

## A review of MRI findings in schizophrenia

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### Abstract

After more than 100 years of research, the neuropathology of schizophrenia remains unknown and this is despite the fact that both Kraepelin (1919/1971: Kraepelin, E., 1919/1971. *Dementia praecox*. Churchill Livingstone Inc., New York) and Bleuler (1911/1950: Bleuler, E., 1911/1950. *Dementia praecox or the group of schizophrenias*. International Universities Press, New York), who first described 'dementia praecox' and the 'schizophrenias', were convinced that schizophrenia would ultimately be linked to an organic brain disorder. Alzheimer (1897: Alzheimer, A., 1897. *Beitrage zur pathologischen anatomie der hirnrinde und zur anatomischen grundlage einiger psychosen*. *Monatsschrift fur Psychiatrie und Neurologie*. 2, 82–120) was the first to investigate the neuropathology of schizophrenia, though he went on to study more tractable brain diseases. The results of subsequent neuropathological studies were disappointing because of conflicting findings. Research interest thus waned and did not flourish again until 1976, following the pivotal computer assisted tomography (CT) finding of lateral ventricular enlargement in schizophrenia by Johnstone and colleagues. Since that time significant progress has been made in brain imaging, particularly with the advent of magnetic resonance imaging (MRI), beginning with the first MRI study of schizophrenia by Smith and coworkers in 1984 (Smith, R.C., Calderon, M., Ravichandran, G.K., et al. (1984). *Nuclear magnetic resonance in schizophrenia: A preliminary study*. *Psychiatry Res*. 12, 137–147). MR in vivo imaging of the brain now confirms brain abnormalities in schizophrenia.

The 193 peer reviewed MRI studies reported in the current review span the period from 1988 to August, 2000. This 12 year period has witnessed a burgeoning of MRI studies and has led to more definitive findings of brain abnormalities in schizophrenia than any other time period in the history of schizophrenia research. Such progress in defining the neuropathology of schizophrenia is largely due to advances in in vivo MRI techniques. These advances have now led to the identification of a number of brain abnormalities in schizophrenia. Some of these abnormalities confirm earlier post-mortem findings, and most are small and subtle, rather than large, thus necessitating more advanced and accurate measurement tools. These findings include ventricular enlargement (80% of studies reviewed) and third ventricle enlargement (73% of studies reviewed). There is also preferential involvement of medial temporal lobe structures (74% of studies reviewed), which include the amygdala, hippocampus, and parahippocampal gyrus, and neocortical temporal lobe regions (superior temporal gyrus) (100% of studies reviewed). When gray and white matter of superior temporal gyrus was combined, 67% of studies reported abnormalities. There was also moderate evidence for frontal lobe abnormalities (59% of studies reviewed), particularly prefrontal gray matter and orbitofrontal regions. Similarly, there was moderate evidence for parietal lobe abnormalities (60% of studies reviewed), particularly of the inferior parietal lobule which includes both supramarginal and angular gyri. Additionally, there was strong to moderate evidence for subcortical abnormalities (i.e. cavum septi pellucidi—92% of studies reviewed, basal ganglia—68% of studies reviewed, corpus callosum—63% of studies reviewed, and thalamus—42% of studies reviewed), but more equivocal evidence for cerebellar abnormalities (31% of studies reviewed).

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The timing of such abnormalities has not yet been determined, although many are evident when a patient first becomes symptomatic. There is, however, also evidence that a subset of brain abnormalities may change over the course of the illness. The most parsimonious explanation is that some brain abnormalities are neurodevelopmental in origin but unfold later in development, thus setting the stage for the development of the symptoms of schizophrenia. Or there may be additional factors, such as stress or neurotoxicity, that occur during adolescence or early adulthood and are necessary for the development of schizophrenia, and may be associated with neurodegenerative changes. Importantly, as several different brain regions are involved in the neuropathology of schizophrenia, new models need to be developed and tested that explain neural circuitry abnormalities effecting brain regions not necessarily structurally proximal to each other but nonetheless functionally interrelated.

Future studies will likely benefit from: (1) studying more homogeneous patient groups so that the relationship between MRI findings and clinical symptoms become more meaningful; (2) studying at risk populations such as family members of patients diagnosed with schizophrenia and subjects diagnosed with schizotypal personality disorder in order to define which abnormalities are specific to schizophrenia spectrum disorders, which are the result of epiphenomena such as medication effects and chronic institutionalization, and which are needed for the development of frank psychosis; (3) examining shape differences not detectable from measuring volume alone; (4) applying newer methods such as diffusion tensor imaging to investigate abnormalities in brain connectivity and white matter fiber tracts; and, (5) using methods that analyze brain function (fMRI) and structure simultaneously. © 2001 Elsevier Science Ltd All rights reserved.

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## 1. Introduction

Schizophrenia is a disabling mental disorder that affects close to 1% of the general population. Although the underlying pathology remains unknown, both Kraepelin (1919/1971) and Bleuler (1911/1950), who first described ‘dementia praecox’ and the ‘schizophrenias’, believed that brain abnormalities would ultimately be linked to the etiology of schizophrenia. This conviction was fueled by important inroads being made, during this same time period, into the neuropathology of Alzheimer’s disease, Huntington’s Chorea, Pick’s disease, tertiary syphilis and some forms of epilepsy (see reviews in Benes, 1995; Bogerts et al., 1993a, 1999; Chua and McKenna, 1995; Harrison, 1999; Heckers, 1997).

In the late nineteenth and early twentieth centuries, efforts to identify post-mortem brain abnormalities, however, led to disappointing and frequently conflicting findings largely due to both the crude measurement tools available and to the expectation of finding large abnormalities when in fact such abnormalities are small and subtle (e.g. Alzheimer, 1897; Crichton-Browne, 1879; Haug, 1962; Hecker, 1871; Jacobi and Winkler, 1928; Kahlbaum, 1874; Southard 1910, 1915). Later, more methodologically controlled studies often led to negative findings (e.g. Dunlap, 1924; Rowland and Mettler, 1949). Consequently, progress as well as interest in the neuropathology of schizophrenia waned until the mid-1970s. And, while some researchers continued to study

the brain and its functions in order to understand schizophrenia (e.g. Kety, 1959; MacLean, 1952; Stevens, 1973; Torrey and Peterson, 1974), the general consensus, as stated by Plum (1972), was that ‘schizophrenia is the graveyard of neuropathologists’.

Research investigating brain abnormalities in schizophrenia thus came to a near standstill and was not rekindled until the first computer assisted tomography (CT) study of schizophrenia (Johnstone et al., 1976), which confirmed earlier pneumoencephalography findings of enlarged lateral ventricles (e.g. Haug, 1962; Jacobi and Winkler, 1928). This one study, coupled with new post-mortem findings of Scheibel and Kovelman (1979, 1981), led to renewed interest and to a proliferation of CT, and later magnetic resonance imaging (MRI) studies of schizophrenia (see reviews by Buckley, 1998; Gur and Pearlson, 1993; Henn and Braus, 1999; Lawrie and Abukmeil, 1998; McCarley et al., 1999b; Nelson et al., 1998; Pearlson and Marsh, 1993, 1999; Pfefferbaum et al., 1990; Pfefferbaum and Zipursky, 1991; Rauch and Renshaw, 1995; Raz and Raz, 1990; Seidman, 1983; Shelton and Weinberger, 1986; Shenton, 1996; Shenton, 1996; Shenton et al., 1997, 2001; Weight and Bigler, 1998; Yurgelun-Todd and Renshaw, 1999), as well as to more methodologically rigorous post-mortem neurochemical and cellular studies (e.g. Benes, 1995; Bogerts et al., 1985, 1993a; Brown et al., 1986; Stevens, 1973).

These newer post-mortem findings reported limbic

Table 1

Summary of MR studies reporting positive and negative findings in schizophrenia (Table is updated from Shenton et al. (1997); McCarley et al. (1999b). Studies are cited by first author/year; 'asym' following year indicates finding was of asymmetry differences; Planum Temporale citations were mainly of asymmetry differences and 'asym' is therefore not used as a qualifier; STG = superior temporal gyrus; GM = gray matter; WM = white matter)

Brain Region	%+	%–	N+	N–	Total N	References
Whole Brain	22	78	11	39	50	+ [Andreasen et al., 1990, 1994a; Gur et al., 1994, 1998b, 1999; Jernigan et al., 1991; Nasrallah et al., 1990; Rajarethinam et al., 2000; Sanfilipo et al., 2000a; Staal et al., 1998; Whitworth et al., 1998] – [Barta et al., 1990; Bilder et al., 1994; Blackwood et al., 1991; Breier et al., 1992; Buchanan et al., 1993, 1998; Cannon et al., 1998; Colombo et al., 1993; Dauphinais et al., 1990; DeLisi et al., 1991, 1992; Flaum et al., 1995; Goldstein et al., 1999; Harvey et al., 1993; Hazlett et al., 1999; Hirayasu et al., 1998, 2000; Johnstone et al., 1989; Kawasaki et al., 1993; Kelson et al., 1988; Keshavan et al., 1998a, 1998b; Lawrie et al., 1999; Marsh et al., 1994, 1999; Meisenzahl et al., 1999; Nopoulos et al., 1995, 1999; Reite et al., 1997; Rossi et al., 1990, 1994a; Schlaepfer et al., 1994; Shenton et al., 1992; Stefanis et al., 1999; Sullivan et al., 1998; Velakoulis et al., 1999; Vita et al., 1995; Zipursky et al., 1992, 1997]
Lateral Ventricles	80	20	44	11	55	+ [Andreasen et al., 1990, 1994a; Barr et al., 1997; Becker, 1990 <sup>a</sup> ; Bogerts, 1990 <sup>a</sup> ; Bornstein et al., 1992; Buchsbaum et al., 1997; Cannon et al., 1998; Corey-Bloom et al., 1995; Dauphinais et al., 1990; Degreef et al., 1990, 1992a; DeLisi et al., 1991; DeLisi et al., 1992; Egan et al., 1994; Flaum et al., 1995; Gur et al., 1994; Harvey et al., 1993; Johnstone et al., 1989; Kawasaki et al., 1993; Kelson et al., 1988; Lauriello et al., 1997; Lim et al., 1996; Marsh et al., 1994, 1997, 1999; McNeil et al., 2000; Narr et al., 2000; Nasrallah et al., 1990; Nieman et al., 2000 <sup>a</sup> ; Nopoulos et al., 1995; Rossi et al., 1988; Roy et al., 1998 <sup>a</sup> ; Sanfilipo et al., 2000a; Staal et al., 2000; Stratta et al., 1989; Suddath et al., 1989, 1990; Sullivan et al., 1998; Symonds et al., 1999; Vita et al., 1995; Whitworth et al., 1998; Zipursky et al., 1998a] – [Blackwood et al., 1991; Colombo et al., 1993; Hoff et al., 1992; Jernigan et al., 1991; Lawrie et al., 1999; Rossi et al., 1990, 1994a; Schwartz et al., 1992; Schwarzkopf et al., 1990; Shenton et al., 1991, 1992]
Third Ventricles	73	27	24	9	33	+ [Becker et al., 1996; Bornstein et al., 1992; Dauphinais et al., 1990; Degreef et al., 1990, 1992a; Egan et al., 1994; Flaum et al., 1995; Kelson et al., 1988; Lauriello et al., 1997; Lawrie et al., 1999; Lim et al., 1996; Marsh et al., 1994, 1997; McNeil et al., 2000; Meisenzahl et al., 1999; Narr et al., 2000; Nasrallah et al., 1990; Pearlson et al., 1997b; Rossi et al., 1994a; Sanfilipo et al., 2000a; Schwarzkopf et al., 1990; Staal et al., 2000; Sullivan et al., 1998; Woodruff et al., 1997b] – [Andreasen et al., 1990; Barta et al., 1990; Colombo et al., 1993; DeLisi et al., 1991; Roy et al., 1998; Schwartz et al., 1992; Shenton et al., 1992; Suddath et al., 1990; Zipursky et al., 1992]
Fourth Ventricles	20	80	1	4	5	+ [Keshavan et al., 1998b] – [Lawrie et al., 1999; Rossi et al., 1988; Shenton et al., 1992; Stratta et al., 1989]
Temporal Lobe TL	–	–			137	
Whole TL	61	39	31	20	51	+ [Andreasen et al., 1994a; Barta et al., 1990; Becker et al., 1996; Bilder et al., 1999asym; Bogerts et al., 1990; Bryant et al., 1999; Cannon et al., 1998; Dauphinais et al., 1990; DeLisi et al., 1991; Di Michele et al., 1992; Egan et al., 1994; Gur et al., 1998b; Harvey et al., 1993; Jernigan et al., 1991; Johnstone et al., 1989; Kikinis et al., 1994 <sup>b</sup> ; Marsh et al., 1997, 1999; Nopoulos et al., 1999; Rossi et al., 1988, 1989a, 1990, 1991; Sanfilipo et al., 2000b; Suddath et al., 1989, 1990; Sullivan et al., 1998; Turetsky, 1995; Woodruff et al., 1997b; Woods et al., 1996; Zipursky et al., 1992]

Table 1 (continued)

Brain Region	%+	%–	N+	N–	Total N	References
						–[Altshuler et al., 1998; Becker et al., 1990; Bilder et al., 1994asym; Blackwood et al., 1991; Colombo et al., 1993; DeLisi et al., 1992; Flaum et al., 1995; Havermans et al., 1999; Hoff et al., 1992; Kawasaki et al., 1993; Kelsoe et al., 1988; Lawrie et al., 1999; Niemann et al., 2000; Nopoulos et al., 1995; Pearlson et al., 1997b; Raine et al., 1992; Roy et al., 1998; Shenton et al., 1992; Swayze et al., 1992; Vita et al., 1995]
Medial TL	74	26	36	13	49	+ [Altshuler et al., 1998; Barta et al., 1990, 1997b; Becker et al., 1990, 1996; Blackwood et al., 1991asym; Bogerts et al., 1990; Bogerts et al., 1993b; Breier et al., 1992; Bryant et al., 1999; Buchanan et al., 1993; Copolov et al., 2000; Dauphinais et al., 1990; DeLisi et al., 1998; Egan et al., 1994; Flaum et al., 1995; Fukuzako et al., 1996a, 1997; Gur et al., 2000a; Hirayasu et al., 1998; Jernigan et al., 1991; Kawasaki et al., 1993; Lawrie et al., 1999; Marsh et al., 1994; McNeil et al., 2000; Ohnuma et al., 1997; Pearlson et al., 1997b; Razi et al., 1999; Rossi et al., 1994a; Shenton et al., 1992; Stefanis et al., 1999; Suddath et al., 1989, 1990; Velakoulis et al., 1999; Whitworth et al., 1998; Woodruff et al., 1997b]
STG GM	100	0	12	0	12	–[Colombo et al., 1993; Corey-Bloom et al., 1995; Deicken et al., 1999; DeLisi et al., 1991; Harvey et al., 1993; Havermans et al., 1999; Marsh et al., 1997; Marsh et al., 1999; Niemann et al., 2000; Sanfilipo et al., 2000b; Staal et al., 2000; Swayze et al., 1992; Zipursky et al., 1994] +[Gur et al., 2000a; Hajek et al., 1997; Hirayasu et al., 1998; Holinger et al., 1999; Keshavan et al., 1998b; Marsh et al., 1999; Menon et al., 1995; Sanfilipo et al., 2000b; Schlaepfer et al., 1994; Shenton et al., 1992; Sullivan et al., 1998; Zipursky et al., 1994]
STG (GM & WM)	67	33	10	5	15	–[None] +[Barta et al., 1990; Barta et al., 1997b; Bryant et al., 1999; Flaum et al., 1995; Keshavan et al., 1998b; Marsh et al., 1997; Pearlson et al., 1997b; Rajarethinam et al., 2000; Reite et al., 1997; Tune et al., 1996]
Planum Temporale	60	40	6	4	10	–[Havermans et al., 1999; Kulynych et al., 1996; Roy et al., 1998; Vita et al., 1995; Woodruff et al., 1997b] +[Barta et al., 1997a; DeLisi et al., 1994; Hirayasu et al., 2000; Kwon et al., 1999; Petty et al., 1995; Rossi et al., 1992]
Frontal Lobe	60	40	30	20	50	–[Frangou et al., 1997; Kleinschmidt et al., 1994; Kulynych et al., 1995; Rossi et al., 1994b] +[Andreasen et al., 1994a; Bilder et al., 1994, 1999asym; Breier et al., 1992; Buchanan et al., 1993, 1998; Bryant et al., 1999; Cannon et al., 1998; Goldstein et al., 1999; Gur et al., 1998b; Gur et al., 2000b; Harvey et al., 1993; Jernigan et al., 1991; Marsh et al., 1999; Nopoulos et al., 1995, 1999; Ohnuma et al., 1997; Raine et al., 1992; Rossi et al., 1988; Sanfilipo et al., 2000b; Schlaepfer et al., 1994; Staal et al., 2000; Stratta et al., 1989; Sullivan et al., 1998; Szeszko et al., 1999asym; Turetsky, 1995; Woodruff et al., 1997b; Woods et al., 1996; Zipursky et al., 1992, 1994]
Parietal Lobe	60	40	9	6	15	–[Andreasen et al., 1990; Baaré et al., 1999; Blackwood et al., 1991; Corey-Bloom et al., 1995; DeLisi et al., 1991; Egan et al., 1994; Hirayasu et al., 1999; Kawasaki et al., 1993; Kelsoe et al., 1988; Kikinis et al., 1994 <sup>b</sup> ; Lawrie et al., 1999; Nasrallah et al., 1990; Noga et al., 1995; Rossi et al., 1990; Shenton et al., 1992; Suddath et al., 1989, 1990; Vita et al., 1995; Wible et al., 1995, 1997] +[Andreasen et al., 1994a; Bilder et al., 1994, 1999asym; Frederikse et al., 2000; Goldstein et al., 1999; Marsh et al., 1999; Niznikiewicz et al., 2000; Schlaepfer et al., 1994; Zipursky et al., 1994] –[Egan et al., 1994; Jernigan et al., 1991; Nopoulos et al., 1995, 1999; Sullivan et al., 1998; Zipursky et al., 1992]

Table 1 (continued)

