Magnetic Resonance Spectroscopy in Schizophrenia: Methodological Issues and Findings—Part II

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Magnetic resonance spectroscopy allows investigation of in vivo neurochemical pathology of schizophrenia. "First generation" studies, focusing on phosphorus and proton magnetic resonance spectroscopy, have suggested alterations in membrane phospholipid metabolism and reductions in N-*acetyl aspartate in the frontal and temporal lobes. Some discrepancies remain in the literature, perhaps related to the variations in medication status and phase of illness in the patients examined, as well as in magnetic resonance spectroscopy methodology; the pathophysiologic significance of the findings also remains unclear. Technologic advances in magnetic resonance spectroscopy in recent years have expanded the potential to measure several other metabolites of interest such as the neurotransmitters glutamate and γ-aminobutyric acid and macromolecules such as membrane phospholipids and synaptic proteins. Issues of sensitivity, specificity, measurement reliability, and functional significance of the magnetic resonance spectroscopy findings need to be further clarified. The noninvasive nature of magnetic resonance spectroscopy allows longitudinal studies of schizophrenia both in its different phases and among individuals at genetic risk for this illness. Future studies also need to address confounds of prior treatment and illness chronicity, take advantage of current pathophysiologic models of schizophrenia, and be hypothesis driven.*
Biol Psychiatry 2000;48:369–380

Key Words: Magnetic resonance spectroscopy, phospholipids, schizophrenia, proton MRS, phosphorus MRS

Introduction

In the past two decades brain research in schizophrenia has made significant advances, largely as a result of neuroimaging and neuropathologic studies. At a *neuroanatomic* level, computed tomography and magnetic resonance imaging (MRI) studies have suggested brain structural changes, including gray matter volume reductions, and ventriculomegaly. Recent studies point to alterations in frontal and temporal lobes, basal ganglia, thalamus, and cerebellum, suggesting a "network disorder" involving the corticostriatal and cortico-thalamo-cerebellar circuits (Andreasen 1999; McCarley et al 1999; Ross and Pearlson 1996).

The *pathophysiologic* basis of such alterations has been debated. Positron emission tomography (PET) and single photon emission computed tomography (SPECT) studies have shown reduced function of critical brain structures such as the frontal cortex ("hypofrontality"; Andreasen et al 1992). Much evidence implicates alterations in early (Weinberger 1995) or late (Feinberg 1982; Keshavan et al 1994) postnatal brain development and possible neurodegenerative processes after illness onset (for a review, see Knoll et al 1998); all these processes may cumulatively interact, leading to the illness (Keshavan and Hogarty 1999).

The *neurochemical* underpinnings of schizophrenia remain speculative. Indirect pharmacologic evidence points to the role of dopamine, but serotonergic, noradrenergic, and cholinergic systems have also been implicated. The excitatory neurotransmitter glutamate and the inhibitory neurotransmitter γ-aminobutyric acid (GABA) have also been implicated; these newer models can help integrate both neurodevelopmental and neurodegenerative models of this disorder (Farber et al 1998; Keshavan 1999; Lewis 1997; Lieberman et al 1997). Neurotransmitter alterations may also be secondary to dysfunctions in neuronal cell membranes that are critical for ion conduction, receptor function, and signal transduction (Horrobin et al 1994). Much of the evidence for the membrane hypothesis, however, stems from studies of peripheral cells and tissues (Rotrosen and Wolkin 1987).

Several important questions continue to face the schizophrenia researcher: 1) What are the neurochemical alterations in schizophrenia? 2) What brain regions are preferentially affected? 3) Are they related to the cardinal symptoms of the disorder? 4) Are they diagnostically specific? 5) Finally, do these alterations change over the longitudinal course of the illness, and/or as a function of

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Received January 12, 2000; revised May 12, 2000; accepted May 19, 2000.

0006-3223/00/$20.00
PII S0006-3223(00)00940-9

treatment? To study such questions, one needs sensitive neurochemical imaging tools to noninvasively and prospectively study relevant aspects of brain biology in individuals at risk for schizophrenia and those at various stages of this illness.

Neurochemical imaging techniques such as PET and SPECT have contributed significantly in efforts to unravel the neurochemistry of schizophrenia but, being invasive, cannot be used in longitudinal studies. Magnetic resonance spectroscopy (MRS), a noninvasive neuroimaging approach—in particular, phosphorus (^{31}P) and proton (^{1}H) MRS—has been applied to investigate schizophrenia. We critically review ^{31}P and ^{1}H MRS studies in schizophrenia. Basic principles and the neurochemical information provided by MRS are detailed elsewhere (Bottomley 1989; Dager and Steen 1992; Kegeles 1998; Keshavan et al 1991a; Pettegrew 1989; Ross and Michaelis 1994; Stanley et al 2000).

