed as GPC+PC) ($p=.004$); Glx trended to significance ($p=0.082$). As seen in previous studies of the thalamus in ASD [134–137], no volumetric differences were found between subjects and controls, despite the presence of metabolic or functional effects.

These results are similar to those of Friedman et al. [90] who also found decreased NAA (right $p<0.05$; left trend), and significantly decreased Cr+PCr and Cho ($p<0.05$) in the left hemisphere in their ASD subjects aged 3–4 years. In addition, a single voxel study [134] in 31 subjects with autism and 15 control subjects (0–13 years of age) found reduced NAA/PCr+Cr.

These findings, taken together with other proton metabolite abnormalities described above in the ACC and caudate, are consistent with PET [136] and fMRI [129] investigations in ASD that implicate fronto-striato-thalamic circuitry in the pathophysiology of ASD.

Proton Spectroscopy and the Amygdala in ASD

The amygdala has been studied intensively in ASD due to this region's involvement in recognizing and interpreting emotional stimuli [6, 138–141]. Morphologic studies of the amygdala have demonstrated similar growth trajectories to overall brain size in autism, i.e., increased volume in young children [26–28], but normal or reduced size in adolescents and adults [23, 74, 142]. Further evaluation of some of these morphometric abnormalities has demonstrated a relationship between size and severity of symptomatology [28, 142]. Numerous fMRI studies have found abnormalities in this region in AD as well [72, 143–146].

The majority of proton spectroscopy studies in the amygdala/hippocampus region have also produced evidence for significant changes in autistic subjects as compared to controls. These findings include reduced NAA [147], reduced NAA/Cr [147–149], increased Cr and Glx (Page et al. 2006), and increased Cho/Cr and mI/Cr [149]. We review each of these below.

Otsuka et al. [147] studied proton metabolites in the right hippocampus–amygdala and left cerebellar hemisphere in 27

autistic patients 2–18 years old (21 boys and 6 girls) and 10 control children 6–14 years old, (4 boys and 6 girls), using short TE (18 ms) single voxel ($2 \times 2 \times 1.5$ cm^3) STEAM. They found reduced NAA ($p = 0.042$) in the autistic subjects in both regions, using quantitation of proton metabolite levels referenced to water, which may reflect true levels of metabolites more accurately than ratios. The age ranges given differ considerably between groups, which may confound the results, although decreased NAA in the cerebellum was also reported by Chugani et al. [150] in nine autistic children compared to five sibling control subjects ($p = 0.043$).

Endo et al. [148] conducted a short TE (35 ms) single voxel study and reported decreased NAA/Cr ratios in the right MTL—amygdala/hippocampus in 38 subjects with ASD as compared to 16 age-matched control subjects ($p < 0.001$). NAA/Cr was also significantly reduced when the subjects with autism were compared to subjects with PDD-NOS ($p < 0.001$). They further analyzed possible correlations between this data and ratings of autistic symptoms on the childhood autistic rating scale Tokyo version [151] and found negative correlations between NAA/Cr on the right and ratings of symptom severity including the total score ($p = 0.01$), and subscales: emotional response $p = 0.02$ and listening response $p = 0.001$.

Gabis et al. [149] also found decreased NAA/Cr ratios in a single voxel (TE 40 ms) study of the MTL ($p < 0.05$) in subjects with ASD (7 children with PDD-nos, 1 child with autism, and 5 with Asperger's disorder) compared to 8 controls (not matched for gender or IQ). Findings were bilateral and occurred across both language impaired and nonlanguage impaired subgroups. In addition, they found increased mI/Cr in bilateral MTL and in the cerebellum, and increased Cho/Cr in the left MTL and cerebellum. The Cho/Cr findings in the left MTL were attributed largely to the language-impaired subjects in the study.