Brain Region	%+	%–	N+	N–	Total N	References
Occipital Lobe	44	56	4	5	9	+ [Andreasen et al., 1994a; Bilder et al., 1994, 1999 <sup>asym</sup> ; Zipursky et al., 1992]
Other <sup>c</sup>	–	–			89	– [Jernigan et al., 1991; Nopoulos et al., 1995, 1999; Schlaepfer et al., 1994; Sullivan et al., 1998]
Cerebellum	31	69	4	9	13	+ [Andreasen et al., 1994a; Breier et al., 1992; DeLisi et al., 1997 <sup>d</sup> ; Levitt et al., 1999] – [Coffman et al., 1989; Flaum et al., 1995; Goldstein et al., 1999; Keshavan et al., 1998b; Mathew and Partain, 1985a; Nopoulos et al., 1999 <sup>e</sup> ; Rossi et al., 1993; Staal et al., 2000; Uematsu and Kaiya, 1989]
Basal Ganglia	68	32	17	8	25	+ [Breier et al., 1992; Bryant et al., 1999; Buchanan et al., 1993; Chakos et al., 1994, 1995; Corson et al., 1999a; Elkashef et al., 1994; Gur et al., 1998a; Hokama et al., 1995; Jernigan et al., 1991; Keshavan et al., 1995, 1998a; Mion et al., 1991; Ohnuma et al., 1997; Shihabuddin et al., 1998; Staal et al., 2000; Swayze et al., 1992] – [Blackwood et al., 1991; Corey-Bloom et al., 1995; DeLisi et al., 1991; Flaum et al., 1995; Kelsoe et al., 1988; Lawrie et al., 1999; Rossi et al., 1994a; Symonds et al., 1999]
Thalamus	42	58	5	7	12	+ [Andreasen et al., 1990, 1994b; Buchsbaum et al., 1996; Flaum et al., 1995; Gur et al., 1998a; Staal et al., 1998] – [Arciniegas et al., 1999; Corey-Bloom et al., 1995; Hazlett et al., 1999; Lawrie et al., 1999; Portas et al., 1998; Symonds et al., 1999]
Corpus Callosum	63	37	17	10	27	+ [Casanova et al., 1990; DeLisi et al., 1997 <sup>e</sup> ; DeQuardo et al., 1996, 1999; Downhill et al., 2000; Gunther et al., 1991; Hoff et al., 1994; Lewine et al., 1990; Narr et al., 2000; Nasrallah et al., 1986; Raine et al., 1990; Rossi et al., 1988, 1989b; Stratta et al., 1989; Tibbo et al., 1998; Uematsu and Kaiya, 1988; Woodruff et al., 1993] – [Blackwood et al., 1991; Chua et al., 2000; Colombo et al., 1994; Guenther et al., 1989; Hauser et al., 1989; Kawasaki et al., 1993; Kelsoe et al., 1988; Meisenzahl, 1999 <sup>f</sup> ; Sachdev and Brodaty, 1999; Woodruff et al., 1997a]
Cavum Septi Pellucidi <sup>g</sup>	92	8	11	1	12	+ [Degreef et al., 1992b; c; DeLisi et al., 1993; Jurjus et al., 1993; Kwon et al., 1998; Mathew et al., 1985b; Nopoulos et al., 1996, 1997; Scott et al., 1993; Shioiri et al., 1996; Uematsu and Kaiya, 1989] – [Fukuzako et al., 1996b]

<sup>a</sup> Temporal Horn only.

<sup>b</sup> Measure of temporal and frontal lobe gyri.

<sup>c</sup> Two categories were not included in the table because of the small number of studies, i.e. olfactory bulb volume reduction in schizophrenia (Turetsky et al., 2000) and adhesio interthalamica where one study reported volume reduction in schizophrenia (Snyder et al., 1998) and the other did not (Meisenzahl et al. 2000).

<sup>d</sup> Delisi et al. (1997) compared rates of change over time and reported in schizophrenics increased left lateral ventricle, no difference for whole TL or hippocampus, but differences in the cerebellum and in corpus callosum; because all of these findings except cerebellar and corpus callosum changes were reported earlier, we cite here only the new findings.

<sup>e</sup> Total cerebellar volume was not reduced in schizophrenia but area of anterior lobe of vermis was reduced.

<sup>f</sup>  $n = 5$  schizophrenic patients with a family history of schizophrenia had smaller corpus callosum and smaller brain volume than sporadic schizophrenics or controls.

<sup>g</sup> Finding (+/–) not based on area, length, or volume measures.

and temporal lobe abnormalities, including the amygdala-hippocampal complex and parahippocampal gyrus, and an increase in the temporal horn portion of the lateral ventricles, a region of cerebrospinal fluid

(CSF) surrounding these structures (e.g. Benes et al., 1991; Bogerts, 1984; Bogerts et al., 1985; Brown et al., 1986; Colter et al., 1987; Crow et al., 1989; Falkai and Bogerts, 1986; Falkai et al., 1988; Jakob and

Beckmann, 1989; Jeste and Lohr, 1989; Kovelman and Scheibel, 1984). Additionally, many of these findings were lateralized to the left side of the brain, leading to the speculation that schizophrenia may be an anomaly of cerebral development (e.g. Crow et al., 1989; Crow, 1990a,b, 1997, 1998). Other post-mortem findings reported smaller brains in schizophrenia (e.g. Brown et al., 1986), abnormalities in the cingulate gyrus (e.g. Benes and Bird, 1987; Benes et al., 1992), as well as abnormalities in the basal ganglia (e.g. Bogerts et al., 1985).

Beginning with the first MRI study of schizophrenia in 1984 by Smith and coworkers (1984), researchers were given a new and unique opportunity to evaluate specific brain regions, *in vivo*, in schizophrenia. (Parenthetically, CT technology, though adequate for visualizing lateral ventricles, did not allow for careful delineation of gray matter, which MRI affords.) In fact MRI studies conducted over the past 12 years, from 1988 to 2000, now provide some of the most compelling evidence for brain abnormalities in schizophrenia. These studies, discussed below, have shown enlarged lateral ventricles and specific gray matter volume reductions that are especially prominent in the superior temporal gyrus and in medial temporal lobe brain regions (amygdala, hippocampus, and parahippocampal gyrus), thus showing a convergence with the post-mortem findings. Frontal and parietal lobe volume reductions have also been reported, though less consistently, as have increased size of cortical sulci. Our own research has focused on temporal lobe structures as we think these brain regions are critically important to understanding the neuropathology of schizophrenia. We do not suggest, however, that the temporal lobe is the only brain region evincing brain abnormalities in schizophrenia. Instead, we recognize that brain regions within the temporal lobe are highly interconnected with other brain regions, including the frontal lobe (e.g. Fuster, 1989; Goldman-Rakic et al., 1984; Pandya and Seltzer, 1982; Pandya et al., 1981; Selemon et al., 1995; Vogt and Pandya, 1987; Vogt et al., 1987), and that normal brain function depends upon such interconnectivity. There is also evidence from both post-mortem and MRI findings to suggest that at least some of these brain abnormalities may originate from neurodevelopmental anomalies (e.g. Akbarian et al., 1993a,b; Benes, 1989; Heyman and Murray,

1992; Jakob and Beckmann, 1986, 1989; Kikinis et al., 1994; Murray and Lewis, 1987: see also reviews in McCarley et al., 1999b; Shenton et al., 1992, 1997, 2001; Weinberger, 1986, 1987, 1996).

Below, we provide an integration and synthesis of MRI findings in schizophrenia. We propose that schizophrenia is best viewed as a brain disorder, with clinical symptoms, cognitive distortions, and course of illness largely determined by neuropathological substrates, with environmental factors playing a contributory role.

## 2. Scope of the review

This review builds upon our earlier review (Shenton et al., 1997) and its recent update (McCarley et al., 1999b). It includes more than 193 MRI findings published between 1988 and August, 2000.<sup>2</sup> The year 1988 was selected because it coincides with major improvements in both MRI hardware and software. We note that by selecting this cut-off, we exclude the early seminal study of Andreasen and coworkers (1986), as well as others.

The MRI findings included in the review are summarized in Table 1 which lists the findings by first author and year (e.g. Andreasen et al., 1990) for each brain region. The percent positive and negative findings for each region of interest (ROI) are also included. Here, as in the text, we count data sets only once. Thus MRI studies reporting data from the same subjects, but using different analyses, as for example a study describing the clinical correlates of previously reported MRI findings, were counted only once (e.g. Bilder et al., 1995; Goldberg et al., 1994; Nestor et al., 1993; O'Donnell et al., 1993; Young et al., 1991). The only exception made was for two studies, using the same subjects, which examined prefrontal cortex in one study, followed by a more refined parcellation of prefrontal cortex in the second study (e.g. Gur et al., 1998b, 2000b; Wible et al., 1995, 1997). Here we treated the parcellation data as a separate measure from the whole prefrontal lobe data.

<sup>2</sup> Note, for cerebellum, cavum septi pellucidi, and corpus callosum findings we include studies prior to 1988 as the methodology for evaluating these brain regions did not change as dramatically as it did for other brain regions (e.g. prior to and after 1988 one midsagittal slice was primarily used to measure the corpus callosum).

Additionally, in follow up studies of first episode patients, we included only new brain findings in Table 1 and did not include in the tally findings reported previously (e.g. DeLisi et al., 1991, 1992, 1997).

In addition to the summary table (Table 1), we include a second table (Table 2) which lists the studies alphabetically and which includes subject sample size. A third table (Table 3) provides more detailed information for each of the medial temporal lobe regions. Finally, we include a fourth (Table 4) of first episode studies, and a fifth table (Table 5) that provides information specific to follow up studies. We chose a tabular presentation of MRI findings because our goal was, first, to include the largest number of studies reported in the literature, second, to present it in an easily readable format (Tables 1–5), and third, to provide a summary of the most compelling and consistent findings.

A possible alternative would have been to provide a meta-analysis that weights each study based on subject N and effect size (e.g. Glass et al., 1981; Gøtzsche 2000; Hunter and Schmidt 1990; Petitti, 1994; Rosenthal and Rubin, 1979, 1982, 1986; Wright et al., 2000). We chose not to use this approach for several reasons. First, information needed to compute effect size was not always available in individual studies and would, therefore, have necessitated including only a small subset of studies. As we wanted to provide a broad review of the literature, a meta-analysis approach was therefore rejected. Second, MR scanner technology has changed rapidly over the past decade, and studies are therefore not comparable. Thus to weight all studies equally seemed premature given the state of the field at the present time. Third, the methods and extent of detailed information to define ROIs varies tremendously over studies, again suggesting that the information is not easily comparable. Fourth, there is a large difference in moderator variables across studies (i.e. gender, chronicity, age of onset, medication, parental socio-economic status, etc.), once again calling into question the direct comparability of one study with another. And, finally, meta-analysis is beset with difficulties in estimating the number of negative findings that do not get published, i.e. the ‘file drawer’ problem (Rosenthal, 1987). We thus concluded that meta-analysis is not appropriate for a review of this broad scope, which covers

more than a decade of published MRI findings in schizophrenia.<sup>3</sup>

For heuristic purposes, we group the studies by region of interest. We begin with whole brain and ventricular studies, followed by a review of temporal, frontal, parietal, and occipital findings. This is then followed by other brain region findings, including the cerebellum, basal ganglia, thalamus, corpus callosum, and septi pellucidi studies. We then review MRI morphometric findings in first episode schizophrenia and in longitudinal studies. We focus on first episode patients because they are free of confounds such as long term effects of neuroleptic medications and illness chronicity. This group of patients is also important because they afford an opportunity to examine changes over time to determine whether or not abnormalities are extant at the time of the first episode, thus lending more credence to the theory that schizophrenia has a neurodevelopmental etiology. We conclude with a synthesis of MRI findings and discuss the direction of future imaging studies that we think will lead to a further understanding and clarification of the specific brain regions and functions that

<sup>3</sup> We chose, nonetheless, to exclude studies that: (1) did not appear in peer reviewed journals (study N not tallied); (2) had 10 or fewer subjects in the main subject groups (e.g. Degreef et al., 1991; Kegeles et al., 2000; Kulynych et al., 1997; Levitt et al., 1994; Torres et al., 1997); (3) did not include a control group (e.g. Corson et al., 1999b; Jeste et al., 1998; Levitan et al., 1999; Maher et al., 1995, 1998; Nair et al., 1997; Scheller-Gilkey and Lewine, 1999; Seidman et al., 1994; Waldo et al., 1994; Wassink et al., 1999); (4) focused primarily upon relatives of patients with schizophrenia (e.g. Honer et al., 1994; Seidman et al., 1997, 1999); (5) relied upon relaxation times, qualitative ratings rather than quantitative measures such as volume, or used only a small number of slices to evaluate brain regions of interest (e.g. Aylward et al., 1994; Dasari et al., 1999; DeMyer et al., 1988; Friedman et al., 1999; Galderisi et al., 2000; Lewine et al., 1995; Lieberman et al., 1992, 1993; Nasrallah et al., 1997; Pfefferbaum et al., 1999; Sharma et al., 1997; Symonds et al., 1999; Williamson et al., 1991, 1992); (6) focused primarily on children or adolescents with schizophrenia (e.g. Friedman et al., 1999; Jacobsen et al., 1996, 1997, 1998; Nicolson and Rapoport, 1999; Nopoulos et al., 1998a; Rapoport et al., 1997, 1999) or (7) used unusual analyses such as a gyrification index (Kulynych et al., 1997), nonlinear deformations applied to schizophrenia (e.g. Gaser et al., 1999), cumulative anatomical risk factors (Leonard et al., 1999), or other measures not easily grouped together (e.g. Bartley et al., 1993; Bartzokis et al., 1996; Buckley et al., 1999; Galderisi et al., 1999; Guerguerian and Lewine, 1998; Kawasaki et al., 1997; Nopoulos et al., 1998b; Tiihonen et al., 1998). The latter studies are, however, discussed when appropriate. (The  $n = 50$  studies listed here are not included in the tally in Table 1.)

Table 2

Study subject N and characteristics (Table is updated from Shenton et al. (1997); McCarley et al. (1999b) Abbreviations: Tot Subjs = Total Subjects; NL Ctrl and NCL = Normal Controls; SZ = Schizophrenics; BP = Bipolar; SZAFF = Schizoaffective Disorder; FE = First Episode; TLE = Temporal Lobe Epilepsy; OBS = Organic Brain Syndrome; AD = Alzheimer's disease; DEL Dis = Delusional Disorder; SZPHM = Schizophreniform Disorder; Maj Dep = Major Depression; SPD = Schizotypal Personality Disorder; 1<sup>0</sup> = First Degree; Tx = Treatment; td = Tardive Dyskinesia; Audhall = Auditory Hallucinations; STATEHOSPSZ = State Hospitalized SZ; VAHOSPSZ = Veterans Affairs Hospitalized SZ; CSP = Cavum Septi Pellucidi; NN = Neuroleptic Naive; TN = Typical Neuroleptic; AN = Atypical Neuroleptic; PBC = Pregnancy and Birth Complications)

Authors	Tot Subjs	NL Ctrl	SZs	Bipolars	SZAFFs	Other	Comments
Altshuler et al., 1998	44	18	14	12			
Andreasen et al., 1990	101	47	54				
Andreasen et al., 1994a	142	90	52				
Andreasen et al., 1994b	86	47	39				
Arciniegas et al., 1999	48	27	21				Paranoid SZ
Baaré et al., 1999	27	14	13				
Barr et al., 1997	113	42	26		6	39	FE SZ, FE SZAFF, Other = TLE
Barta et al., 1990	30	15	15				
Barta et al., 1997a	60	32	28				
Barta et al., 1997b	41	18	11			12	SZ = Late onset, Other = AD
Becker et al., 1990	20	10	10				
Becker et al., 1996	40	20	20				
Bilder et al., 1994asym	121	51	58		12		FE SZ, FE SZAFF
Bilder et al., 1999asym	235	67	87		81		SZ FE/SZPHM, SZAFF or SZAFF/Mood Disorder
Blackwood et al., 1991	64	33	31				
Bogerts et al., 1990	59	25	34				FE SZ
Bogerts, 1993b	37	18	19				
Bornstein et al., 1992	103	31	72				
Breier et al., 1992	73	29	44				
Bryant et al., 1999	96	37	59				
Buchanan et al., 1993	71	30	41				17SZ = Deficit Symptoms, 24 SZ = no Deficit Symptoms
Buchanan et al., 1998	42	24	18				
Buchsbaum et al., 1996	35	15	20				
Buchsbaum et al., 1997	46	23	11			12	SZ or SZAFF, Other = SPD
Cannon et al., 1998	191	56	63		12	60	Familial SZ, Other = 1 <sup>0</sup> non-psychotic relatives
Casanova et al., 1990	32	16	16				NL MZ twin/SZ MZ Twin
Chakos et al., 1994	39	10	21		8		FE SZ
Chakos et al., 1995	15		15				8SZ neuroleptics/changed to atypical, 7SZ
Chua et al., 2000	115	35	27			53	Familial SZ, Other = 1 <sup>0</sup> non-psychotic relatives
Coffman et al., 1989	143	34	58			51	Other = Bipolar Disorder and SZAFF Disorder
Colombo et al., 1993	36	18	18				
Colombo et al., 1994	34	15	19				
Copolov et al., 2000	218	140	46,16	10	4	2	46FE SZ,10FE BP,4FE SZAFF, 2FE = other psychosis
Corey-Bloom et al., 1995	58	28	30				
Corson et al., 1999a	79	43	36				FE SZ
Dauphinais et al., 1990	49	21	28				SZ or SZAFF
Degreef et al., 1990	42	17	25				FE SZ
Degreef et al., 1992a	65	25	40				FE SZ
Degreef et al., 1992b	108	46	62				FE SZ
Degreef et al., 1992c	194	46	19,62			67	19SZ, 62FE SZ, Other = post-mortem study, 39 NCL, 28SZ
Deicken et al., 1999	41	18	23				
DeLisi et al., 1988	42	18	24				
DeLisi et al., 1991	65	20	15,30				15SZ, 30FE SZ

Table 2 (continued)