^{31}P MRS Studies in Schizophrenia

Studies to Date

Phosphorus MRS (^{31}P MRS) studies reveal important information about the integrity of neuronal cell membranes. Specifically, the phosphomonoester (PME) resonance in ^{31}P MRS includes the freely mobile precursors of membrane phospholipids such as phosphocholine, phosphoethanolamine, and the phosphodiester (PDE) resonance is comprised of breakdown products such as glycerophosphocholine and glycerophosphoethanolamine (Pettegrew et al 1987). Underlying these freely mobile resonances are less mobile molecules such as phosphorylated proteins, micelles, vesicles, and phospholipids (Burnell et al 1980).

Observations that schizophrenia is associated with reduced prefrontal function (Andreasen et al 1992) and membrane phospholipid alterations in peripheral cells (Horrobin et al 1994) stimulated early ^{31}P MRS studies. One of the first MRS studies in psychiatry examined brain high-energy phosphate and membrane phospholipid metabolism in the dorsal prefrontal cortex (PFC) of neuroleptic-naive, first-episode schizophrenic patients and matched healthy control subjects. Phosphorus MRS revealed decreased levels of PMEs and inorganic phosphate and increased levels of PDEs and adenosine triphosphate (β ATP; Keshavan et al 1989; Pettegrew et al 1991). Other in vivo ^{31}P MRS studies have observed PME decreases in treatment-naive first-episode (Stanley et al 1995) and chronic medicated schizophrenia subjects (Kato et al 1995; Potwarka et al 1999), and in schizophrenia with prominent negative symptoms (Shioiri et al 1994). Phosphodiester increases have been seen in first-episode treatment-naive schizophrenic patients (Stanley et al 1995). In chronic medicated subjects PDE increases (Deicken et al 1994), no change (Fujimoto et al 1992; Shioiri et al 1994), or decreases (Volz et al 1997) have been observed. These studies widely vary in methodology, and this can potentially account for discrepancies in findings between studies (Table 1).

Recently, Fukuzako et al (1999a) reported decreased PMEs and increased PDEs in neuroleptic-naive first-episode schizophrenic patients in the temporal lobe; however, in chronic patients PDEs have been found to be increased (Fujimoto et al 1992) or unchanged (Calabrese et al 1992; O'Callaghan et al 1991). Overall, there appear to be alterations in membrane phospholipids in the PFC and temporal lobes in schizophrenia, especially in first-episode patients. Again, inconsistencies remain and may be related to variable methodology and studies of patients in different phases of illness and medication states (Table 1).

Proton-decoupled ^{31}P MRS can help measure individual metabolites and the broad underlying components of the PME and PDE resonances. Using this approach in chronic medicated schizophrenic patients, Potwarka et al (1999) observed increases in the broad components comprised of less mobile molecules with PDE moieties such as small vesicles and micelles but not in the freely mobile membrane breakdown products; however, in another proton-decoupled ^{31}P MRS study increases in the mobile PDEs (glycerophosphocholine and glycerophosphoethanolamine) were seen in the parietal region of chronic medicated subjects (Bluml et al 1999). Techniques that either acquire the signal with a relatively long echo time or long preacquisition delay time to minimize the broad signal or attempt to remove the broad signal in the postprocessing may result in a negative finding. This could account, in part, for the discrepancies observed in the above ^{31}P MRS studies. A much longer echo time was used in the Bluml study; this minimized the signal from the broad underlying component, which was removed in the processing of PMEs and PDEs that are heavily T_2 weighted. The latter findings suggest that a change in the physical/motional environment to alter the relaxation time and not a concentration difference may explain the PDE difference between the two groups.