Page et al. [81] used single voxel PRESS TE 35 ms to investigate proton metabolites in the right amygdala–hippocampus and right parietal lobe in 25 adults with autism and 21 control subjects. MRS metabolite concentrations were corrected for tissue and CSF content, and LCModel was used, plus in-house software, to quantify the results. Cr+PCr as well as Glx was increased significantly in the amygdala/hippocampus region, but not in right parietal lobe. The parietal findings are consistent with a previous ^{1}H-MRS study finding abnormalities in the left, but not right parietal lobe in autistic subjects [36].

These results of increased Cr in the amygdala, quantified using referencing standards, must be taken into account when considering reports of metabolite ratios in this region [148, 149]. While the findings are consistent across the Endo and Gabis studies, e.g., demonstrating decreased NAA/Cr in both, the extent to which increased Cr content may have contributed to these findings renders the results difficult to interpret.

Kleinhans et al. [152] emphasize this point in discussing the results of their bilateral amygdala study using water referencing and quantitative analysis of single voxels at short TE (30 ms). The investigator and colleagues measured proton metabolites in 20 adults with high functioning autism or Asperger's disorder and 19 age- and IQ-matched controls, and found no significant difference between controls and subjects. However, they did find an inverse correlation between measures of NAA and Cr, and symptom severity on the ADI-R. These results are consistent with the findings of an inverse correlation between NAA/Cr and symptom severity in Endo et al. [148], as well as with the studies of amygdala size and severity of symptomatology described above [28, 142], and with a previous fMRI study by Kleinhans et al., [146] demonstrating an inverse correlation between ADI-R severity and functional connectivity between the amygdala and fusiform face area.

Two other studies have also found correlations between symptom severity and proton metabolites in this region in ASD [153, 154]. Sokol et al. [153] reported an association between Cho/Cr+PCr in the hippocampal/amygdala complex and severity of autism as measured by the Children's Autistic Rating Scale (Pearson $r = 0.657$, $p = 0.04$) in ten children with autism, aged 2–12 years. The authors interpreted their results as potentially indicative of increased membrane turnover or cell growth. Results must be interpreted with caution as noted above, Cr+PCr levels may be abnormal in the brains of autistic children, and three of the children had seizures.

Suzuki et al. [154] investigated the hippocampus in relation to aggression in subjects with autism, due to the body of literature demonstrating a modulating influence of the hippocampus upon aggression [155–158]. They used a rectangular voxel, slanted to cover the long axis of the hippocampus on a coronal oblique image, a PRESS sequence (TE = 144 ms) in 12 non-medicated autistic males and 12 age- and gender-matched controls. The investigators found significantly increased concentrations of Cho ($p < 0.001$) and Cr+PCr ($p < 0.001$) in the hippocampal region of autistic subjects as compared to controls, and significantly decreased concentration of NAA in the cerebellum of the autistic subjects. Both Cho and Cr+PCr were related to aggression severity as measured by the Japanese version of the Aggression Questionnaire [159].

Proton Spectroscopy in the Cerebellum in ASD

Three ^{1}H-MRS studies in the cerebellum [106, 119, 149] have found no differences in ASD, while others have found significant decrements in NAA [147, 150, 154] and decreased Glx [68]. Reductions of NAA and Glx in this region may be a marker of decreased Purkinje cells in the cerebellum found in neuropathologic investigations of subjects with ASD [160]. There are reciprocal loops between the cerebellum

and sensorimotor regions of the cortex [161], disruption of which might lead to dysfunction of higher cognitive functions involving the cerebellum to some degree [162]. These data support long-standing evidence of a cerebellar contribution to the symptom profile in ASD [163].

Future Directions

The convergence of differing imaging methods demonstrating abnormalities of structure, function, and biochemical metabolites in numerous regions throughout the brain in subjects with ASD provides ample evidence for this being a disorder of diffuse cortical and subcortical involvement. Future studies combining these methodologies in multimodal investigations will greatly enhance our ability to understand the biochemistry underlying functional and structural abnormalities in ASD. Combining such investigations with genetic data should help to elucidate the pathways leading to disruptions of development in this disorder.

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