Authors	Tot Subjs	NL Ctrl	SZs	Bipolars	SZAFFs	Other	Comments
DeLisi et al., 1992	111	33	50,28				50FE SZAFF/SZ, 28SZAFF/SZ 2yr FUP
DeLisi et al., 1993	132	47	50,19		13	3	50FE SZPHM, 19FE SZ, 13FE SZAFF,3FE other
DeLisi et al., 1994	125	40	85				All FE SZ, SZPHM, or SZAFF
DeLisi et al., 1997	70	20	50				All FE SZ, SZPHM, or SZAFF
DeQuardo et al., 1996	28	14	14				
DeQuardo et al., 1999	42	22	20				FE SZ
Di Michele et al., 1992	42	17	25				
Downhill et al., 2000	70	30	27			13	Other = SPD
Egan et al., 1994	32	16	16				
Elkashef et al., 1994	51	26	25				
Flaum et al., 1995	189	87	102				
Frangou et al., 1997	126	39	32			55	Familial SZ, Other = 1 <sup>0</sup> non-psychotic relatives
Frederikse et al., 2000	60	30	30				
Fukuzako et al., 1996a	36	18	18				
Fukuzako et al., 1996b	113	41	72				
Fukuzako et al., 1997	56	28	28				
Goldstein et al., 1999	55	26	29				
Guenther et al., 1989	62	31	31				
Gunther et al., 1991	62	31	31				
Gur et al., 1994	162	81	81				
Gur et al., 1998a	224	128	96				21NN, 48TN, 27F/up and AN
Gur et al., 1998b	57	17	20,20				20SZ, 20 FE SZ
Gur et al., 1999	260	130	130				51NN, 79 previously Tx
Gur et al., 2000a	210	110	100				39NN, 61 previously Tx
Gur et al., 2000b	151	81	70				29NN, 41 previously Tx
Hajek, 1997	20	10	10				
Harvey et al., 1993	82	34	48				
Hauser et al., 1989	71	25	24	22			
Havermans et al., 1999	47	17	30				15SZ with Audhall, 15SZ no Audhall
Hazlett et al., 1999	72	32	27			13	Other = SPD
Hirayasu et al., 1998	51	18	17	14		2	FE SZ, FE BP, other = depressed, psychotic
Hirayasu et al., 1999	61	20	17	21		3	FE SZ, FE BP, other = depressed, psychotic
Hirayasu et al., 2000	66	22	20	24			FE SZ, FE BP
Hoff et al., 1992	113	57	56				SZPHM
Hoff et al., 1994	97	35	56				FE SZ, SZPHM, SZAFF, all but 1 NN
Hokama et al., 1995	30	15	15				
Holinger, et al., 1999	18	10	8				
Jernigan et al., 1991	66	24	42				
Johnstone et al., 1989	62	21	21	20			
Jurjus et al., 1993	164	37	67	60			BP and SZAFF
Kawasaki et al., 1993	30	10	20				
Kelsoe et al., 1988	38	14	24				
Keshavan et al., 1995	11		11				6FE SZ, 5 Other Psychoses
Keshavan et al., 1998a	42	17	16			9	FE SZ, Other = non-SZ Psychotic
Keshavan et al., 1998b	42	17	17			8	FE SZ, Other = non-SZ Psychotic
Kikinis et al., 1994	30	15	15				
Kleinschmidt et al., 1994	52	26	26				FE SZ
Kulynych et al., 1995	24	12	12				
Kulynych et al., 1996	24	12	12				
Kwon et al., 1998	113	46	15,15	14		21,2	15SZ,15FE SZ,21SPD,2FE Dp Psychotic Depressed Psychotic
Kwon et al., 1999	32	16	16				
Lauriello et al., 1997	74	37	37				

Table 2 (continued)

Authors	Tot Subjs	NL Ctrl	SZs	Bipolars	SZAFFs	Other	Comments
Lawrie et al., 1999	150	30	20			100	FE SZ, Other = high risk for SZ
Levitt et al., 1999	30	15	15				
Lewine et al., 1990	59		31			28	Other = 12 MAJ DEP/SZAFF, 14 Unspec, 2 OBS FE SZ
Lim et al., 1996	73	51	22				
Marsh et al., 1994	74	41	33				
Marsh et al., 1997	108	52	56				
Marsh et al., 1999	152	52	100				55STATEHOSPSZ, 44VAHOSPSZ
Mathew et al., 1985a	24	12	12				
Mathew et al., 1985b	36	18	18				
McNeil et al., 2000	44	22	22				NL MZ twin/SZ MZ Twin
Meisenzahl et al., 1999	46	23	23				
Meisenzahl et al., 2000	60	30	30				
Menon, et al., 1995	40	20	20				
Mion et al., 1991	48	16	32				16SZ with td, 16SZ without td
Narr et al., 2000	53	28	25				
Nasrallah et al., 1986	79	41	38				
Nasrallah et al., 1990	91	35	56				
Niemann et al., 2000	40	20	20				FE SZ
Niznikiewicz et al., 2000	30	15	15				
Noga et al., 1995	28	14	14				
Nopoulos et al., 1995	48	24	22		2		FE SZ, FE SZAFF
Nopoulos et al., 1996	101	47	54				44SZ with no large CSP, 10 SZ with large CSP
Nopoulos et al., 1997	130	75	52		3		
Nopoulos et al., 1999	130	65	65				
Ohnuma et al., 1997	20	10	10				FE SZ
Pearlson et al., 1997b	133	60	46	27			
Petty et al., 1995	28	14	14				
Portas et al., 1998	30	15	15				
Raine et al., 1990	46	18	15			13	Other = psychiatric controls
Raine et al., 1992	54	19	17			18	Other = psychiatric controls
Rajarethinam et al., 2000	40	20	20				
Razi et al., 1999	71	31	27,13				27SZ, 13FE SZ/SZAFF/SZPHN
Reite et al., 1997	40	20	20				Paranoid SZ
Rossi et al., 1988	24	12	12				
Rossi et al., 1989a	26	11	15				
Rossi et al., 1989b	24	12	12				
Rossi et al., 1990	30	13	17				
Rossi et al., 1991	26		10	16			
Rossi et al., 1992	32	12	20				
Rossi et al., 1993	39	16	23				
Rossi et al., 1994a	33	14	19				
Rossi et al., 1994b	45	23	22				
Roy et al., 1998	51	15	22	14			
Sachdev and Brodaty, 1999	79	30	49				25 Late onset SZ, 24 Early onset SZ
Sanfilipo et al., 2000a	102	29	73				
Sanfilipo et al., 2000b	82	29	53				
Schlaepfer et al., 1994	133	60	46	27			
Schwartz et al., 1992	99	51	48				
Schwarzkopf et al., 1990	40	20	20				
Scott et al., 1993	140	79	52		9		Controls = non-SZ Inpatients
Shenton et al., 1991	22	10	12				
Shenton et al., 1992	30	15	15				

Table 2 (continued)

Authors	Tot Subjs	NL Ctrl	SZs	Bipolars	SZAFFs	Other	Comments
Shihabuddin et al., 1998	42	24	16		2		7NN, 11 Drug Free SZ/SZAFF
Shioiri et al., 1996	245	92	40	69		44	Other = Unipolar Depression
Snyder et al., 1998	134	52	82				FE SZ
Staal et al., 1998	64	32	16			16	Other = Same Sex Sib of SZ
Staal et al., 2000	64	32	16			16	Other = Same Sex Sib of SZ
Stefanis et al., 1999	74	26	48				27SZ with no PBCs, 21SZ with PBCs
Stratta et al., 1989	40	20	20				
Suddath et al., 1989	34	17	17				
Suddath et al., 1990	30	15	15				NL MZ twin/SZ MZ Twin
Sullivan et al., 1998	198	65	71			62	Other = Detoxified Chronic Etoh
Swayze et al., 1992	149	47	54	48			
Symonds et al., 1999	287	63	62			162	58 AD, 52 Etoh, 52 +HIV
Szeszko et al., 1999	45	26	19				FE SZ
Tibbo et al., 1998	144	65	79				
Tune et al., 1996	29	15	14				
Turetsky et al., 1995	224	128	96				75 SZ previously Tx, 21 SZ NN
Turetsky et al., 2000	48	22	26				
Uematsu and Kaiya, 1988	57	17	40				
Uematsu and Kaiya, 1989	57	17	40				
Velakoulis et al., 1999	218	140	46,32				46SZ, 32FE SZ
Vita et al., 1995	34	15	19				
Whitworth et al., 1998	103	32	30,41				30SZ, 41FE SZ
Wible et al., 1995	29	15	14				
Wible et al., 1997	30	15	15				
Woodruff et al., 1993	74	44	30				
Woodruff et al., 1997a	85	43	42				
Woodruff et al., 1997b	85	43	42				
Woods et al., 1996	38	19	17		2		
Zipursky et al., 1992	42	20	22				
Zipursky et al., 1994	42	20	22				
Zipursky et al., 1997	54	17	23	14			
Zipursky et al., 1998a	138	61	77				FE SZ, FE SZPHM, FE SZAFF, FE DEL DIS, Psychosis NOS
Zipursky et al., 1998b	108	82	26				FE of non-affective Psychosis

are disrupted in schizophrenia and schizophrenia related disorders.

### 3. Evidence for structural brain abnormalities in schizophrenia

#### 3.1. Whole brain volume and ventricle findings

##### 3.1.1. Whole brain volume

As early as 1801 with Pinel's work (Pinel, 1801), and later Kretschmer's (1925), there has been an interest in brain/cranium size in mental illness. Initially, this interest was based on the presumed association between brain size and mental illness, socioeconomic

status, IQ, and cognitive deficits. More recently, some researchers have hypothesized that smaller brain size may be related to perinatal complications or to neurodevelopmental abnormalities, or both, though the interpretation of these findings remains unclear (see for example Andreasen et al., 1986; letters to the editor by Pearlson et al., 1991, and by Zipursky et al., 1991; see also meta-analysis of post-mortem, MRI, and CT studies by Ward et al., 1996).

Whole brain volumes are also computed to control for brain/head size when investigating smaller, specific brain regions. For example, if smaller hippocampi are identified in one subject relative to another, it is important to determine whether or not the smaller size is due to smaller overall brain size or to

Table 3

Medial temporal lobe findings in schizophrenia. SZ = Schizophrenia; PHG = Parahippocampal Gyrus; AMYG-HIPP = Amygdala-Hippocampal Complex; PBC = Pregnancy and Birth Complications

Author(s)	Findings
Altshuler et al., 1998	↓ HIPP volume in SZ, but AMYG ↑ in Bipolar Disorder
Barta et al., 1990	↓ Left AMYG (did not measure HIPP)
Barta et al., 1997b	↓ Left AMYG (did not measure HIPP)
Becker et al., 1990	↓ HIPP and PHG
Becker et al., 1996	↓ HIPP
Blackwood et al., 1991	Left < Right AMYG in controls, no such asymmetry noted in SZs, also asymmetry differences in PHG between groups
Bogerts et al., 1990	↓ Left Posterior HIPP; ↓ Total Left AMYG-HIPP Complex (Male FE SZ)
Bogerts et al., 1993b	↓ Posterior Portion of AMYG-HIPP (20% Left; 15% Right) (Chronic SZ)
Brier et al., 1992	↓ AMYG Bilaterally; ↓ Left HIPP
Bryant et al., 1999	↓ AMYG-HIPP Complex
Buchanan et al., 1993	↓ AMYG-HIPP Complex
Colombo et al., 1993	No differences in the HIPP
Copolov et al., 2000	↓ HIPP in FE SZ
Corey-Bloom et al., 1995	No difference in mesial temporal lobe gray matter (included AMYG-HIPP Complex and PHG)
Dauphinais et al., 1990	↓ Right AMYG-HIPP Complex and ↓ Right PHG
Deicken et al., 1999	No difference in HIPP but ↓ NAA in HIPP bilaterally
DeLisi et al., 1988	↓ AMYG-HIPP Complex and PHG bilaterally; trend ↓ Left AMYG-HIPP Complex
DeLisi et al., 1991	No difference in AMYG-HIPP Complex or PHG
Egan et al., 1994	↓ AMYG-HIPP Complex, especially on the Left
Flaum et al., 1995	↓ HIPP
Fukuzako et al., 1996a	↓ HIPP
Fukuzako et al., 1997	↓ HIPP
Gur et al., 2000a	↓ HIPP gray matter in men and women; ↓ AMYG in men, but ↑ in women
Harvey et al., 1993	No Difference AMYG-HIPP Complex
Havermans et al., 1999	No difference in Anterior AMYG-HIPP or in PHG
Hirayasu et al., 1998	↓ Left Posterior AMYG-HIPP in both FE schizophrenics and in FE Bipolar patients

Table 3 (continued)

Author(s)	Findings
Jernigan et al., 1991	↓ AMYG, HIPP, and PHG
Kawasaki et al., 1993	↓ Left PHG but no difference in AMYG-HIPP Complex
Lawrie et al., 1999	↓ AMYG-HIPP Complex in FE SZ
Marsh et al., 1994	↓ Bilaterally in AMYG, HIPP, and AMYG-HIPP Complex
Marsh et al., 1997	No Difference HIPP
Marsh et al., 1999	No Difference HIPP
McNeil et al., 2000	↓ HIPP bilaterally in patients with PBCs, and Left HIPP
Niemann et al., 2000	↓ correlated with longer labor No Difference in AMYG or in HIPP
Ohnuma et al., 1997	↓ Left HIPP and Left PHG
Pearlson et al., 1997b	↓ Right AMYG and ↓ Entorhinal Cortex in SZ and ↓ Left AMYG in Bipolar patients
Razi et al., 1999	↓ PHG, particularly on the Left
Rossi et al., 1994a	↓ AMYG-HIPP Complex, particularly on the Left
Sanfilippo et al., 2000b	No Difference in HIPP or PHG (Prefrontal GM correlated with (-) Symptoms)
Shenton et al., 1992	↓ Left Anterior portion of the AMYG-HIPP Complex, ↓ PHG bilaterally, but more on the Left
Staal et al., 2000	No Difference in AMYG, HIPP, or PHG
Stefanis et al., 1999	↓ Left HIPP in SZ with severe PBCs and no family history of SZ; ↓ HIPP correlated with earlier age of onset
Suddath et al., 1989	↓ Temporal Lobe Gray matter in central sections corresponding anatomically to portions of the temporal lobe that contain the AMYG-HIPP Complex
Suddath et al., 1990	↓ HIPP
Swayze et al., 1992	No Difference AMYG or HIPP
Velakoulis et al., 1999	↓ HIPP in Chronic and FE SZ; ↓ Left HIPP in both FE SZs and FE Affective Psychotic patients (↓ Right HIPP correlated with age and illness duration in Chronic SZ)
Whitworth et al., 1998	↓ Posterior portion of the AMYG-HIPP Complex in Chronic and FE SZ
Woodruff et al., 1997b	↓ Left HIPP
Zipursky et al., 1994	No Difference HIPP

Table 4

First episode MRI studies listed by brain region of interest, author (year), and positive or negative findings (Abbreviations: asym = Asymmetry; Chr SZ = Chronic Schizophrenic; LAT = Lateral Ventricle; PHG = Parahippocampal Gyrus; Neurol. = Neuroleptic; Tx = Treatment)

Brain Region	References
Whole Brain	+James et al., 1999 <sup>a</sup> –Bilder et al., 1994 (asym) –DeLisi et al., 1991, 1992 –Hirayasu et al., 1998, 2000 –Keshavan et al., 1998a,b –Lawrie et al., 1999 –Nopoulos et al., 1995 –Velakoulis et al., 1999 –Whitworth et al., 1998 (↓ Chr SZ)
Gray Matter	+Gur et al., 1999 +Lim et al., 1996 +Ohnuma et al., 1997 (Cortical Gray Matter) +Zipursky et al., 1998a (Gray Matter, includes Basal Ganglia) +Zipursky et al., 1998b (Cortical Gray Matter)
Ventricles	+Barr et al., 1997 +Bogerts et al., 1990 <sup>b</sup> +Degreef et al., 1990, 1992a +DeLisi et al., 1991, 1998 +Hoff et al., 1992 +James et al., 1999 +Keshavan et al., 1998b +Lawrie et al., 1999 (3rd ventricle) +Lieberman et al., 1993 <sup>c</sup> +Lim et al., 1996 +Nopoulos et al., 1995 +Snyder et al., 1998 +Whitworth et al., 1998 +Zipursky et al., 1998a –DeLisi et al., 1992 –Lawrie et al., 1999 (LAT and 4th) –Niemann et al., 2000 –Ohnuma et al., 1997
Temporal Lobe (Whole)	+Bilder et al., 1999 (asym) +Bogerts et al., 1990 +DeLisi et al., 1991 +Gur et al., 1998b +Gur et al., 2000a (Temporal Pole) –Bilder et al., 1994 (asym) –Hoff et al., 1992 –Lawrie et al., 1999 –Niemann et al., 2000 –Nopoulos et al., 1995 –Ohnuma et al., 1997
Medial Temporal Lobe Structures (Amygdala-hippocampal Complex measured together)	+Bogerts et al., 1990 –DeLisi et al., 1991 +Hirayasu et al., 1998 +Lawrie et al., 1999 +Lieberman et al., 1993 <sup>c</sup> +Whitworth et al., 1998
Superior Temporal Gyrus	+Gur et al., 2000a (males only) +Hirayasu et al., 1998 +Keshavan et al., 1998b
Planum Temporale	+DeLisi et al., 1994 +Hirayasu et al., 2000 +Hoff et al., 1992 (abnormal asymmetry, lateral sulcus in females) –Kleinschmidt et al., 1994
Hippocampus	+Kwon et al., 1999 +Bilder et al., 1995 +Bogerts et al., 1990 (males only) +Copolov et al., 2000 –DeLisi et al., 1991 –Niemann et al., 2000

Table 4 (continued)

Brain Region	References
	+Gur et al., 2000a +Hirayasu et al., 1998 +Ohnuma et al., 1997 +Velakoulis et al., 1999 +Whitworth et al., 1998
Amygdala	+Gur et al., 2000a (↑ females, ↓ males)  –Bilder et al., 1995 –DeLisi et al., 1991 –Niemann et al., 2000 –Ohnuma et al., 1997
Parahippocampus	+Bogerts et al., 1990 +Ohnuma et al., 1997  –Razi et al., 1999 (PHG ↓ Chr SZ)
Frontal Lobe (Whole)	+Bilder et al., 1994, 1999 (asym) +Gur et al., 1998b, 2000b <sup>d</sup> +Ohnuma et al., 1997 +Nopoulos et al., 1995 +Szeszko et al., 1999  –DeLisi et al., 1991 –Hirayasu et al., 1999 –Lawrie et al., 1999
Premotor	+Bilder et al., 1994 (asym)  –Bilder et al., 1999 (asym)
Prefrontal	+Bilder et al., 1994, 1999 (asym)
Cingulate	+Ohnuma et al., 1997  –Hirayasu et al., 1999
Sensorimotor	  –Bilder et al., 1999 (asym)
Parietal Lobe	  –Nopoulos et al., 1995
Occipital Lobe	  –Nopoulos et al., 1995
Occipitoparietal	+Bilder et al., 1994, 1999 (asym)
Corpus Callosum	+DeLisi et al., 1997 +DeQuardo et al., 1999 +Hoff et al., 1994 (females only) +Degreef et al., 1992b, c +DeLisi et al., 1993 +Kwon et al., 1998  –Ohnuma et al., 1997
Cavum Septi Pellucidi	
Basal Ganglia	+Chakos et al., 1994 +Corson et al., 1999a +Gur et al., 1998a (previously Tx) +Keshavan et al., 1995, 1998a +Ohnuma et al., 1997 +Shihabuddin et al., 1998 <sup>c</sup>  –DeLisi et al., 1991 –Gur et al., 1998a (neurol. naive) –Lawrie et al., 1999
Thalamus	+Gur et al., 1998a  –Lawrie et al., 1999
Adhesio Interthalamica	+Snyder et al., 1998
Cerebellum	+DeLisi et al., 1997  –Keshavan et al., 1998b

<sup>a</sup> Study of childhood schizophrenia.