Specificity and Trait–State Issues

Membrane phospholipid alterations as evidenced by ^{31}P MRS have been noted in polysubstance abuse (MacKay et al 1993), depressive and bipolar patients (Soares et al 1996), and Alzheimer's disease (Pettegrew et al 1988). In Alzheimer's disease a different profile is seen in ^{31}P MRS findings (increases in PMEs and PDEs), suggesting that the ^{31}P MRS findings of schizophrenia may have a measure of diagnostic specificity. These abnormalities

may also suggest trait-related alterations. Reduced PME levels in the PFC correlate with negative symptoms (Shioiri et al 1994), poor performance on the Wisconsin Card Sort Test (Deicken et al 1995b), and reduced delta sleep (Keshavan et al 1995). On the other hand, PDE elevations correlate with positive symptoms of schizophrenia (Fukuzako et al 1996). The possibility that PME alterations may represent "trait" markers underscores the importance of longitudinal MRS studies in schizophrenia. In a longitudinal study of temporal lobe ^{31}P MRS in schizophrenia PMEs were unchanged, but PDE levels declined after 12 weeks of haloperidol treatment (Fukuzako et al 1999b). Alterations in phospholipid metabolites similar to those observed in schizophrenia (decreased PME, increased PDE) were seen in a presumed "healthy" control subject who was studied for 2 years before her first psychotic episode (Keshavan et al 1991b). Longitudinal studies of subjects at risk for schizophrenia (e.g., first-degree relatives of schizophrenic probands) are needed in our efforts to clarify state–trait issues.

Pathophysiologic Significance

The pathophysiologic basis of ^{31}P MRS alterations in schizophrenia has been much debated. Decreased PMEs and increased PDEs have been thought to reflect decreased synthesis and increased breakdown of membrane phospholipids in early schizophrenia. The ^{31}P MRS findings in schizophrenia are similar to what happens during normative postnatal development. Phosphomonoester levels decrease during the period of normal synaptic pruning occurring during late childhood and early adolescence. It has been proposed (Feinberg 1982; Keshavan et al 1994; Pettegrew et al 1991) that the membrane alterations in schizophrenia may be related to an exaggeration of normative periadolescent synaptic pruning. Recent neuropathologic work showing neuropil reductions in the dorsolateral PFC in schizophrenia also is consistent with the synaptic hyperpruning theory (for a review, see Selemon and Goldman-Rakic 1999). The view that schizophrenia results from an abnormality in postnatal (or "late") synaptic elimination processes is consistent with its typical onset in adolescence; however, PMEs and PDEs are not merely comprised of the precursors and breakdown products, respectively, but also contain the broader components. Thus, Potwarka and colleagues' (1999) observation of increases in the broad components of PDE points to alternative mechanisms of PDE increases in schizophrenia such as changes in membrane structure.

Alterations in high-energy phosphate metabolism in schizophrenia have been inconsistent, perhaps due to variability in the MRS or clinical methodology. Pettegrew et al (1991) and Shioiri et al (1994) observed increased ATP, suggesting reduced energy metabolism in the PFC; however, Stanley et al (1995), Volz et al (1997), Bluml et al (1999), and Fukuzako et al (1999a) found no significant differences in the high-energy phosphate metabolite levels in schizophrenic patients. Phosphocreatine (PCr) levels have also been variable, with both increases (Kato et al 1995) and decreases being observed (Deicken et al 1994).

^{1}H MRS Studies in Schizophrenia

Proton MRS comprises several important signals that reveal information about neuronal metabolism. Measurement of *N*-acetyl aspartate (NAA), a marker of neuronal integrity, has been of considerable interest in schizophrenia research. *N*-Acetyl aspartate is consistently reduced in disorders associated with persistent or reversible neuronal loss (Birken and Oldendorf 1989). Other metabolite resonances in the in vivo ^{1}H MRS include the PCr+Cr signal, the choline-containing trimethylamine (TMA) signal, *myo*-inositol, and lactate.

Studies to Date

In first-episode treatment-naive schizophrenic patients, decreases in NAA (Cecil et al 1999; Choe et al 1996), as well as no change, have been observed in the frontal lobes (Bartha et al 1999; Stanley et al 1996). In contrast, several studies (Deicken et al 1998; Fukuzako et al 1995; Lim et al 1998; Maier et al 1995; Nasrallah et al 1994; Yurgelun-Todd et al 1996), though not all (Buckley and Waddington 1994; Heimberg et al 1998), have observed reductions in NAA (or NAA/PCr ratios) in temporal lobes in chronic schizophrenia—in particular, medial temporal structures (Table 2). Frontal lobe NAA/PCr+Cr was reduced in chronic schizophrenic patients in some studies (Bertolino et al 1996; Fukuzako et al 1995), but not all (Buckley and Waddington 1994; Fukuzako et al 1995). These ^{1}H MRS studies have diverse methodologies, with varying pulse sequences (single vs. multivoxel), echo times (short vs. long), and voxel sizes, and present NAA data as ratios to other metabolites (Table 2). Few studies report the position and the size of the voxel(s), factors that are important in view of the possibility of partial voluming leading to variable contributions of gray, white, and cerebrospinal fluid to the voxel; studies that have attempted to separately quantify these tissue compartments have suggested that NAA reductions may be more prominent in white matter (Choe et al 1994; Lim et al 1998). The age of patients included has varied widely, and they have had variable medication status and phase of illness. Overall, NAA reductions are inconsistently seen in the early stage of illness, but more consistently in the chronic patients, in the frontal lobe and the temporal lobes.