<sup>b</sup> Only temporal horn portion of lateral ventricle increased.

<sup>c</sup> Qualitative measures used.

<sup>d</sup> These investigators reported reduced gray matter in prefrontal regions, including dorsolateral areas in males and females, dorsomedial areas in male patients, and orbital regions in female patients.

<sup>e</sup> These investigators reported smaller caudate nuclei in never medicated patients and larger caudate nuclei in previously medicated patients.

disproportionately smaller hippocampi, independent of brain size. Methods to measure brain size have included measures of intracranial cavity contents (gray matter, white matter, and CSF), as well as measures of gray and white matter that include or exclude the cerebellum. Additionally, given the large individual variation in

head/brain size, investigators have sought an appropriate correction factor, believing that such variation needs to be accounted for particularly when evaluating smaller brain ROIs (e.g. Arndt et al., 1991; Flaum et al., 1994; Mathalon et al., 1993).

From our review of 50 MRI studies of whole brain

Table 5  
MRI studies of progressive volume changes in schizophrenia (SZ)

Study	Sample	N	ROIs	Follow-up interval	Findings
Chakos et al. (1994)	First episode SZ Schizophreniform Controls	21 8 10	caudate	18 months	Increased caudate volume with typical neuroleptics. Volume correlated with dose; inversely correlated with age of onset.
Chakos et al. (1995)	SZ	15	caudate	1 year	Reduced caudate volume with atypical neuroleptics.
Corson et al. (1999b)	Chronic SZ  SPD Psychosis NOS Controls	19  1 3 0	caudate, lenticular nucleus	2 years	Typical neuroleptics increase size of caudate/lenticular nucleus, atypical neuroleptics decrease size.
Degreef et al. (1991)	First episode SZ Controls	13 8	cortical volume, ventricular volume	1–2 years	No difference in rate of change for either. <sup>a</sup>
DeLisi et al. (1992)	First episode SZ Controls	50 33	temporal lobes, ventricular volume	2 years	No difference in temporal lobe or ventricular volume. Change in ventricular volume was inversely correlated with amount of time in hospital for SZ.
	(Note, some subjects overlap with 1991 report, and some SZ subjects were characterized as schizophreniform or schizoaffective)				
DeLisi et al. (1995)	First episode SZ Controls	20 5	cerebral hemispheres, medial temporal lobe, temporal lobe, lateral ventricles, caudate nucleus, corpus callosum	4 years	Rate of change greater in SZ for left ventricle. <sup>a</sup>
DeLisi et al. (1997)	First episode SZ Controls	50 20	cerebral hemispheres, temporal lobe, medial temporal lobe, lateral ventricles, cerebellum, caudate nucleus, corpus callosum, Sylvian fissure	≥ 4 years	Rate of change greater in SZ for left and right hemispheres, right cerebellum, corpus callosum segment, and ventricles. <sup>a</sup>
DeLisi et al. (1998)	First episode SZ	50	cerebral hemispheres ventricles,	5 years	Larger ventricles at baseline correlated with poorer premorbid functioning. Larger ventricles at baseline also showed less of an increase in size at follow up compared with smaller ventricles at baseline.

Table 5 (continued)

Study	Sample	N	ROIs	Follow-up interval	Findings
Gur et al. (1998b)	SZ patients (20 first episode, 20 chronic) Controls	40 17	whole brain CSF, frontal lobes, temporal lobes	2–3 years	Rate of change of frontal lobe volume increased in SZ. <sup>a</sup> Both subject groups showed a reduction in temporal lobe volume.
Jacobson et al. (1998)	Childhood onset SZ Controls	10 17	cerebral volume, superior, anterior temporal lobe, amygdala, hippocampus	2 years	Rate of change of total cerebral volume and temporal lobe structures increased in SZ. <sup>a</sup>
Keshavan et al. (1998b)	First episode psychosis Controls	17 17	cerebral volume, superior temporal gyrus, cerebellum	1 year	Volume of superior temporal gyrus was inversely correlated with prodrome and psychosis duration. Rate of change of superior temporal gyrus was greater in patients. <sup>a</sup> Superior temporal gyrus volume enlarged with treatment in some patients (i.e. reversal of volume reduction after 1 year).
Lieberman et al. (1996)	First episode SZ or schizoaffective Controls	62 42	qualitative measure of lateral ventricles, third ventricle, frontal/parietal cortex, medial temporal	18 months	Patients with poor response to treatment showed more ventricle enlargement and reduced cortical volumes compared with patients with better response to treatment.
Nair et al. (1997)	Patients with symptoms of schizophrenia Controls	18 5	total ventricular volume	2–3 years	Rate of change greater in SZ-like patients. <sup>a</sup>
Rapoport et al. (1997)	Childhood onset SZ Controls	16 24	ventricular volume, thalamic area, caudate nucleus, putamen, globus pallidus	2 years	Rate of change of ventricular volume and thalamic area increased in SZ. <sup>a</sup>
Rapoport et al. (1999)	Childhood onset SZ Controls	15 34	gray and white matter volume (frontal, temporal, parietal, occipital lobes)	4 years	Rate of change of gray, but not white matter in frontal, temporal, and parietal lobes increased in SZ. <sup>a</sup>

<sup>a</sup> Rate of change increased in patient group means that the structure in question changed volume at a faster rate (larger volume for given period of time) than in the control group.

volume, we note that only 11 (22%) report differences between patients with schizophrenia and control subjects, whereas 39 (78%) report negative findings (Table 1). There is, nonetheless, some evidence to suggest that small reductions in brain size (i.e. small effect size), may be evident in schizophrenia. For example, Ward and coworkers (1996) concluded that there are small yet statistically significant reductions in brain size and ICC in schizophrenia (effect

size approximately 0.18–0.20). The clinical importance of these findings, however, is unknown, although Jacobsen and coworkers (1996), who reported smaller brain volume in patients with childhood schizophrenia, suggest that brain volume reduction might be related to more ‘severe genetic and/or environmental neurodevelopmental insult, leading to earlier onset’. These latter findings suggest that whole brain volume reduction, while not generally observed

in schizophrenia, may be evident in a subset of cases, and thus it may be too early to conclude that small brain volume differences, or small effect sizes, are inconsequential.

In summary, most MRI studies do not report statistically significant differences in brain size between patients with schizophrenia and normal controls. There is, however, enormous individual variation in head/brain size in the general population and confounds such as age, gender, socioeconomic status, and possible nutritional deficits need to be more carefully considered. These confounds, in addition to MRI methodological problems, reviewed above, could easily have obscured small but important differences. Further research is thus needed before definitive conclusions can be drawn concerning the importance and meaning of small reductions in brain size in a subset of patients diagnosed with schizophrenia.

### 3.1.2. Ventricles

**3.1.2.1. Lateral ventricles** Initially, ventricular enlargement was measured by creating casts of the ventricles from post-mortem brains. The first in vivo studies were conducted using invasive pneumoencephalography techniques, followed many years later with more non-invasive CT studies (see introduction for references). Shelton and Weinberger (1986) reviewed CT findings in schizophrenia and found that over 75% of these studies report enlarged lateral ventricles. Enlarged lateral ventricles are, however, not specific to schizophrenia as they occur in many disorders, including Alzheimer's disease, hydrocephalus, and Huntington's Chorea. Chemotherapy agents and corticosteroids may also cause enlarged lateral ventricles. Nonetheless, lateral ventricular enlargement may indicate tissue loss in surrounding brain regions or it may indicate a failure in development, and for these reasons such findings are of great interest to schizophrenia researchers.

In our review of 55 MRI studies, 44 (80%) studies report enlarged lateral ventricles, thus making it one of the most robust MRI findings in the literature (Table 1). Moreover, even studies not reporting lateral ventricle enlargement have reported enlargement in the temporal horn portion of the lateral ventricular system (e.g. Shenton et al., 1992—listed as a negative

finding in Table 1). This enlargement was most prominent in the left side lateral ventricle.

Enlarged temporal horns of the lateral ventricles, with left-sided prominence, have also been reported in several other MRI studies (e.g. Becker et al., 1990; Bogerts et al., 1990; Dauphinais et al., 1990; Degreef et al., 1990; DeLisi et al., 1991; Johnstone et al., 1989; Kawasaki et al., 1993; Niemann et al., 2000; Roy et al., 1998; Shenton et al., 1992). These MRI findings are also consistent with several post-mortem findings which have reported both reduced volume in the amygdala-hippocampal complex and increased temporal horn volume (e.g. Bogerts et al., 1985; Brown et al., 1986; Colter et al., 1987; Crow et al., 1989; Falkai and Bogerts, 1986; Falkai et al., 1988; Jakob and Beckmann, 1989; Jeste and Lohr, 1989; Kovelman and Scheibel, 1984). These findings are also consistent with a post-mortem study of Alzheimer's patients and schizophrenic patients by Crow et al. (1989), which showed enlarged temporal horn region of the lateral ventricles in schizophrenic patients compared with Alzheimer patients. Moreover, Suddath and coworkers (1989) reported a correlation between reduced left temporal lobe gray matter and increased CSF volume in the left temporal horn in the ill twin of monozygotic twins discordant for schizophrenia, again emphasizing that tissue in the region surrounding temporal horn may be reduced in schizophrenia. Fig. 1 provides an illustration of the ventricular system showing the temporal horn of the lateral ventricles, as well as other parts of the ventricular system.

**3.1.2.2. Third and fourth ventricles** In 33 MR studies of third ventricle, 24 (73%) of the findings are positive, and nine (27%) are negative (Table 1). This is in contrast to one of five (20%) MRI studies of fourth ventricle being positive and four (80%) studies being negative. The proximity of the third ventricle to the thalamus is likely important, as increased fluid in the third ventricle may be related to reduced thalamic volume in schizophrenia (see discussion below). Moreover, the vast interconnections between the thalamus and most other brain regions has led to the thalamus being described as the major region of abnormality in schizophrenia (see Andreasen's paper describing the 'cognitive dysmetria hypothesis' of schizophrenia which highlights the

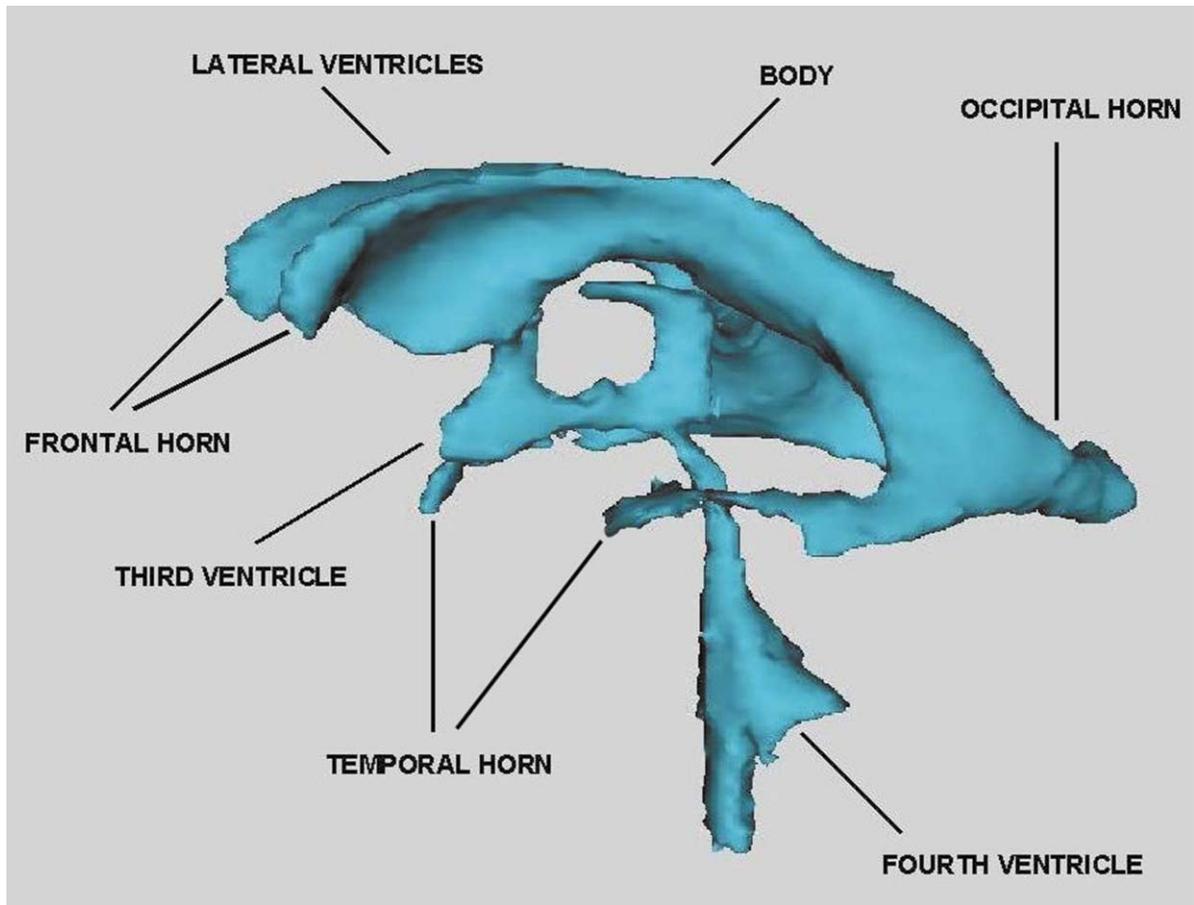


Fig. 1. This image shows the ventricular system derived from 1.5-mm contiguous MR images which were segmented to delineate the ventricles. A three-dimensional reconstruction surface rendering program was used to visualize the labeled MR data set. The component parts of the ventricular system (see labels) include: the lateral ventricles (body, temporal horns, frontal horns, occipital horns), and third and fourth ventricles. [Courtesy of Aleksandra Ciszewski, B.A., Marianna Jakab, M.S., Marek Kubicki, M.D., PhD, Elizabeth David, A.B., and Michael Halle, PhD Clinical Neuroscience Division, Laboratory of Neuroscience, Department of Psychiatry, and Surgical Planning Laboratory, Department of Radiology, Harvard Medical School.]

thalamus as a critical site underlying the neuropathology and clinical and cognitive dysfunctions in schizophrenia –Andreasen et al., 1999). An enlarged third ventricle may thus be suggestive of either aberrant development of the thalamus or neurodegeneration of this critical structure (see thalamic and cerebellum sections, below).

### 3.2. Temporal lobe findings

#### 3.2.1. Introduction

Kraepelin (1919/1971) believed that delusions and auditory hallucinations were the result of temporal

lobe abnormalities. Southard (1910, 1915) also noted abnormalities in the temporal lobe in post-mortem brains of patients diagnosed with schizophrenia. He was particularly impressed with gross neuroanatomical abnormalities in the cortex of the left temporal lobe which he, too, thought were related to the symptom of auditory hallucinations.

Until recently, however, there has been little empirical evidence to support these earlier speculations. The first MRI study to evaluate superior temporal gyrus was conducted by Barta et al. (1990). Work in our own laboratory has focused primarily on temporal

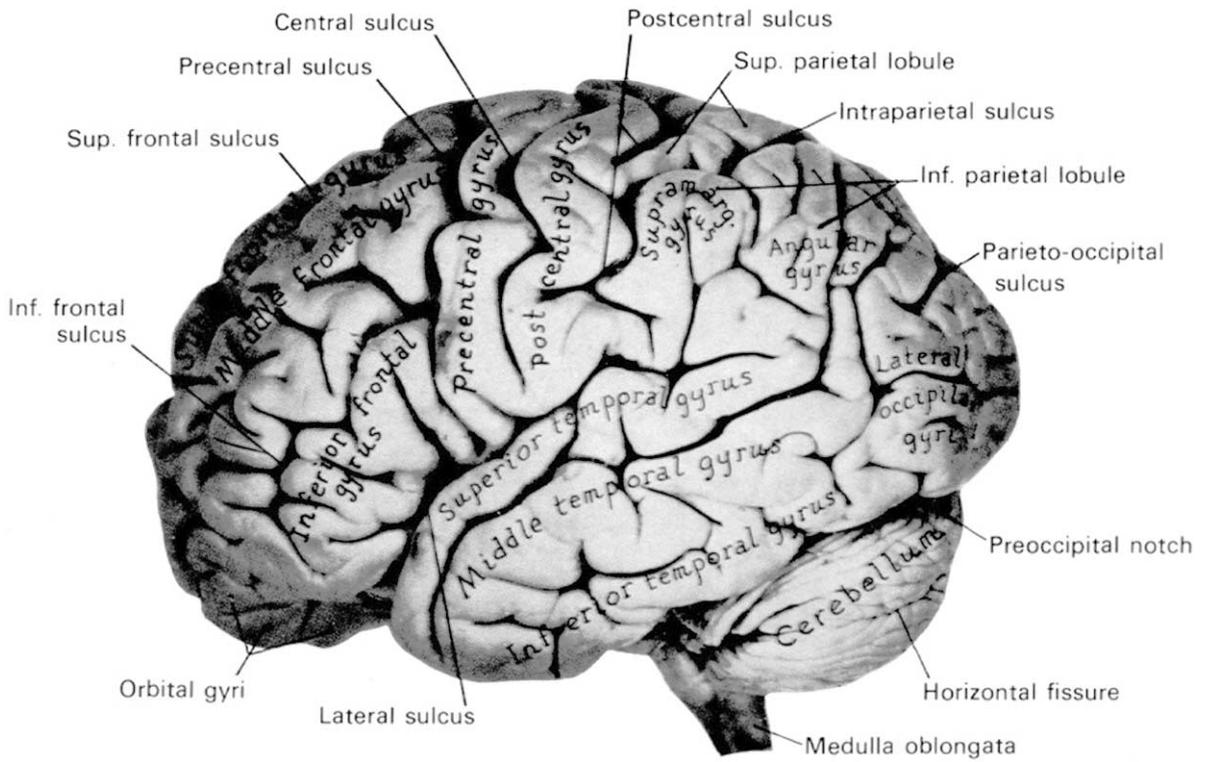


Fig. 2. Photograph of a lateral view of the human brain. [From Carpenter, *Human Neuroanatomy*, 1983, reprinted with permission of Williams & Wilkins, New York, New York.]

lobe abnormalities, specifically the superior temporal gyrus (STG), including Heschl's gyrus and planum temporale, as well as medial temporal lobe structures. We hypothesize that the hallucinatory symptoms and cognitive deficits in schizophrenia may be associated with disturbances in auditory and language processing functions, which likely also involve brain regions important for associative and retrieval processes in memory. These processes involve interconnections between the hippocampus, amygdala, parahippocampal gyrus, and STG, as well as other neocortical brain regions (e.g. McCarley et al., 1993, 1996; Nestor et al., 1993, 1997; Niznikiewicz et al., 2000; O'Donnell et al., 1993; Shenton et al., 1992). More specifically, the hippocampus and adjacent parahippocampal gyrus and entorhinal cortex are thought to be involved in the laying down and retrieval of memory through interconnections with neocortical regions (STG perhaps for verbal memories; e.g. Squire and Zola-Morgan, 1991; Squire, 1992; see also Wible et al., 1997),

while the amygdala is thought to be importantly involved in the emotional valence given to stimuli and memories, thus serving to facilitate encoding (e.g. Gloor, 1986).

Below we review the findings for whole temporal lobe, followed by medial temporal lobe (amygdala-hippocampal complex, parahippocampal gyrus) and neocortical temporal lobe structures (superior temporal gyrus [STG], including planum temporale [PT] and Heschl's gyrus). Fig. 2 provides a lateral view of the brain, where the three main gyri are illustrated: the STG, which lies closest to the Sylvian fissure, superior to two parallel gyri, the middle temporal gyrus and the inferior temporal gyrus. Medial temporal lobe structures run along the longitudinal or parallel axis in the medial portion of the temporal lobe and include the hippocampus and adjacent amygdala (the parahippocampal gyrus lies inferior to these structures). The PT and Heschl's gyrus lie along the surface of the STG, not visible in

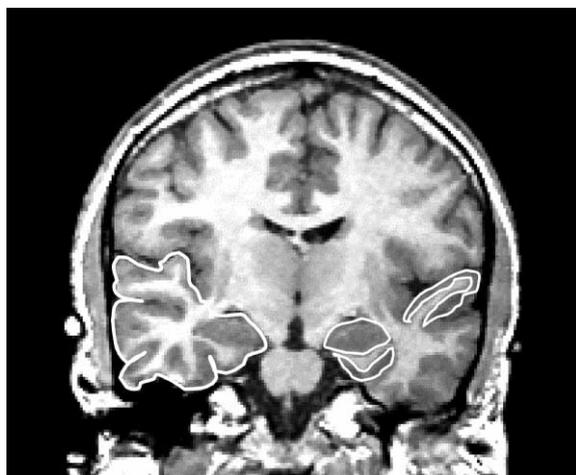


Fig. 3. Coronal 1.5-mm slice showing medial temporal lobe and neocortical structures. The region delineated in white on the left side of the image (subject's right) is the temporal lobe. The regions delineated in white on the right side of the image (subject's left) include the superior temporal gyrus, which borders the Sylvian fissure, the amygdala (almond shaped region in the medial temporal lobe), and the parahippocampal gyrus, delineated beneath the amygdala. [Reprinted with permission of *The New England Journal of Medicine*, Shenton ME, Kikinis R, Jolesz FA, Pollak SD, LeMay M, Wible CG, Hokama H, Martin J, Metcalf D, Coleman M, McCarley RW, 327, 602, 1992, Copyright (1992), *Massachusetts Medical Society*.]

Fig. 2. These brain regions are discussed below, where we review more than 137 MRI studies conducted since 1988.

### 3.2.2. Whole temporal lobe findings

Of 51 MRI studies evaluating the volume of whole temporal lobe, 31 (61%) report smaller temporal lobe volume, while 20 (39%) report negative findings (Table 1). Methodological differences likely contribute to the conflicting findings. For example, some studies relied upon a small number of thicker slices to estimate overall temporal lobe volume (e.g. Kelsoe et al., 1988; Rossi et al., 1989a), while other studies relied upon a large number of thin slices to estimate overall temporal lobe volume, thus allowing for more accurate volume estimations (e.g. Gur et al., 1998b; Shenton et al., 1992). Other methodological differences between studies include: (1) different landmarks to define the boundaries of the temporal lobe; (2) measurement of gray matter versus gray and white matter combined; and (3) interpolations over slices

with no gaps versus interpolations over slices with gaps between slices. Again, such methodological differences are relevant to all MRI studies in schizophrenia but become more problematic when evaluating brain regions where differences between groups are likely quite small.

Of note, in our 1997 review (Shenton et al., 1997), 55% of the 31 MRI studies showed smaller temporal lobe volume in schizophrenia, while 45% of the studies reported no differences. The increase in more positive findings (60%) is likely the result of studies using thinner slices, stronger magnets, and more uniform segmentation. It is nonetheless important to note that overall temporal lobe volume may be less informative with respect to the neuropathology of schizophrenia than volume differences in specific structures within the temporal lobe (see discussion below). Fig. 3 illustrates an outline of the temporal lobe, manually drawn on a 1.5-mm coronal MR image (viewer's left is subject's right).

Of the studies evaluating asymmetry differences, all reported right > left temporal lobe volume in both patients and controls (Becker et al., 1990; Bilder et al., 1994; Blackwood et al., 1991; Johnstone et al., 1989; Kawasaki et al., 1993; Rossi et al., 1989a, 1990, 1991; Suddath et al., 1989; Swayze et al., 1992). These findings are consistent with right > left temporal lobe volumes from data in the normal population, as the Sylvian fissure extends further posteriorly on the left, but is steeper on the right due to the larger area of the posterior vertical ramus (e.g. Geschwind and Levitsky, 1968; LeMay and Kidd, 1978; LeMay 1986).

### 3.2.3. Medial temporal lobe findings

Medial temporal lobe structures include the amygdala-hippocampal complex and the parahippocampal gyrus. The impetus for much of this work comes from post-mortem studies demonstrating tissue loss in these regions, and a corresponding volume increase in the temporal horn of the lateral ventricles which surround these structures (e.g. Benes et al., 1991; Bogerts, 1984; Bogerts et al., 1985; Brown et al., 1986; Colter et al., 1987; Crow et al., 1989; Falkai and Bogerts, 1986; Falkai et al., 1988; Jeste and Lohr, 1989). Fig. 3 illustrates the spatial relationship of these structures and their proximity to the STG. The outline of the amygdala (almond shape) can be seen on the viewer's

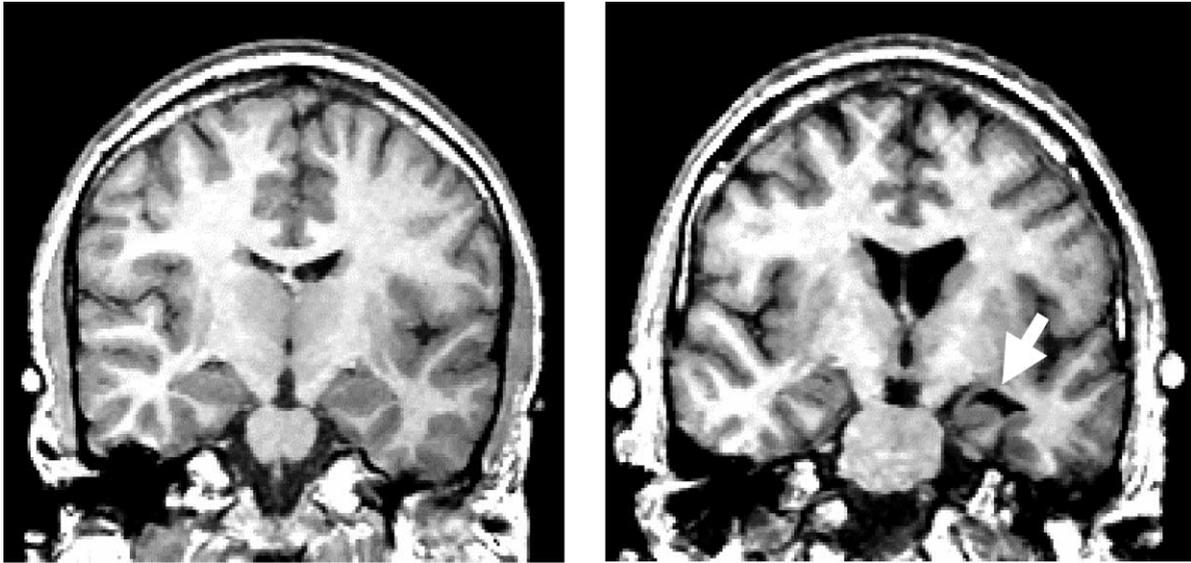


Fig. 4. Coronal 1.5-mm slice of a normal control (left panel) and a schizophrenic patient (right panel). Note the increased CSF (black) in the *left* Sylvian fissure in the patient image (right panel, viewer's right), as well as the increased CSF in the *left* temporal horn which surrounds the amygdala (see white arrow), and tissue reduction in the *left* superior temporal gyrus. The lateral ventricles are also enlarged in the patient image as can be seen by the black CSF regions in the center of the image. Contrast this with the slice at approximately the same neuroanatomical level for the normal control (left panel). [Reprinted with permission of *The New England Journal of Medicine*, Shenton ME, Kikinis R, Jolesz FA, Pollak SD, LeMay M, Wible CG, Hokama H, Martin J, Metcalf D, Coleman M, McCarley RW, 327, 602, 1992, Copyright (1992), *Massachusetts Medical Society*.]

right (subject left). Below the amygdala (viewer's right), the parahippocampal gyrus is outlined.

Most MRI studies combine the amygdala and hippocampus into the amygdala-hippocampal complex because it is difficult to separate them on coronal slices (e.g. Becker et al., 1990, 1996; Bogerts et al., 1990, 1993b; Breier et al., 1992; Chua and McKenna, 1995; DeLisi et al., 1988, 1991; Hirayasu et al., 1998; Kawasaki et al., 1993; Lawrie et al., 1999; Shenton et al., 1992). There has nonetheless generally been an attempt made to delineate an anterior portion which is primarily amygdala, and a posterior portion which is primarily hippocampus. A small number of recent studies have made separate measurements of these two brain regions (e.g. Staal et al., 2000). Given that these structures have quite different functions (i.e. hippocampus with more immediate aspects of memory and the amygdala with the emotional valence given to stimuli), both of which may be implicated in schizophrenia pathology, it is important to continue to delineate these structures in future studies.

Table 1 lists 49 MRI studies that have evaluated

medial temporal lobe structures, with 74% reporting positive findings and 26% reporting negative findings. These findings are consistent with post-mortem findings and are among the most robust MRI findings in schizophrenia. Table 3 lists, by author, the main findings for each study. Fig. 4 illustrates the increase of CSF in the *left* temporal lobe horn of the lateral ventricle, in the region of the amygdala, in a patient with schizophrenia as compared to a normal control (viewer right; see arrow).

Volume reductions in the amygdala-hippocampal complex and parahippocampal gyrus are thus present in chronic patients. Volume reductions in the amygdala-hippocampal complex are also evident in first episode patients with schizophrenia (e.g. Bogerts et al., 1990; Copolov et al., 2000; Hirayasu et al., 1998; Lawrie et al., 1999; Velakoulis et al., 1999). The specificity of these findings to schizophrenia are, however, more equivocal as reduced amygdala-hippocampal complex, particularly posteriorly, has been reported to be abnormal in first psychotic episode bipolar patients (e.g. Hirayasu et al., 1998; Velakoulis

et al., 1999), in chronic mood disordered patients (e.g. Altshuler et al., 1998; Drevets et al., 1992; Mayberg, 1993; see also reviews of MR studies in affective disorder by Norris et al., 1997; Steffens and Krishnan, 1998; Soares and Mann, 1997), in normal elderly persons (e.g. Golomb et al., 1993), in patients with Cushing's syndrome (e.g. Starkman et al., 1992), as well as in patients diagnosed with post traumatic stress disorder (e.g. Bremner et al., 1995; Gurvits et al., 1996). Thus, it remains to be determined whether or not hippocampal volume is a non-specific risk factor for developing psychiatric illness, is related to cognitive impairments, including memory, in schizophrenic patients, as suggested by several investigators (e.g. Goldberg et al., 1994; Nestor et al., 1993, 1997; Weinberger et al., 1992), and, or, whether such anomalies are familial and perhaps represent a marker of vulnerability, as suggested by several recent studies of family members of patients with schizophrenia (e.g. Adler et al., 1998; Callicott et al., 1998; Seidman et al., 1999). Weinberger (1999), in fact, suggests that 'genes involved in the development and maintenance of hippocampal circuitry or in the expression of molecules that mediate certain aspects of neural plasticity' in the hippocampus, may play a critical role in the genetic predisposition to schizophrenia.

The implications of bilateral versus lateralized findings are also unknown. Many post-mortem findings of medial temporal lobe structures suggest more left lateralized involvement (see references in Introduction). In a recent meta-analysis of 18 studies, Nelson and coworkers (1998) concluded that there was only a 4% bilateral volume difference between patients with schizophrenia and controls. However, in our review of 49 MRI studies, we note a large number of studies that demonstrate left-lateralized findings for the amygdala-hippocampal complex, particularly in male patients (e.g. Barta et al., 1990, 1997a; Bogerts et al., 1990, 1993b; Breier et al., 1992; DeLisi et al., 1988; Hirayasu et al., 1998; Kawasaki et al., 1993—parahippocampal gyrus only; McNeil et al., 2000; Ohnuma et al., 1997; Razi et al., 1999; Rossi et al., 1994a; Shenton et al., 1992; Stefanis et al., 1999; Velakoulis et al., 1999; Woodruff et al., 1997b).

With respect to left lateralized findings, of particular interest is the study by Stefanis and coworkers (1999) that reported reduced left hippocampal volume

in patients with schizophrenia who had a history of severe pregnancy and birth complications and no familial history of schizophrenia. This was not true for patients with familial schizophrenia who were free from such complications. Additionally, McNeil and coworkers (2000) reported a relationship between smaller bilateral hippocampi and labor and delivery complications in the schizophrenic twin of monozygotic twins discordant for schizophrenia. They further noted a relationship between smaller left hippocampi and prolonged labor in the ill twin. These findings suggest that, at least among some patients with schizophrenia, a neurodevelopmental factor may play a critical role in the etiology of the illness.

In another twin study of monozygotic twins discordant for schizophrenia, Suddath and coworkers (1989, 1990) reported bilateral volume reductions in the hippocampus in the ill twin compared to the well twin. Finally, Velakoulis and coworkers (1999) noted bilateral hippocampal volume reduction in both chronic and first episode patients. However, when the first episode patients were evaluated separately from the chronic patients, the left hippocampus was smaller in both the schizophrenic and affective groups. Additionally, smaller right hippocampal volume was correlated with increased age and longer duration of illness in chronic patients, suggesting that bilateral reductions may be associated with poorer outcome and neurodegeneration.

These findings suggest that a neurodevelopmental abnormality, possibly associated with complications in utero or at birth, may contribute to hippocampal abnormalities in schizophrenia. This explanation gains further support from findings suggesting that the hippocampus and subiculum are adversely affected by both pre- and perinatal hypoxia. Much of this work comes from animal studies (e.g. McEwen and Magarinos, 1997; Mizoguchi et al., 1992; Uno et al., 1989; Watanabe et al., 1992). For example, studies of placental insufficiency in the guinea pig, induced by unilateral uterine artery ligation, have shown a 26% hippocampal volume reduction compared to control animals, further suggesting that complications during pregnancy may be a predisposing factor for hippocampal damage (Copolov et al., 2000). Such findings hark back to Mednick and McNeil's (1968) hypothesis that pregnancy complications resulting from hypoxia in the developing fetus

represent a vulnerability factor that predispose individuals to developing schizophrenia (see also discussion of ‘two-hit’ model below in Section 4 Neurodevelopmental versus Neurodegenerative Processes: Evidence from First Episode and Longitudinal Studies, 4.1 the Issues).

In summary, findings of medial temporal lobe volume reductions in schizophrenia, particularly of the amygdala-hippocampal complex, suggest that at least a subgroup of patients diagnosed with schizophrenia may have experienced excitotoxic damage to the hippocampus either in utero, at birth, or later. Moreover, while excitotoxicity, steroid toxicity (e.g. related to adult and prenatal stress), and hypoxia may lead to neuronal damage in the hippocampus, genetic factors may also be contributory. Further research is needed to examine the relationship between birth history and MRI findings of reduced hippocampal volume. It would also be of interest to determine whether or not such abnormalities are related to other pre- and perinatal abnormalities. One study by Kwon et al. (1998) suggests such a relationship. These investigators reported a correlation between hippocampal volume reduction and enlarged cavum septi pellucidi in male patients with chronic schizophrenia (see section below on cavum septi pellucidi abnormalities). Further, given the lateralized findings in first episode patients (see above), it would be of interest to study patients longitudinally to determine whether or not bilateral neurodegenerative processes are evident in patients who have a more chronic course. By determining the timing of brain changes, neuroprotective agents might be developed to prevent further neurodegenerative processes. This would seem important given recent findings suggesting plasticity and reversal of hippocampal damage in humans (e.g. Eriksson et al., 1998).

#### 3.2.4. Superior temporal gyrus (STG) findings

The superior temporal gyrus (STG) is the temporal gyrus that is just ventral to the Sylvian fissure (see Fig. 2). Along the superior surface of the STG is Heschl’s gyrus, which contains primary auditory cortex. More posteriorly, and on the *left*, is part of Wernicke’s area (Brodmann’s area 41 and 42), which includes the planum temporale (PT), a brain region thought to be a neurological substrate of language (e.g. Penfield and Roberts, 1959; Penfield and Perot, 1963; Wernicke, 1874). Of particular interest, disordered thinking has

been elicited in electrical stimulation studies of the posterior portion of STG in patients undergoing neurosurgery for epilepsy (e.g. Haglund et al., 1992). Studies of electrical stimulation to more anterior portions of STG have resulted in complex auditory hallucinations and verbal memories (Penfield and Roberts, 1959). These findings are similar to the hallmark symptoms of schizophrenia which include verbal memory deficits, disordered thinking, and auditory hallucinations, thus making this brain region of particular interest to schizophrenia researchers.

Of 15 MRI studies that evaluated STG gray and white matter volume combined, 10 (67%) report STG volume reductions in schizophrenia (Table 1). Of the 12 MRI studies that evaluated just STG gray matter volume, all 12 (100%) report volume reduction (see also Pearlson 1997a for a review). These findings underscore the importance of evaluating STG gray matter separately.