Table 1. Phosphorus MRS Studies in Schizophrenia

Study	Technique (cm^3 volume SC/SV/CSI)	Subjects: FE SCZ	Subjects: Non-FE SCZ	Subjects: Control	Patient mean age ± SD (range)	Brain region	Spectroscopy results: PME	PDE	PCr	ATP	Pi	Other	Comments
O'Callaghan et al (1991)	Voxel size unclear; SC/single RF pulse		18[a]	10	31 ± 8 (21–55)	L TL	X	X	X	X	X	—	
Pettegrew et al (1991)	15–20-cm^3 SC/single RF pulse	11		10	24 ± 2 (19–35)	L+R dorsal PFL	↓	↑	X	↑	↓	—	
Fujimoto et al (1992)	36-cm^3 CSI		16[a]	20	39 ± 5	L&R PFL, TL, BG&TL/BS	↑ L BG	↑ L TL ↓ L&R BG	↓ L PFL	X	X	—	
Calabrese et al (1992)	87-cm^3 SV ISIS		11[a]	9	39 ± 6	L&R TL	X	X	X	X	X	↑ PCr/β-ATP in R TL	Very short TR resulting in poor localization. PCr/β-ATP correlates negatively with psychosis.
Deicken et al (1994)	25-cm^3 spin echo CSI (TE = 3.5 msec)		20[b]	16	39 ± 6 (30–53)	L&R PFL and PL	X	↑ FL	↓ FL	X	X	— —	Positive PDE (R FL) and psychosis correlation. Very short TR. Processing included convolution difference.
Shioiri et al (1994)	? cm^3 SC/slice selective RF pulse		26[b]	26	32 ± 12 (15–63)	L+R PFL	X	X	X	X	X	—	Processing included convolution difference. ↓ PMEs in subjects with high negative symptoms. ↓ PDEs in subjects with low negative symptoms.
Deicken et al (1995a)	25-cm^3 spin echo CSI (TE = 3.5 msec)		18[b]	16	39 ± 6	L&R BG	X	X	X	↓	X	—	Very short TR. Processing included convolution difference.
Kato et al (1995)	? cm^3 SC/CSI		27[b]	26	30 ± 10 (15–52)	L&R PFL	↓	X	↑ K PFL	↑ L PFL	X	— —	Positive β-ATP (L) and length of illness correlation. ↑ PCr (L) in subjects with high negative symptoms.
Stanley et al (1995)	15–20 cm^3 SC/saturation slice/single RF pulse	11		21	26 ± 7 (18–39)	L dorsolateral PFL	↓	↑	X	X	X	↑ Mg in all three patient groups	
			8[a]	21	23 ± 6 (17–?)		↓	X	X	X	↓		
			10[a]	21	43 ± 7 (?–59)		↓	X	X	X	X		

Table 1. Continued

Study	Technique (cm^3 volume SC/SV/CSI)	Subjects: FE SCZ	Subjects: Non-FE SCZ	Subjects: Control	Patient mean age ± SD (range)	Brain region	Spectroscopy results: PME	PDE	PCr	ATP	Pi	Other	Comments
Volz et al (1997)	35–40-cm^3 double volume ISIS		10	36	34 ± 13	L+R dorsolateral PFL	X	↓	X	X	X		Negative β-ATP and psychosis correlation.
			50[a]		38 ± 11		X	↓	X	X	X		Negative β-ATP and SANS correlation.
													Very short TR.
													↑ PCr in treated vs. off-medication subjects.
Bluml et al (1999)	97.5-cm^3 SV PRESS (TE = 12 msec)	2		15	34 ± 6	L+R PL	X	X	X	X	X	↑ GPC	A model function representing the broader underlying peaks was subtracted in each spectrum.
			11[a]	15	(25–45)	L+R PL	↑	X	↑	X	X	↑ GPE	Resolution enhancement applied.
													PE or PC not significantly different.
Fukuzako et al (1999a)	72-cm^3 CSI	17		17	23 ± ?	L&R TL	↓	↑	X	X	X	—	↑ PCr left side.
Potwarka et al (1999)	27-cm^3 CSI (^{1}H decoupled)		11[a]	11	46 ± 6	L&R PFL, MC, and POL	↓ PFL	↑ PFL	↓ PFL	X↓ PFL		—	↓ PMEs due to ↓ PC.
													↑ PDEs due to the ↑ broader underlying peak and not due to ↑ GPC or ↑ GPE.

SC, surface coil; SV, single voxel; CSI, chemical shift imaging; FE, first episode; SCZ, schizophrenia; PME, phosphomonoester; PDE, phosphodiester; PCr, phosphocreatine; ATP, adenosine triphosphate; Pi, inorganic phosphate; RF, radio frequency; L, left; TL, temporal lobe; X, no significant difference; R, right; L+R, bilateral, measured together; PFL, prefrontal lobe; L&R, bilateral, measured separately; BG, basal ganglia; BS, brain stem; ISIS, image-selected in vivo spectroscopy; TR, repetition time; TE, echo time; SANS, Schedule for the Assessment of Negative Symptoms; PRESS, point-resolved spectroscopy; PL, parietal lobe; GPC, glycerophosphorylcholine; GPE, glycerophosphorylethanolamine; PE, phosphoethanolamine; PC, phosphocholine; MC, motor cortex; POL, parieto-occipital lobe.

[a]Medicated.

[b]Mixed medicated and unmedicated.

Table 2. Proton MRS Studies in Schizophrenia

Study	Technique (cm^3 volume SV/MRSI (TE)—metabolites unit)	Subjects: FE SCZ	Subjects: Non-FE SCZ	Subjects: Control	Patient mean age ± SD (range)	Brain region	Spectroscopy results: NAA	PCr+Cr	TMAs	myo-Inositol	Other	Comments
Buckley and Waddington (1994)	11-cm^3 SV (68)—%	4	24[a]	20	31 ± 7	L PFL	X	X	X	—	—	↓ NAA and ↑ TMAs in males.
						R Med TL	X	X	X	—	—	
Nasrallah et al (1994)	12-cm^3 SV (50)—Abs (RMS noise)		11[a]	11	33 ± 5	L HC	X	X	X	—	—	Only singlets quantified.
						R HC	↓	X	↓	—	—	
Choe et al (1994)	8-cm^3 SV (?)—ratio		23	10		R PFL WM	↓	—	↓	—	↑ (GABA+Glu) ratio	Crude approximation of the complex multiplets (Gln ignored).
Fukuzako et al (1995)	27-cm^3 SV (135)—ratio		15[a]	15	41 ± ?	L PFL	X	—	X	—	—	
	8-cm^3 SV (135)—ratio		15[a]	15	(23–51)	L Med TL	↓	—	↑	—	—	
Maier et al (1995)	4–9-cm^3 SV (135)—Abs (water)		25[a]	32	36 ± 9	L HC	↓	↓	↓	—	—	Control subjects not age matched.
					(18–55)	R HC	X	X	X	—	—	
Bertolino et al (1996)	9–12-cm^3 MRSI (272)—ratio		10[a]	10	37 ± 9	L+R DL PFL	↓	—	X	—	—	No significant differences in nine other regions.
					(22–51)	L+R HC	↓	—	X	—	—	
Choe et al (1996)	8-cm^3 SV (20)—ratio	37	18	20	(17–57)	L PFL	↓	—	X	X	↑ (GABA+Glu) ratio	Control subjects age matched? Crude approximation of the complex multiplets (Gln ignored). (GABA+Glu) ratio tended to be lower.
						R PFL						
						L PFL						
		?	34[a]	20	(19–49)	R PFL	—	—	—	—	—	
Fujimoto et al (1996)	15.6-cm^3 SV (135)—ratio		14[a]	12	39 ± 6	L BG	X	—	↓	—	—	↓ NAA/TMA ratios in both right and left sides.
					(29–47)	R BG	X	—	X	—	—	
Maier and Ron (1996)	5–7-cm^3 SV (135)—Abs (water)		26[a]	38	36 ± 9	L HC	—	—	—	—	—	Age–diagnosis interaction for TMAs in the L HC, independent of duration of illness.
					(18–55)	R HC	—	—	—	—	—	
Shioiri et al (1996)	27-cm^3 SV (135)—ratio		21[a]	21	30 ± 10 (16–55)	L BG	X	—	X	—	—	↑ TMA% levels and ↑ TMA/NAA ratios in patients.
Stanley et al (1996)	8-cm^3 SV (20)—Abs (water)	13		24	26 ± 7		X	X	X	—		↓ Gln pre- vs. postmedication.
			12[a]	24	26 ± 7	L DL PFL	X	X	X	—		Positive Gln correlation with illness duration. Complex overlapping multiplets quantified using *a priori* knowledge.
			12[a]	24	41 ± 5		X	X	X	—	↑ Gln	
Yurgelun-Todd et al (1996)	8-cm^3 SV (20)—ratio		16[a]	14	36 ± 5	L Med TL	↓	—	X	—	—	Control subjects not age matched. Only singlets quantified.
					(26–43)	R Med TL	↓	—	X	—	—	
Bartha et al (1999)	4.5-cm^3 SV (20)—Abs (water)	10		10	26 ± 6 (17–33)	L Med PFL	X	X	X	—	↑ Gln	Negative NAA correlation with psychosis scores. Complex overlapping multiplets were quantified using *a priori* knowledge.