The first two MRI studies of STG reported left STG volume reductions, thus confirming Southard’s (1910,1915) early anecdotal findings of ‘suprasylvian atrophy’ and a ‘withering away’ of left STG in post-mortem brains of schizophrenia. In the first study, Barta and coworkers (1990) reported an 11% left STG volume reduction that was correlated, anteriorly, with auditory hallucinations. The second study, from our laboratory (Shenton et al., 1992), reported a 15% left STG volume reduction that was correlated, posteriorly, with increased thought disorder. [Parenthetically, the latter correlation with thought disorder has been confirmed in several other studies (e.g. Barta et al., 1997a; Holinger et al., 1999; Marsh et al., 1997; Menon et al., 1995; Vita et al., 1995).]

More recently, Hirayasu et al. (1998) reported STG gray matter volume reduction in first episode patients with schizophrenia compared with controls, but not in first episode psychotic bipolar patients. Velakoulis et al. (1999) reported similar findings. Moreover, Dickey et al. (1999) reported STG gray matter reduction in untreated and unmedicated subjects from the community diagnosed with schizotypal personality disorder. These findings suggest the specificity of STG abnormalities to schizophrenia and schizophrenia spectrum disorders. The exception to these findings is a study by Pearlson and coworkers (1997b) which reported smaller left amygdala and right anterior STG in bipolar patients, but not in

schizophrenic patients. However, patients with schizophrenia could still be differentiated from bipolar patients by differences in posterior STG posterior asymmetry and by smaller left anterior STG and right amygdala.

There is also some suggestion that in early stages of the disorder, left STG volume reductions may be reversible (Keshavan et al., 1998b). This finding is based on a 1 year follow-up of only 11 patients with schizophrenia treated with neuroleptics, although if confirmed in a larger sample, it would strongly suggest that pharmacological treatment interventions may be critical to halting and perhaps reversing such brain anomalies.

With respect to correlations with other brain regions, it is interesting to note that volume reduction in the hippocampus, amygdala, parahippocampal gyrus and STG is highly intercorrelated (e.g. Shenton et al., 1992), suggesting that regions that are functionally interrelated also evince volume reductions. Wible and coworkers (1995) showed correlations between left prefrontal gray matter and left amygdala-hippocampal complex, left parahippocampal gyrus, and left STG. Moreover, Nestor et al. (1993) observed an association between poor performance on verbal memory, abstraction, and categorization, and volume reduction in both the parahippocampal gyrus and posterior STG. These cognitive deficits are consistent with the function of these brain regions and their role in associative links in memory, particularly verbal memory. Nestor et al. (1997) interpreted these findings as indicative of a dysfunctional semantic system in schizophrenia.

Additionally, Flaum et al. (1995) reported that positive psychotic symptoms were correlated with whole STG volume reduction. Finally, Holinger et al. (1999) reported a right STG volume reduction in left-handed male patients compared to left-handed male controls that was associated with increased formal thought disorder. These findings are thus consonant with studies showing functional abnormalities in P300 in schizophrenia (e.g. McCarley et al., 1993), with positron emission tomography (PET) studies (see review in Pearlson, 1997a), with attentional processing deficits (e.g. Posner et al., 1988), and with the theory that abnormal asymmetries in the brain represent a genetic/neurodevelopmental abnormality in schizophrenia (e.g. Crow et al., 1989; Crow, 1990b). Such

cerebral anomalies likely set the stage for disruptions in functions subserving memory and associations involving language and speech, particularly in the left hemisphere (e.g. Shenton et al., 1992; Wible et al., 1997).

### 3.2.5. *Planum temporale (PT) findings*

Findings from STG studies in schizophrenia have led to more focused evaluations of the PT, a brain region critical for language and speech processing (e.g. Galaburda et al., 1978, 1987; Galaburda and Sanides, 1980; Geschwind and Levitsky, 1968). There is also a well documented left greater than right asymmetry in PT in two thirds of normal brains. As this asymmetry is evident at between 29 and 31 weeks gestation, abnormalities in PT asymmetry may be indicative of a disruption in hemisphere lateralization in neurodevelopment (Chi et al., 1977).

Shapleske et al. (1999) provide a meta-analysis of 21 MRI studies of PT in normals and seven MRI studies of PT in patients with schizophrenia. These investigators concluded that even with the different methods for measurement, there is a left asymmetry in normals that is much reduced in patients with schizophrenia. They concluded that this difference was due primarily to the relatively larger right PT in patients with schizophrenia compared to control subjects. Our own review of 10 MRI PT studies in schizophrenia suggests that of six (60%) studies reporting PT abnormalities in schizophrenia, five reported a reversal of left greater than right PT asymmetry (Barta et al., 1997a; Hirayasu et al., 2000; Kwon et al., 1999; Petty et al., 1995; Rossi et al., 1992), and one reported less asymmetry anteriorly and more asymmetry posteriorly in patients with schizophrenia compared to controls (DeLisi et al., 1994). In addition, volume reduction in left PT has also been reported (e.g. Barta et al., 1997a; Hirayasu et al., 2000; Kwon et al., 1999). Additionally, Kwon et al. (1999) reported a correlation between left PT volume reduction and higher scores on the Suspiciousness/Persecution subscale of the Positive and Negative Symptom Scale (PANSS; Kay et al., 1986). PT asymmetry has also been associated with formal thought disorder (e.g. Petty et al., 1995; Rossi et al., 1994b).

In summary, PT findings in schizophrenia are important as they are likely related to disturbances

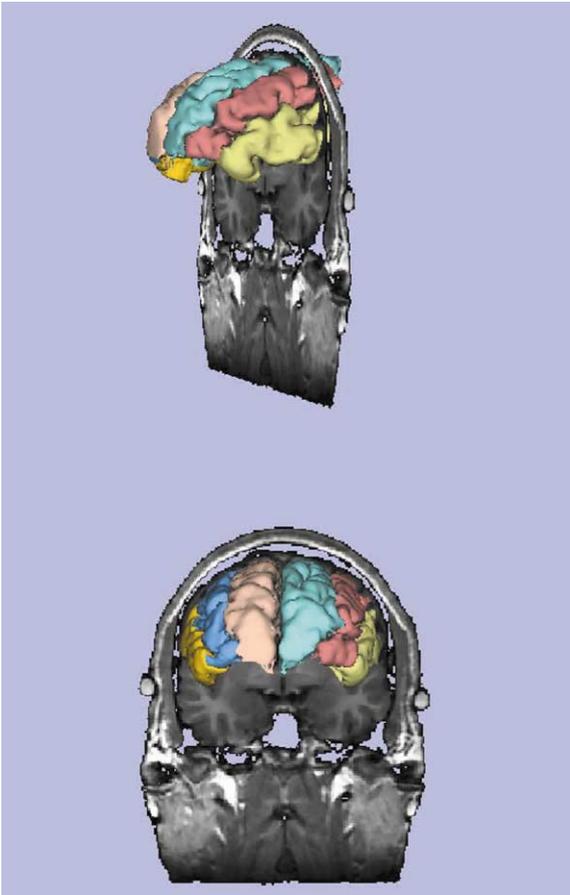


Fig. 5. 3D surface rendering of the superior, middle and frontal lobe gyri is shown along with a coronal 1.5-mm slice that illustrates the relationship of the gyri to the coronal slice. The side view depicts the gyri just at the beginning of the amygdala (top), and the front view (bottom) shows the same slice and 3D reconstruction but in a different orientation. Superior frontal (flesh/aqua color), middle frontal (blue/peach color), and inferior frontal (gold/yellow) gyri are depicted. [Courtesy of Aleksandra Ciszewski, B.A. and Marianna Jakab, M.S., Clinical Neuroscience Division, Laboratory of Neuroscience, Department of Psychiatry, and Surgical Planning Laboratory, Department of Radiology, Harvard Medical School.]

in language and thought. These findings would likely be more consistent if the measurements (e.g. surface and volume) and the neuroanatomical landmarks for defining this brain region were more uniform. Despite these methodological limitations, it is clear that schizophrenia is likely a disorder with marked abnormalities in the left hemisphere, particularly in the left temporal lobe and in regions such as the PT which are important for language processing and are

also left lateralized. Crow has postulated the ‘lateralization hypothesis of schizophrenia’ (Crow et al., 1989), where he emphasizes abnormal neural development of brain lateralization in the etiology of schizophrenia. Crow further notes that the left hemisphere may be more vulnerable to insult or damage because it develops later than the right hemisphere (see also Geschwind and Galaburda, 1985). It is not known, however, whether such disturbances result from genetic or exogenous insults that occur during fetal development.

Pearlson and coworkers (1996) further suggest that PT abnormalities in schizophrenia are related to heteromodal association cortex abnormalities, which they view as the primary site for neuroanatomical disturbances in schizophrenia. These regions include posterior portions of STG, dorsolateral prefrontal cortex, and the inferior parietal lobule. Finally, PT abnormalities are present at first episode (e.g. Hirayasu et al., 2000), but are not present in first psychotic episode bipolar patients. Thus far PT abnormalities have not been reported in any other psychiatric disorders although such abnormalities are reported in individuals with dyslexia, who show a somewhat different pattern of abnormalities. Future studies are needed which use more standardized methods in order to determine whether or not particular PT abnormalities are specific to schizophrenia.

### 3.3. Frontal lobe

The prefrontal cortex is one of the mostly highly complex and evolved neocortical regions of the human brain, comprising close to 30% of neocortex in humans, with both afferent and efferent connections to all other areas of cortex, as well as to limbic and basal ganglia structures (Fuster, 1989; Goldman-Rakic et al., 1984; Pandya and Seltzer, 1982). This brain region serves an important modulatory role in all aspects of human functioning (see also Zakzanis and Heinrichs, 1999).

Interest in frontal lobe abnormalities in schizophrenia is generated from observations of cognitive and behavioral deficits that are associated with measures of frontal lobe damage (e.g. Wisconsin Card Sorting Task, eye tracking abnormalities, spatial working memory deficits, PET and fMRI functional measures showing hypo and hyperfrontality—see review in

Wible et al., 1995, 1997, see also Andreasen et al., 1992; Goldberg et al., 1987; Weinberger et al., 1992). Converging findings from post-mortem studies of schizophrenia also support the presence of prefrontal lobe abnormalities in schizophrenia (e.g. Benes et al., 1991; Goldman-Rakic and Selemon, 1997; Selemon et al., 1998). Fig. 5 illustrates a three-dimensional surface reconstruction of the prefrontal cortex and its subdivision into frontal, middle, and inferior gyri, juxtaposed with a coronal 1.5-mm slice.

Structural MRI findings of frontal lobe abnormalities in schizophrenia are equivocal. In our review of 50 MRI studies, 30 (60%) reported positive findings, while 20 (40%) reported negative findings (Table 1). It is noteworthy that most of these studies measured the frontal lobe as one structure, despite the fact that the frontal cortex is highly differentiated functionally and that different subregions within the frontal lobe have quite different and specific brain functions (e.g. Fuster, 1989). Thus, if investigators are attempting to discern small differences in specific subregions within the frontal lobe, measurement of the entire frontal lobe will likely obscure any small, local abnormalities.

The first study to measure the whole prefrontal cortex, using thin 1.5-mm slices, was conducted in our laboratory by Wible and coworkers (1995). We found no differences between patients with schizophrenia and controls, although left prefrontal gray matter volume was highly correlated with volume reductions in the left amygdala-hippocampal complex, left STG, and left parahippocampal complex in the schizophrenia group only. Moreover, there was a correlation between patients evincing more negative symptoms and left prefrontal volume reduction. These findings suggest that differences in the prefrontal cortex may be too small to detect, but which are nonetheless correlated with reductions in areas of the left temporal lobe that are neuroanatomically and functionally related, as well as with symptoms thought to be associated with frontal lobe functioning.

Breier et al. (1992) also noted correlations between prefrontal and temporal lobe volume. Additionally, their measure of right prefrontal white matter volume was correlated with right amygdala-hippocampus volume, which they interpreted as supporting the hypothesis of abnormal limbic-cortical connections in schizophrenia. Further, Weinberger et al. (1992) reported an association between left hippocampal

volume reduction in the affected twin of monozygotic twins discordant for schizophrenia and decreased cerebral blood flow in the dorsolateral prefrontal cortex during the Wisconsin Card Sorting Task. These findings further support direct and indirect connections between prefrontal and limbic structures in the brain, which may be abnormal in schizophrenia.

Finally, we note that small, subtle differences in the whole prefrontal lobe may be just at the threshold for MRI detection, and hence different subject samples or methodology may obscure detecting such differences. Moreover, Selemon and coworkers (1998) found only a small (8%) reduction in prefrontal cortical thickness in schizophrenia, a reduction that was not statistically significant, although abnormalities in cell density were present. A reduction of 8%, however, may not be detected using MRI, again suggesting that when the differences are small, more care is needed in defining homogeneous subject populations and using more uniform methods.

Very few studies, however, and only the most recent, have evaluated subregions within the frontal lobe. Buchanan et al. (1998) reported volume reductions in prefrontal white matter in patients with schizophrenia as well as right and left inferior gyri volume reductions. Goldstein et al. (1999) reported between 7 and 15% volume reduction in the middle frontal, middle, medial, and right sided fronto-orbital subregions in schizophrenia. Gur et al. (2000b) studied male and female patients with schizophrenia, and matched controls, and reported reduced prefrontal gray matter volume in dorsolateral regions of 9% in men and 11% in women. Dorsomedial volume reduction was evident only in male patients, and orbitofrontal volume reduction was evident only in female patients. Additionally, a larger dorsal cortex was correlated in the patient group with better performance on abstraction and attention measures whereas smaller volume in orbito-frontal regions in female patients was correlated with poorer premorbid functioning, more negative symptoms, and depression. Baaré et al. (1999), however, reported no differences between controls and schizophrenics in parcellated prefrontal regions, although these investigators noted a correlation between left and right prefrontal gray matter volume reduction and decreased performance on tests of verbal recall, visual memory, and semantic fluency. Further, reduced orbitofrontal

volume was correlated with more negative symptoms ( $r = -0.76$ ). These findings, taken together, suggest that parcellating the frontal cortex into subregions is important not only for detecting volume differences but also for examining the association between reduced prefrontal volume and cognitive and clinical deficits.

### 3.4. *Parietal and occipital lobes*

The parietal lobe has received very little attention in schizophrenia research despite the fact that it is a brain region important to processes that are disturbed in schizophrenia such as language (e.g. Mesulam, 1990, 1998), spatial working memory (e.g. Park and Holzman, 1992), and attention (e.g. Nuechterlein and Dawson, 1984). This paucity of attention is further highlighted by the fact that there have been only 15 MRI studies that have investigated the parietal lobe. This is in contrast to the more than 137 studies of temporal lobe structures (see Table 1). The parietal lobe is also part of heteromodal association cortex, a highly organized and interconnected neocortical brain system that is highly lateralized and includes the superior posterior section of the temporal lobe, the dorsolateral prefrontal cortex, Broca's area, and the inferior parietal lobule (IPL) (Mesulam, 1990, 1998). Pearlson, in fact, views heteromodal association cortex abnormalities as the primary deficit in schizophrenia (Pearlson et al., 1996).

The parietal lobe is comprised of post-central gyrus, superior parietal gyrus, and inferior parietal lobule (IPL), with the latter further subdivided into supramarginal and angular gyri (Brodmann's areas 40 and 39 respectively). Of note, both supramarginal gyrus and angular gyrus are described as part of a semantic-lexical network that supports 'word meanings' represented by a 'grid of connectivity' that constitutes a 'final common pathway for the chunking of words into thought' (Mesulam, 1990). The role of the IPL in language comprehension, particularly the angular gyrus, has also been confirmed by fMRI and positron emission studies (e.g. Binder, 1997; Frackowiak, 1994; Howard et al., 1992). Further, the semantic-lexical network proposed by Mesulam includes both the IPL and posterior portions of the STG. Additionally the IPL, like the PT, exhibits marked lateral asymmetry (e.g. Eidelberg and Gala-

burda, 1984; Galaburda and Geschwind, 1980). The presence of left greater than right asymmetry is important for normal language development [i.e. abnormal development in these regions is associated with autism (Hier et al., 1978, 1979) as well as other language disorders (Rosenberger and Hier, 1980)]. Finally, the relevance of the supramarginal gyrus and angular gyrus to schizophrenia stems not only from their functions as part of heteromodal association cortex, but also from their reciprocal connections to both prefrontal (e.g. Cavada and Goldman-Rakic, 1989) and temporal lobe brain regions (Seltzer and Pandya, 1984).

In our review of MRI parietal lobe findings in schizophrenia, of 15 studies, nine (60%) have report abnormalities while six (41%) have not (Table 1). Methods of measurement, however, have varied tremendously, asymmetry has not always been assessed, nor has the parietal lobe generally been subdivided into functional subdivisions. For example, Egan et al. (1994) used only a 1-cm slice to measure the whole parietal lobe, and two other studies measured the parietal lobe combined with other brain regions (e.g. Harvey et al., 1993; Zipursky et al., 1994).

Several recent studies have focused on subdivisions within the parietal lobe. For example, Goldstein and coworkers (1999) evaluated subdivisions within the parietal lobe and reported volume reductions in the supramarginal gyrus in patients with schizophrenia, in addition to prefrontal volume reductions including cingulate gyrus. Schlaepfer and coworkers (1994) reported dorsolateral prefrontal cortex, IPL, and STG gray matter volume reductions in schizophrenia.

Niznikiewicz and coworkers (2000), from our laboratory, measured the component parts of the parietal lobe including the post-central gyrus, the superior parietal lobule, and the IPL, including both the supramarginal and angular gyri. The angular gyrus was highly lateralized in controls, but showed a reversal of the normal left greater than right angular gyrus in male patients with schizophrenia compared to male controls. There were also correlations between IPL and neuroanatomically connected cortical regions of the prefrontal cortex (superior and inferior frontal gyrus and orbital gyrus) and of the temporal cortex (anterior STG, amygdala, and hippocampus), further supporting the notion that heteromodal associative

cortex, and highly interrelated brain regions important for language functioning and integrating multimodal stimuli, might be preferentially affected in schizophrenia.

Frederikse and coworkers (2000) also evaluated the IPL in both male and female patients with schizophrenia and controls, and reported a reversal of the normal left greater than right asymmetry in male patients as well as a gray matter volume reduction. No such differences were observed in female patients with schizophrenia compared to female control subjects.

These findings suggest that structures belonging to the inferior parietal lobule, and which involve semantic-lexical networks, may help us to understand more fully the neural substrates of language and thought disorder in schizophrenia which are likely related to these highly lateralized brain regions. Future research will benefit from the selection of homogeneous patient groups, the examination of gender differences, and the careful parcellation and evaluation of subdivisions within the parietal lobe.