Table 2. Continued

Study	Technique (cm^3 volume SV/ MRSI (TE)—metabolites unit)	Subjects: FE SCZ	Subjects: Non-FE SCZ	Subjects: Control	Patient mean age ± SD (range)	Brain region	Spectroscopy results: NAA	PCr+Cr	TMAs	myo-Inositol	Other	Comments
Deicken et al (1997)	1.3-cm^3 MRSI (135)—Abs (RF pulse)		24[a]	15	36 ± 12	L PFL	↓	↑	X	—	—	
						R PFL	X	↑	X	—	—	
Deicken et al (1997)	1.3-cm^3 MRSI (135)—Abs (RF pulse)		26[a]	16	37 ± 11 (16–59)	L AC	↓	X	X	—	—	
						R AC	↓	X	X	—		
Bertolino et al (1998)	9–12-cm^3 MRSI (272)—ratio		10[a]	10	35 ± 6	L+R DL	↓	—	X	—	—	Test–retest study. No significant differences in nine other regions.
						PFL	↓	—	X	—	—	
						L+R HC						
Deicken et al (1998)	1.6-cm^3 MRSI (135)—Abs (RF pulse)		30[a]	18	39 ± 11 (16–59)	L HC	↓	↑	X	—	—	
						R HC	↓	X	X	—	—	
Eluri et al (1998)	8-cm^3 SV (30)—ratio		12[a]	8	36 ± ? (26–46)	L CBL	X	—	X	X	—	Only singlets quantified.
						R CBL	↓	—	X	X		
						Pons						
Heimberg et al (1998)	8-cm^3 SV (30)—ratio		13[a]	14		L PFL	X	—	X	X	—	Matching for age between groups for each region is unclear. Only singlets quantified. ↓TMA ratio (BG) and ↑NAA ratio (PFL) in patients on atypical antipsychotics.
			15[a]	26		LTL	X	—	X	X	—	
			18[a]	31	43 ± 10	L BG	X	—	X	X	—	
			9[a]	23	(25–67)	L Th	X	—	X	X	—	
			2[a]	14		R Th	X	—	X	X	—	
Lim et al (1998)	1.1-cm^3 MRSI (144)—Abs (RF pulse)		10[a]	9	44 ± 6 (34–54)	GM	X	X	X	—	—	
						WM	↓	X	X	—	—	
Bluml et al (1999)	24-cm^3 SV (30)—Abs (?)	2		15	34 ± 6 (25–45)	L+R PL	X	X	X	X		↑NAA in FE vs. chronic.
			11[a]	15			X	X	↑	X		
Cecil et al (1999)	8-cm^3 SV (21)—ratio	8		14	26 ± 7	PFL WM	↓	—	↑	—	X	Measurements alternated between left and right sides. TEs varied. Crude approximation of the complex multiplets. TL measurements not age matched.
	4.5-cm^3 SV (16–21)—ratio	10		10	27 ± 5	Med TL	↓	—	↓	—	↑AA ratio	

MRS, magnetic resonance spectroscopy; SV, single voxel; MRSI, magnetic resonance spectroscopic imaging; TE, echo time; FE, first episode; SCZ, schizophrenia; NAA, *N*-acetyl aspartate; PCr, phosphocreatine; TMAs, trimethylamines (choline + phosphocholine); L, left; PFL, prefrontal lobe; R, right; Med, medial; TL, temporal lobe; X, no significant difference; Abs, absolute quantification; RMS, root mean square; HC, hippocampus; WM, white matter; GABA, α-aminobutyric acid; Glu, glutamate; Gln, glutamine; BG, basal ganglia; DL, dorsolateral; RF, radio frequency; AC, anterior cingulate; CBL, cerebellum; Th, thalamus; GM, grey matter.