Of the nine MRI studies of the occipital lobe, four (44%) have reported volume reductions between patients with schizophrenia and normal controls, while five (56%) do not report volume differences (Table 1). As subdivisions within the occipital lobe have not been evaluated, it is not known whether regions within the occipital lobe are abnormal in schizophrenia. The evidence to date suggests that the occipital lobe is not critical to the neuropathology of schizophrenia.

### 3.5. Other brain regions

#### 3.5.1. Cerebellum

Shelton and Weinberger (1986) suggest that about 10% of CT scan studies reported cerebellar atrophy in schizophrenia. The cerebellum, however, is difficult to visualize with CT technology. With the advent of MRI, measuring the cerebellum became easier, although few studies have focused on this brain region in schizophrenia. Recent evidence, however, suggests that this brain region may play a critical role in higher cognitive functioning and may be implicated in the neuropathology of schizophrenia (e.g. Wassink et al., 1999). Schmahmann (1996), in fact, describes the cerebellum's contribution to cognitive processing, and he highlights the connectivity between the cere-

bellar hemispheres and cortical association areas which subserve cognition, as well as the connectivity between the cerebellar vermis and limbic structures, including the hippocampus and amygdala. As cortical association areas and limbic structures have figured prominently in studies of schizophrenia, the cerebellum becomes an important brain region to investigate.

In our review of 13 MRI studies of the cerebellum in schizophrenia, four (31%) report positive findings, while nine (69%) report negative findings (Table 1). Of the negative findings, Nopoulos and coworkers (1999), while not reporting overall cerebellar volume reduction, did report volume reduction in the anterior lobe of the vermis. In another study reporting negative findings, Rossi and coworkers (1993) showed a decrease in vermal-to-brain ratio in male patients with schizophrenia compared to female patients with schizophrenia.

In the first study of gray and white matter of the whole cerebellum and vermis, Levitt, from our laboratory (Levitt et al., 1999), reported an *increase* in vermis volume in chronic male schizophrenic patients as well as an *increase* in white matter volume that was correlated with positive symptoms, thought disorder, and impaired verbal memory. [Parenthetically, smaller cerebellar volume predicted more negative and positive symptoms and poorer psychosocial outcome at follow up of 7 years in a study reported by Wassink et al. (1999).] Similarly, Seidman and coworkers (2000) reported no significant differences in cerebellar gray matter volume in schizophrenics, but did report a significant *increase* in cerebellar white matter, a finding they are investigating further.

An increase in white matter may represent a neurodevelopmental anomaly or it may be a medication effect, as there are reports of axonal sprouting in rats given neuroleptic medications (e.g. Benes et al., 1983). In the Levitt et al. (1999) study, however, increases in white matter volume were not correlated with indirect measures of neuroleptic medication exposure. Finally, Levitt et al. (1999) found trend level left greater than right cerebellum hemisphere in patients with schizophrenia, which was not found in the controls. This finding suggests that the right hemisphere of the cerebellum, where language and memory activate the inferior portion, and the crossed cerebellar cerebral cortical connections, make the left greater than right cerebellum in schizophrenia

consistent with the greater left hemisphere cerebrum abnormalities in schizophrenia (see previous references in temporal lobe section).

The cortical-cerebellar-thalamic-cortical-circuit (CCTCC) involves a feedback loop that allows for the smooth coordination of both motor and cognitive functioning (e.g. Schmahmann, 1996). Andreasen and coworkers (1999) have proposed a model of schizophrenia that involves a disturbance of the CCTCC. These investigators view the cerebellar portion of this circuit as a ‘metron’ that guides the ‘fine-tuning’ of both motor and cognitive functioning. A dysfunction in the CCTCC leads to ‘cognitive dysmetria’, or to a lack of coordination in the processing and retrieval of cognitive information, leading to, and underlying, the cognitive impairments in schizophrenia.

Middleton and Strick (2000) describe several loops involving cerebellum, basal ganglia and cortical brain regions, which are important to both motor and cognitive functions. They further note that an appreciation and reappraisal of these connections may reveal important new behavioral and cognitive findings. Further studies are thus needed to evaluate the role of the cerebellum in schizophrenia, particularly given the small number of studies to date and still fewer studies which have attempted to parcellate the cerebellum into functional subdivisions.

### 3.5.2. *Subcortical structures*

**3.5.2.1. Basal ganglia** The basal ganglia structures (caudate, putamen, and globus pallidus) have become an important focus of research in schizophrenia primarily because of: (1) the extensive dopaminergic inputs into the striatum (caudate, putamen, and nucleus accumbens); (2) the therapeutic efficacy of neuroleptic medications acting on dopamine receptors; and (3) the importance of these structures in cognitive, sensory, and motor processing (see Keshavan et al., 1998a for a recent concise review). Of note, the first post-mortem study of these structures in schizophrenia reported no abnormalities (Bogerts et al., 1985), although a later study by Heckers et al. (1991) reported bilateral volume increases of 9% in the striatum and 14% in the globus pallidus.

There have been 25 MRI studies of basal ganglia structures in schizophrenia. Seventeen (68%) report positive findings and eight (32%) report negative find-

ings (Table 1). Most of the positive findings report increases in volume, with the exceptions being: (1) Mion et al. (1991) reported decreased volume in the caudate in patients with tardive dyskinesia but not in patients without tardive dyskinesia; (2) DeLisi et al. (1991) reported trend decreases in the caudate and lenticular nuclei; and (3) Rossi et al. (1994a) reported trend decreases in the caudate and lenticular nuclei in male patients.

Prior neuroleptic exposure is an important factor in findings of increased volume in basal ganglia structures. For example, Chakos and coworkers (1994) evaluated first-episode patients and observed a 5.7% increase in caudate size from baseline to follow up scan 18 months later. These investigators also noted that earlier age of onset and higher neuroleptic dosage predicted larger caudate at follow up. This finding suggests that an increase in basal ganglia volume may be a result of neuroleptic medication. Work by Keshavan et al. (1994) confirms this finding as these investigators reported increased caudate in first-episode patients from baseline MRI scan to follow up 6 and 24 months later.

The effect of atypical neuroleptics on the size of the caudate, with diminished effects on D2 receptors and increased affinity for 5-HT<sub>2</sub> receptors, has also been studied. Chakos et al. (1995) switched some patients to atypical neuroleptics, imaged them again 1 year later, and demonstrated a decrease in caudate volume. These findings suggest that increased volume of basal ganglia structures may be a function of conventional neuroleptic medications whereas atypical neuroleptics do not exert the same effect.

In a later study by Keshavan et al. (1998a), caudate volume, but not putamen volume, was bilaterally reduced in newly diagnosed psychotic patients. Reduction in caudate volume in drug naive patients is of interest because it suggests that such volume reduction may be related to the pathophysiology of schizophrenia and not a medication effect. Our laboratory has also recently reported smaller caudate in a group of neuroleptic naive subjects with related schizotypal personality disorder (Levitt et al., 2000). Additionally, Shihabuddin et al. (1998) have shown decreased caudate volume in never medicated patients and increased caudate volume in previously medicated patients. Corson et al. (1999a) have also shown decreased caudate volume in first episode,

neuroleptic naive, patients with schizophrenia. Finally, Gur and coworkers (1998a) evaluated basal ganglia structures in neuroleptically naive and previously treated patients and reported no differences in the volume of basal ganglia structures between the neuroleptically naive group and controls, although higher putamen volume was associated with more positive symptoms. In contrast, the previously medicated patients showed increased volumes in the putamen and globus pallidus, which is consistent with an earlier report from our group, in which Hokama et al. (1995) reported increased size of the caudate, putamen, and globus pallidus in medicated male schizophrenic patients. Of note, patients treated with atypical neuroleptics did not show an increase in the volumes of basal ganglia structures (Gur et al., 1998a).

Thus the increases in volume in basal ganglia structures may reflect the effects of some neuroleptic medications. Decreases in volume in some studies of first episode and neuroleptic naive schizophrenics, however, suggest that abnormalities may be extant prior to the introduction of neuroleptic medications. Further, reduced caudate volume has also been reported in depression (e.g. Krishnan et al., 1992), and thus the issue of the specificity of basal ganglia abnormalities to schizophrenia warrants further investigation. Finally, Seidman and coworkers (1997) reported smaller right putamen in a sample of six sisters of schizophrenic patients, suggesting that some never psychotic and never medicated relatives of schizophrenic patients may show abnormalities in basal ganglia structures. These findings, taken together, suggest that basal ganglia structures, medication effects, and the functions of these structures should be investigated further using state-of-the-art neuroimaging techniques that include both structural and functional measures.

**3.5.2.2. Thalamus** The thalamus, comprised of several nuclei, is a major relay station in the brain which modulates input from many cortical areas, as well as from the reticular activating system and the limbic system (e.g. Fuster, 1989). The thalamus is also involved in attention and information processing and serves as a ‘filter’ for gating the input of sensory signals (e.g. Fuster, 1989; Jones, 1985). These functions evolve from reciprocal connections

between the ventral anterior and dorsomedial nuclei of the thalamus and the prefrontal cortex, and between the associational thalamo-cortico-thalamic loop of the orbito-frontal and dorsolateral prefrontal cortices. Andreasen et al. (1994b) postulate its critical role in schizophrenia (see above discussion under cerebellum), and several post-mortem findings have reported abnormalities in thalamic nuclei (e.g. Pakkenberg, 1987).

Measurement of thalamic nuclei on MRI scans is, however, difficult as this brain region fades from gray to white matter with ghost like edges, even with thin 1.5-mm slices. It was for this reason, in fact, that Andreasen et al. were reluctant to highlight their early findings of thalamic abnormalities in schizophrenia, particularly given that the reliability for measuring this brain structure was lower than for other brain regions (e.g. Andreasen et al., 1990, 1994b; Flaum et al., 1995). Using a novel method of image averaging, Andreasen et al. (1994b) reported reduced signal intensity in the thalamus, particularly in the lateral region. This group has also published a new method for visualizing subthalamic nuclei using inversion recovery imaging (Magnotta et al., 2000). This new pulse sequence may make it possible to measure the thalamic nuclei in a manner that was not previously possible. Such improved imaging may also result in even more positive findings for thalamic abnormalities in schizophrenia than we report today.

In our review of 12 MRI studies of the thalamus, five (42%) report decreased thalami and seven (58%) report no differences between patients with schizophrenia and control subjects (Table 1). Of the negative findings, Corey-Bloom and coworkers (1995) reported a correlation between early onset patients and smaller thalamus, although there were no differences observed when the patients were compared to controls. This finding is of interest as Jeste et al. (1998) have also reported an association between early onset schizophrenia and poorer performance in learning, abstraction and cognitive flexibility, and smaller thalamic volumes (this study did not include a control group). In our laboratory, while reporting no volume differences between controls and patients, we did report a correlation between smaller thalamic volumes and smaller prefrontal white matter in the patient group (Portas et al., 1998).

Snyder et al. (1998) found an absence of the adhesio interthalamica, or massa intermedia, and third ventricle enlargement in first episode schizophrenia. As the borders of the thalamus fuse to create this midline structure between the 13th and 14th week of gestation, these investigators concluded that the absence of the adhesio interthalamica and third ventricle enlargement were neurodevelopmental in origin. Meisenzahl et al. (2000), however, did not report this abnormality in patients with schizophrenia compared with controls, although they noted that patients without adhesio interthalamica evinced more negative symptoms than patients with adhesio interthalamica. As these are the only studies reported in the literature, further research is needed to evaluate this midline structure.

In a study of neuroleptic naive patients with schizophrenia, Gur and coworkers (1998a) reported smaller thalamic volumes compared to controls (non-significant trend level of  $P = 0.08$ ). Moreover, larger thalamic and putamen volumes correlated with a greater number of positive symptoms. Additionally, in those patients previously treated with both atypical and typical neuroleptics, higher neuroleptic dosage was correlated with larger thalamic volumes. Finally, in two studies of relatives of patients with schizophrenia, thalamic volumes were significantly smaller in the relatives compared with controls (left thalamus only for the Seidman et al., 1997 study; Staal et al., 1998). These findings suggest that the thalamus may be implicated in the neuropathology of schizophrenia. Further studies are needed, however, which evaluate subnuclei within the thalamus using imaging techniques that allow for a better visualization of this brain structure, such as proposed by Magnotta and coworkers (2000).

**3.5.2.3. Corpus callosum** The corpus callosum is a midline brain structure comprised of white matter fiber tracts that connect the two hemispheres. Gruzelier (1991) has speculated that the information processing deficits observed in schizophrenia are related to defective interhemispheric communication which is largely mediated by the corpus callosum. One of the first studies of the corpus callosum in schizophrenia was a post-mortem study by Rosenthal and Bigelow (1972) that showed a thicker corpus callosum in patients with schizophrenia

compared with controls (see Raine et al., 1990 for a review of early studies).

In 27 MRI studies of the corpus callosum (CC), 17 (63%) report positive findings and 10 (37%) report negative findings (Table 1). We suspect that the large variation in methods might contribute to inconsistent findings. More specifically, most studies use a single midsagittal slice to measure the whole corpus callosum, while other studies parcellate the slice into presumed functional subdivisions. With only one slice to examine, the data are more vulnerable to errors in the alignment of the head in the MR scanner. Slice thickness, the selection of the ‘best midsagittal slice’, and gender dimorphism in both shape and size further contribute to possible sources of error (e.g. Hoff et al., 1994). More recent studies examining shape (e.g. DeQuardo et al., 1996; Downhill et al., 2000; Frumin et al., 1998) may help to clarify further the role of corpus callosum abnormalities in schizophrenia.

**3.5.2.4. Cavum septi pellucidum** The septum pellucidum is a triangular shaped membrane that separates the two frontal horns of the lateral ventricles. Developmental abnormalities in the formation of structures bordering the septum pellucidum (i.e. the corpus callosum and hippocampus) are thought to be reflected in a space, or ‘cavum’, in this membrane (e.g. Rakic and Yakovlev, 1968).

One of the first reports of cavum septi pellucidi (CSP) abnormalities and psychosis was a report by Lewis and Mezey (1985). This was followed by the first MRI study of CSP by Mathew and coworkers (1985b). There are now 12 MRI studies in the literature of which 11 (92%) report positive findings and one (8%) reports negative findings, thus making it one of the most robust MRI findings in the literature (Table 1). These findings are most commonly based on counting the number of slices in which CSP is observed (e.g. Kwon et al., 1998; Nopoulos et al., 1996, 1997). Large CSP in schizophrenic patients has ranged from 15% of patients to 45% (e.g. Degreeef et al., 1992b,c; DeLisi et al., 1993; Jurjus et al., 1993; Kwon et al., 1998; Nopoulos et al., 1996; Scott et al., 1993). Additionally, large CSP has been reported in first episode schizophrenics (e.g. Degreeef et al., 1992c; DeLisi et al., 1993; Kwon et al., 1998). Moreover, large CSP has been correlated with a family

history of schizophrenia in schizophrenic patients (Uematsu and Kaiya, 1988), as well as with left temporal lobe volume reduction in male schizophrenics (Nopoulos et al., 1996), and with hippocampal volume reduction in chronic male schizophrenics (Kwon et al., 1998). Kwon et al. (1998) also reported large CSP in first psychotic episode bipolar patients and in schizotypal personality disorder. This suggests that while CSP abnormalities are evident in schizophrenia, they are also present in other psychiatric disorders and, therefore, are not specific to schizophrenia.

Of note, Degreeef et al. (1992a,b), Jurjus et al. (1993), Nopoulos et al. (1996, 1997), and Kwon et al. (1998) all reported large CSP in male patients with schizophrenia, suggesting the importance of gender, particularly in evaluating possible prenatal neurodevelopmental abnormalities, which tend to show a greater prevalence in males (e.g. Shaw and Alvord, 1969). Nopoulos and coworkers (1996, 1997), in fact, suggest that the pattern of abnormalities involving large CSP and left temporal lobe volume reductions in male schizophrenics, may reflect regional, localized tissue reduction. They further speculate that an asymmetry in the development of the cerebral hemispheres, which creates ‘diverging growth vectors’, may disrupt the normal fusion process of the septum pellucidum (i.e. ‘lateralized temporal lobe dysgenesis’).

In summary, MRI findings of CSP are among the most robust in the literature and suggest that this neurodevelopmental anomaly is relevant to the neuropathology of schizophrenia for at least a subgroup of individuals diagnosed with this disorder.

### 3.5.3. *Olfactory bulbs*

The olfactory system is of interest to schizophrenia researchers because it receives input from several brain regions thought to be implicated in the neuropathology of schizophrenia, including ventromedial temporal lobe, basal forebrain, and the prefrontal cortex. The olfactory bulbs are unique in that there is a single synapse between peripheral olfactory receptors and primary olfactory cortex, thus representing a direct link between the brain and the outside world. There is also some suggestion that it is more influenced by neurodevelopmental factors and also resistant to progressive changes (e.g. see review in

Turetsky et al., 2000). Turetsky and coworkers (2000) conducted the first MRI study of olfactory bulb volume in schizophrenia and reported a 23% bilateral volume reduction compared with controls. They also noted an association between olfactory sensitivity and olfactory bulb volume in control subjects that was not observed in the patients. As this is the first study to evaluate olfactory bulbs, and as 3-mm slices were used, this finding needs to be replicated.

## 4. Neurodevelopmental and neurodegenerative abnormalities: first episode and longitudinal studies

### 4.1. *The issues*

Previously, we focused on answering the questions: (1) ‘Are there brain abnormalities in schizophrenia?’ (2) ‘If so, which regions are affected?’ and finally, (3) ‘Are brain abnormalities related to cognitive and clinical symptoms observed in schizophrenia?’ Another set of important questions include: ‘Are the brain abnormalities observed due to events that occurred pre- or perinatally (i.e. have a neurodevelopmental origin), are they progressive (neurodegenerative), or are they a combination of both?’

That some structural brain abnormalities may be due to neurodevelopmental anomalies does not explain why the onset of schizophrenia generally occurs in late adolescence or early adulthood. One explanation might be that brain abnormalities that occur in late adolescence or early adulthood are related to neurodevelopmental abnormalities, but simply unfold over the course of development. Feinberg (1982), for example, posits such an anomaly, which results in aberrant synaptic pruning during adolescence and early adulthood. A potential model for such phenomena is also supported by animal studies. More specifically, rat pups with hippocampi lesioned early in development show delayed aberrant behavior occurring during adolescence (Lipska et al., 1993, 1995, 1998). These findings suggest that a neurodevelopmental lesion in a critical area, such as the hippocampus, may have delayed manifestations.