[a]Neuroleptic treated.

The lack of consistent NAA alterations in adult-onset first-episode patients contrasts with observations of reduced NAA/PCr+Cr ratios in the frontal lobe in childhood-onset schizophrenia. Lower NAA/PCr+Cr in frontal lobes (Thomas et al 1998) and in frontal and hippocampal regions (Bertolino et al 1998) have been seen in childhood-onset schizophrenic patients. Brooks et al (1998) found frontal NAA/PCr+Cr reductions in schizophrenia spectrum disorder, including schizotypal patients. It is possible that neurodevelopmental pathophysiology may more prominently underlie childhood-onset schizophrenia; however, normative data on ^{1}H MRS changes in this age range are needed and rigorous MRS techniques as well as close age matching should be deployed to confirm possible NAA reductions in this population. Notably, all the childhood-onset schizophrenia studies included medicated patients, making it unclear if NAA reductions may have resulted from illness chronicity or are an effect of treatment.

Specificity and State–Trait Issues

N-Acetyl aspartate reductions have been seen in a variety of neuropsychiatric disorders (Birken and Oldendorf 1989; Dager and Steen 1992; Howe et al 1993; Kegeles et al 1998; Keshavan et al 1991a) and may therefore have little diagnostic specificity. *N*-Acetyl aspartate reductions have been seen in young and old patients, and neuroleptic-naive and medicated schizophrenic patients (Table 2); NAA does not appear to be affected by neuroleptic treatment (Choe et al 1996; Stanley et al 1996). No consistent correlations have been seen between frontal or temporal lobe NAA and cognitive or symptomatologic measures (Buckley and Waddington 1994) or illness duration (Deicken et al 1998), however, though younger age of onset is related to NAA reduction in the temporal lobe (Fukuzako et al 1995). These observations suggest that NAA alterations may be trait related, though careful longitudinal studies are needed to clarify this issue. Another intriguing question is whether NAA reductions may characterize individuals at risk for the schizophrenic illness. Indeed, frontal NAA reductions have been reported in adolescent (Keshavan et al 1997) and older relatives at risk for schizophrenia (Callicott et al 1998).

Pathophysiologic Significance

Though the pathophysiologic significance of NAA reduction in schizophrenia remains unclear, NAA decreases after neuronal loss both in animal models and in disorders characterized by neuronal loss (Birken and Oldendorf 1989). Thus, reduced NAA may reflect the volume loss observed in the temporal and frontal cortex (McCarley et al 1999) and may be related to reductions in synaptic neuropil (in the neuronal or axonal number, density, and volume) or to changes in energy metabolism. *N*-Acetyl aspartate reductions in schizophrenia may be confined to white matter, suggesting abnormal white matter pathways, which perhaps involve myelinated axons (Lim et al 1998). Reductions in the TMA signal observed in some studies (Table 2) have been attributed to such myelin changes; a reduction in TMA signal in MRS (more abundant in white matter) could result from an overall reduction in synthesis of choline-containing phospholipids observed in vitro and in vivo, as reviewed earlier. But as Table 2 reveals, TMA signal alterations have been inconsistent across studies.

How does frontotemporal NAA reduction relate to the neurodevelopmental models of schizophrenia? Weinberger (1987) has argued that reduced neuronal integrity in the PFC, suggested by NAA reductions, may lead to psychosis by resulting in limbic dopaminergic hyperactivity. A recent study (Bertolino et al 1999) indeed found an association between NAA reductions in the PFC and dopamine concentration in the striatum. Frontostriatal pathways are glutamatergically mediated; it may therefore be argued that NAA reductions in the PFC reflect abnormal glutamatergic neurotransmission in these pathways. Careful examination of the glutamate signal using ^{1}H MRS might therefore be instructive; however, Stanley et al (1996) and Bartha et al (1999) reported no change in glutamate, but an increase in the glutamine signal; this correlated with length of illness in the Stanley study. They interpreted these findings to reflect altered glutamatergic neurotransmission and suggest that glutamine may be a more sensitive marker of altered glutamatergic neurotransmission (Stanley et al 1996). Magnetic resonance spectroscopy studies with a short echo time (e.g., 20 msec) result in complex spectra because of overlap between multiple proton-containing metabolites. Such overlap makes it difficult to assign the spectral metabolites. Recent advances in MRS quantification procedures can help better resolve the individual spectral metabolites. First, the use of high-field ^{1}H MRS studies (~3 T or higher) can improve spectral resolution. Second, incorporating *a priori* knowledge about each metabolite into the quantification approach can improve the specificity of resolving overlapping resonances (Provencher 1993). Finally, spectral editing techniques can also allow quantification of smaller signals (Rothman et al 1993).

Conclusions and Future Directions

The "first generation" MRS studies have revealed noteworthy findings of alterations in membrane phospholipid metabolism using ^{31}P MRS and reduction in NAA in the PFC and temporal lobes using ^{1}H MRS. Magnetic resonance spectroscopy studies are unlikely to be of diagnostic

value at this time, but may have pathophysiologic significance. These caveats merit discussion:

1. First generation MRS studies have often been explorative, perhaps in part due to the lack of adequate theoretical models. Newer conceptualizations such as the neurodevelopmental model and the glutamatergic model have generated many testable predictions, and MRS in the future may allow testing these predictions in a more hypothesis-driven manner. Further, the view that schizophrenia may involve multiple "nodes" of neuroanatomic abnormality as a result of a "network" dysfunction is gaining wider acceptance. This model helps us to better understand the observed abnormalities in a variety of brain regions and also points the way to set up more precise *a priori* predictions in designing future multivoxel MRS studies.
2. Most MRS studies in schizophrenia thus far have been cross-sectional. The noninvasiveness of MRS lends itself to longitudinal studies in schizophrenia; this can help separate state from trait markers and to distinguish progressive versus static aspects of the illness. Studying untreated first-episode patients (Keshavan and Schooler 1992) can minimize confounds of illness chronicity and medication. Longitudinal MRS studies of relatives at risk for schizophrenia can elucidate early predictors of vulnerability and hopefully aid in early diagnosis and prevention.
3. As this review indicates, a major difficulty in comparing cross-sectional studies stems from differences in MRS methods, research design, and patient populations. Consistent reporting in future publications of at least a minimum set of standard parameters will likely enable better interpretation of the findings in the literature and move the field closer to standardization. This should include details of demographic characteristics (age, gender, race, and approaches to matching patient and comparison groups) and clinical features (illness phase, approach to diagnosis, and medication status). A minimum set of details regarding acquisition, postprocessing, and quantification procedures should also be provided, and are discussed more fully in Stanley et al (2000).
4. Magnetic resonance spectroscopy studies thus far have focused mainly on metabolites that are relatively easy to quantify, such as NAA, PMEs, and PDEs. Future studies should additionally deploy MRS to examine neurochemical parameters, unavailable with other techniques, such as amino acid and macromolecular metabolites. Newly emerging techniques may allow spectroscopic measurement of metabolites that may be central to schizophrenia such as GABA (Rothman et al 1993) and glutamate (Stanley et al 1996); however, such efforts have to consider several methodological issues being addressed by the more recent studies (Stanley et al 2000): 1) *Neuroanatomic specificity* can be improved by morphometric measurements of the regions of interest deploying MR images acquired in the same setting, as well as the use of MRI-compatible brain atlases and quantification of tissue types within the voxel of interest. 2) The *sensitivity of the MR signal* (important for separating relevant small signals such as glutamate from the glutamine) can be enhanced by high-field magnets (e.g., 3- or 4-T magnets). 3) *Reliability* of data processing can be improved by fully automated spectral processing routines and the use of quantification techniques with *a priori* knowledge data bases. 4) The issue of *validity* also has to be addressed. For example, it is possible that patient–control subject differences in MRS metabolites may be confounded by potential group differences in relaxation times (T_1 and T_2) of these metabolites; future research is needed to address these possible sources of systematic error. "Second generation" study designers therefore need to keep in mind these specific scientific and practical issues.

The eventual aim of any new investigative tool in medicine is to benefit diagnosis and treatment monitoring of the patient. Magnetic resonance spectroscopy is on its way to accomplish that goal in other areas of medicine, such as cancer and heart disease (for a review, see Ross and Michaelis 1994); however, in the field of schizophrenia it is still at best only a window into neurochemical pathology, albeit a rather blurred one, because the field is young and methodological hurdles remain. The next decade of MRS research is likely to overcome these hurdles and move us closer to piecing together the puzzle of schizophrenia.

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