Alternatively, though not mutually exclusive, some researchers suggest that a ‘two-hit model’, often

described in medicine, may be operative in schizophrenia (McCarley et al., 1991, 1996; Mednick and McNeil, 1968; Meehl, 1962). Such a model was proposed by Mednick and McNeil (1968) who noted the importance of a genetic component that was necessary but not sufficient for the development of schizophrenia. These investigators believed that another risk factor such as hypoxia during child birth, with possible hippocampal damage, was required.

Several research investigators have focused on glutamate, the major excitatory neurotransmitter in the central nervous system, as playing an important role in the pathogenesis of schizophrenia (e.g. Coyle 1996; McCarley et al., 1991; Olney, 1989, 1990; Olney and Farber, 1995; Robinson and Coyle, 1987; Tsai and Coyle, 1995). More specifically, abnormal Excitatory-Amino-Acid (EAA) transmission is the likely mechanism for abnormalities in neurodevelopment which are secondary to a disruption of EAA-mediated neural guide mechanisms (i.e. 'first-hit'), and may also result in ongoing, use dependent excitotoxic cell damage or death (Coyle, 1996; Coyle and Puttfarcken, 1993; McCarley et al., 1991, 1999a; Komuro and Rakic, 1993, 1998; Olney, 1989, 1990). Thus both developmental and excitotoxic aspects of EAA neurotransmission abnormalities could be explanatory mechanisms for the gray matter reductions reported in MRI and post-mortem studies (see also Grunze et al., 1996). Such toxic actions may also exert their effects in an age-dependent fashion, for example, in late adolescence, when there is myelination of frontal glutamate pathways (Benes, 1989). Whether or not specific brain regions are more susceptible to such excitotoxicity warrants further investigation.

Currently, two strategies have been used in MRI studies to address questions concerning neurodevelopmental versus neurodegenerative brain abnormalities. The first is to evaluate the brain early in the course of the illness, at first episode or first hospitalization, prior to neuroleptic exposure and/or the stress of having a serious chronic illness. This approach is predicated on the belief that studying first episode patients obviates confounds such as medication, chronicity of illness, and progressive changes. Research interest in childhood schizophrenia (Frazier et al., 1996, 1997; Rapoport et al., 1997; Yeo et al.,

1997) and adolescent schizophrenia (Dasari et al., 1999; James et al., 1999; Friedman et al., 1999) is also increasing. While these groups are not representative of the schizophrenia population and therefore may not be generalizable, they nonetheless offer important insights into the course of the illness and in change in brain morphology.

The second strategy is to evaluate changes in structural brain morphometry over time. The general assumption is that changes over time are indicative of neurodegeneration, although such changes might also reflect neurodevelopmental anomalies. These studies are difficult to conduct and have many confounds, including: (1) patient drop out, possibly leading to a systematic error of more or less severely ill subjects being studied; (2) the time interval to identify progressive changes is not known as some brain regions may change at different rates than others (DeLisi et al., 1997; Gur et al., 1998b); (3) little is known about the effect of normal aging on brain morphology; and (4) psychotropic medications can effect brain structures. With respect to the latter, as previously noted, typical neuroleptics have often resulted in an increase in basal ganglia structures, and atypical neuroleptics, with effects on multiple neurotransmitters, may also change the morphology of brain regions. Thus such caveats need to be kept in mind in reviewing the current longitudinal studies.

Below, we highlight findings first from 124 first episode MRI studies, listed by brain region finding, followed by a review of 15 longitudinal, or follow up, studies (see Tables 4 and 5).

#### *4.2. Evidence from first episode patients*

Results of studies with first episode patients are quite similar to those reported for chronic patients (Table 4). Specifically, findings for whole brain volume reduction are primarily negative (seven out of eight studies), with the exception of one study of adolescent with schizophrenia (James et al., 1999). Additionally, similar to findings for chronic patients, enlarged lateral ventricles are among the most robust findings, with 15 studies reporting positive findings and four studies reporting negative findings (see Table 4; note Lawrie et al., 1999 showed increased third ventricle only). Several investigators have also reported enlarged left temporal horn of the lateral

ventricles (e.g. Bogerts et al., 1990; Degreef et al., 1992a; James et al., 1999), again similar to what has been reported in chronic patients and in post-mortem studies. Clinical correlations have also been reported between enlarged lateral ventricles and poor premorbid functioning (DeLisi et al., 1998), and between enlarged lateral ventricles and increased positive and negative symptoms (Degreef et al., 1992a). Finally, Snyder et al. (1998) reported an association between the absence of adhesio interthalamica, a medial adhesion between the two thalami, and enlarged third ventricle in first episode patients.

With respect to temporal lobe findings, 11 MRI studies have investigated whole temporal lobe volume, five of which report positive findings and six report negative findings (Table 4). When just medial temporal lobe structures are evaluated, the findings are more positive, with five studies reporting differences between schizophrenic patients and controls and one reporting no differences (DeLisi et al., 1991). In studies examining the amygdala and hippocampus separately, eight out of ten studies report hippocampal volume reduction but only one out of five studies report amygdala volume reduction and that is in male schizophrenic patients, only (Gur et al., 2000a;). Additionally, Bilder et al. (1995) reported a correlation between anterior hippocampus volume reduction and neuropsychological measures considered to reflect frontal lobe function. This finding suggests the importance of fronto-temporal connections in the neuropathology of schizophrenia. However, these findings do not appear to be specific to first episode patients diagnosed with schizophrenia, as two studies report hippocampal volume reductions in first episode bipolar patients (e.g. Hirayasu et al., 1998; Velakoulis et al., 1999). In reviewing STG findings, however, Hirayasu et al. (1998) reported left STG volume reduction in first psychotic episode schizophrenics that was not evident in first psychotic episode bipolar patients. Keshavan et al. (1998b) also reported reduced STG volume which reversed over time following psychotropic medications (Table 4).

For MRI studies of the whole frontal lobe, seven out of ten studies showed abnormalities (Table 4). Bilder et al. (1994, 1999) also reported asymmetry abnormalities in prefrontal cortex, and one study reported volume reduction in the cingulate (Ohnuma et al., 1997),

while another study of subgenual cingulate did not (Hirayasu et al., 1999). Additionally, Szeszko et al. (1999) reported right > left orbitofrontal regions with the ratio of right orbitofrontal to dorsolateral volume being correlated with severity of delusions. Gur et al. (2000b) also observed gray matter volume reduction in dorsolateral areas, in dorsomedial areas (males only), and in orbital frontal regions (females only). These prefrontal and orbitofrontal asymmetry findings also favor a neurodevelopmental origin as the sulco-gyral patterns are established in utero.

The corpus callosum, CSP, basal ganglia, thalamus adhesio interthalamica and cerebellum have also been investigated in first episode schizophrenia (Table 4). Three out of four corpus callosum studies report abnormalities, seven out of 10 basal ganglia studies report abnormalities (though these are complicated by the medication status of the patient), three out of three studies of CSP report abnormalities, and one out of two studies report thalamic or cerebellar abnormalities. Finally one study of the adhesio thalamic reports abnormalities in first episode schizophrenic patients (Table 4). MRI findings thus demonstrate that brain abnormalities are present at first episode of illness, and that the brain regions involved are the same brain regions observed in more chronic patients.

#### 4.3. Evidence from longitudinal studies

In reviewing 15 follow up studies, DeLisi and coworkers (e.g. 1992, 1995, 1997) have conducted the most extensive work in this area as part of the Stony Brook First Episode Study (Table 5). In their earliest reports (DeLisi et al., 1991, 1992), no differences in ventricular size were noted between first episode patients and controls, although change in ventricular size was inversely correlated with duration of hospitalization (Table 5). As the subject sample increased, subsequent studies reported enlarged lateral ventricles (e.g. DeLisi et al., 1995, 1997). Interestingly, the rate of change in the left ventricle was greater in the patient group. Patients with the smallest ventricles at baseline had the greatest change in ventricle size, and subjects with larger ventricles at baseline had the worse premorbid social adjustment (DeLisi et al., 1998). These findings were interpreted as indicating that pathologic changes had occurred prior to the onset of psychosis. Finally, Nair and

coworkers (1997) report that patients who showed larger ventricles over time and differed from controls at follow up had a more severe illness and prodromal phase than patients who had larger ventricles than controls, though not statistically significantly so (Table 5). These findings also suggest that ventricle size is not static but rather there appears to be an early enlargement with later stabilization at the larger size. These findings are also consistent with early CT findings of enlarged lateral ventricles which were associated with poorer prognosis (e.g. Shelton and Weinberger, 1986). In reviewing temporal lobe findings (Table 5), we note that DeLisi and coworkers (1997) report no changes over 4 years in the amygdala-hippocampal complex or in temporal lobe volume (DeLisi et al., 1992, 1995). Of particular interest, Gur and coworkers (1998a) report temporal lobe volume changes in both schizophrenics and controls. Keshavan et al. (1998b) evaluated the STG at baseline and then again 1 year later and observed a reversal of the STG volume with neuroleptic treatment (Table 5). As only 11 subjects were included in this part of the study, it will be important to confirm these results in future studies.

Gur and coworkers (1998b) report temporal and frontal lobe volume reduction over time, though the percent difference is quite small (e.g. 4.2% for left frontal and 2.8% for right frontal). Other follow up studies have evaluated basal ganglia structures where increases and decreases in the volume of these structures is complicated by the confound of medication (see previous discussions).

Finally, we conclude this section with a comment on one series of childhood schizophrenia studies that deserve special mention. Rapoport and colleagues (e.g. Jacobson et al., 1996; Rapoport et al., 1997, 1999) have followed a cohort of severely ill children with onset of psychosis before age 12 (Table 5). At a 4 year follow up, these investigators reported that normal controls showed a decrease in cortical gray matter, particularly in frontal and parietal regions (Rapoport et al., 1999). In contrast, the children with schizophrenia showed a marked decrease in frontal areas, greater than controls, as well as a decrease in temporal lobe gray matter. These findings again suggest the importance of fronto-temporal brain regions in the pathophysiology of schizophrenia and also highlight the importance of following normal

populations over time to discern brain volume changes.

#### 4.4. Conclusion

In conclusion, there appear to be progressive changes in the frontal lobes and possibly in the parietal lobes, superior temporal gyrus, and lateral ventricles. Basal ganglia changes seem to be more directly related to type and duration of neuroleptic treatment. Amygdala-hippocampal volume reduction appears not to change over time. In contrast, STG volume reduction does appear to change over time. More work is, however, needed to confirm these important studies, particularly in the temporal lobe region, as findings suggest that treatment intervention may possibly retard the progression of this devastating disease.

#### 5. Summary of MRI findings and future directions for research

Our understanding of the neuropathology of schizophrenia has increased dramatically over the past decade. MRI findings now confirm structural brain abnormalities in schizophrenia. These findings have widened the scope of both clinical and basic science research and have led to an important research focus on the neurobiology of this disorder. MRI structural findings in schizophrenia include: (1) ventricular enlargement; (2) medial temporal lobe involvement (amygdala, hippocampus and parahippocampal gyrus); (3) STG involvement; (4) parietal lobe involvement (particularly the inferior parietal lobule and its subdivision into angular and supramarginal gyrus); as well as, (5) subcortical brain region involvement, including the cerebellum, basal ganglia, corpus callosum, thalamus, and CSP. The pattern and number of abnormalities are consistent with a disturbance of connectivity within and between brain regions, most likely neurodevelopmental in origin.

Several theories have been proposed in an attempt to understand the involvement of such a large number of abnormal brain regions in schizophrenia, many of which are likely highly functionally related. Andreasen and coworkers (1994a,b, 1999), for example, suggest that the 'cognitive dysmetria' of schizophrenia can be explained by abnormalities in the thalamus

and its connections with the cortex and cerebellum. Buchsbaum and colleagues (1990) have focused on abnormalities in the frontal lobes, basal ganglia and temporal lobe connections. In contrast, Weinberger and coworkers (1992; Weinberger, 1987, 1995) describe schizophrenia as a neurodevelopmental encephalopathy and they propose a ‘disconnection model’ to explain how alterations in temporal lobe structures might interrupt connections between the temporo-limbic and prefrontal regions, and vice versa. This model has been extended to basic science studies where these investigators have reported the effect of neonatal lesions on medial temporal lobe structures and their disruption of prefrontal cortical brain regions (Saunders et al., 1998).

Feinberg (1982) proposes that neurodevelopmental abnormalities in schizophrenia result from errors in synaptic pruning that occur at the onset of this disorder, during adolescence and early adulthood. Crow (1990a,b, 1997, 1998) also invokes a neurodevelopmental explanation for schizophrenia but has focused on temporal lobe brain regions that are highly lateralized and important for language production. Our laboratory has also focused on temporal lobe abnormalities as being key to understanding the neuropathology of schizophrenia and we highlight damage to an interconnected neural network that is functionally important for language and associative links in memory as a fundamental defect in schizophrenia (e.g. Shenton et al., 1992, 1997; McCarley et al., 1996, 1999a,b; Nestor et al., 1997). And, finally, Pearlson et al. (1996) highlights heteromodal association areas of the brain as being fundamental to the neuropathology of schizophrenia.

All of these theories have evolved from earlier theories of brain abnormalities in schizophrenia, though confirmation and then refinement was not possible until the application of *in vivo* neuroimaging techniques. This technology, in fact, has led to the most important discoveries of brain abnormalities in the history of research in schizophrenia. Future research studies will include characterizing basic mechanisms using molecular biology techniques and their application to post-mortem brain tissue, as well as animal models of lesions and their effect on interconnected brain regions. Such studies will likely advance our knowledge of the neural circuitry of the brain. Additionally, clinical studies will need to iden-

tify more homogeneous subject groups, evaluate early prenatal and birth history, and follow patients longitudinally from first onset of illness, throughout the life stages, in order to better inform our understanding of neurodevelopmental abnormalities and neurodegenerative changes in the brain.

Future research studies will also need to investigate brain abnormalities in high risk individuals such as family members of patients diagnosed with schizophrenia, as such investigations will likely further our understanding of the genetics of schizophrenia and perhaps suggest which insults or genes result in the development of schizophrenia. While some studies have been conducted in this area (e.g. Seidman et al., 1999), more are needed. Moreover, an investigation of brain abnormalities in individuals diagnosed with schizotypal personality disorder, a disorder which is genetically linked to schizophrenia, will likely be fruitful as these individuals are genetically linked to schizophrenia but the symptoms are more attenuated, and they are not psychotic (e.g. Kendler et al., 1993). And, while work in this area has begun (e.g. Dickey et al., 1999; Siever, 1994), further studies are needed. These individuals are of particular interest since they have generally not been exposed to neuroleptic medications nor have they experienced the effects of chronic hospitalization, both confounds in patients diagnosed with schizophrenia.

In terms of technical advances, the quality of *in vivo* images using MRI has dramatically increased over the past decade. For example, we are now able to evaluate nearly isotropic voxels in brain images (e.g. 1-mm<sup>3</sup>). New segmentation algorithms have also been developed which facilitate the accuracy and speed with which brains can be segmented into gray matter, white matter, and CSF. It will be important for future studies to combine structural and functional measures.

Another important advance will be in measuring brain regions of interest. Specific regions of interest are still generally drawn manually and the process is quite labor intensive. Improvements will include techniques that utilize template driven segmentation based on techniques such as ‘warping’. For example, a brain atlas, with multiple segmented brain regions, will be ‘warped’ into new MRI data sets in order to delineate specific regions of interest (e.g. Anderson et al., 1998; Collins et al., 1992; Evans et al., 1991; Gee et al.,

1993; Iosifescu et al., 1997; Kikinis et al., 1996; Shenton et al., 1995; Tiede et al., 1993). This approach will enable the segmentation of multiple regions of interest in a large number of subjects. Moreover, such an approach will be critical for investigating multiple brain regions in the same subjects rather than being limited to only a small subset of ROI for a given study. Investigators will also be able to evaluate intercorrelations among brain regions. By increasing both the number of brain ROIs and the number of subjects that can be analyzed in a given study, further links may also be made between structural brain abnormalities and clinical and cognitive measures.

Other methods for investigating brain regions in MR data sets, which will be important in future studies, include the use of: (1) artificial neural networks (e.g. Magnotta et al., 1999); (2) landmark based shape analysis (e.g. Arndt et al., 1996; Bookstein, 1991, 1997a,b; Buckley et al., 1999; Casanova et al., 1990; Corson et al., 1999a; DeQuardo et al., 1996, 1999; Tibbo et al., 1998); (3) surface parametrization techniques for shape extraction (e.g. Brechbühler et al., 1995; Narr et al., 2000); (4) skeletonization techniques for extracting shape (e.g. Frumin et al., 1998; Golland et al., 1999; Golland and Grimson, 2000; Näf et al., 1996; Pizer et al., 1998); and (5) high dimensional transformations to extract shape (e.g. Csernansky et al., 1998; Haller et al., 1997). Image averaging (e.g. Andreasen et al., 1994a,b; Wolkin et al., 1998), and voxel based approaches may also be important in future studies defining brain regions (see Pearlson and Marsh, 1999 for a review of the latter approaches).

A focus on shape deformations of brain regions, as opposed to only volume measures, may also provide important information relevant to neurodevelopmental theories of schizophrenia, because such deformations may be associated with neurodevelopmental abnormalities. Support for this hypothesis comes from Van Essen (1997) who has shown that the course of development in cortical-cortical and subcortical-cortical connections determines their pattern of growth and shape.

Another area likely to receive attention in future studies is the evaluation of white matter abnormalities. Many studies have reported gray matter abnormalities in schizophrenia, but few have reported white matter changes. White matter is harder to define and to evaluate

using conventional MRI as it appears uniform and homogeneous. MR brain diffusion tensor imaging (DTI), however, is a new technique that has recently been developed for use with humans which makes it possible to investigate white matter more closely. This technique has been used to evaluate changes in the brain following acute stroke (e.g. Le Bihan et al., 1986; Maier et al., 1998; Moseley et al., 1990; Warach et al., 1992). It has also been used to evaluate brain tumors (e.g. Le Bihan et al., 1986; Hajnal et al., 1991) and normal and abnormal white matter via diffusion anisotropy (Chien et al., 1990; Doran et al., 1990; Douek et al., 1991; Le Bihan, 1995; Peled et al., 1998).

With respect to white matter, MR brain diffusion tensor imaging is well suited for evaluating white matter because water diffusion is restricted by the physical characteristics of the fiber tracts. There are currently only a small number of studies of schizophrenia using this technique. Specifically, Buchsbaum and colleagues (1998) reported diminished anisotropic diffusion in the right inferior prefrontal region in six schizophrenic patients. A study by Lim et al. (1999) reported reduced anisotropy, indicative of reduced white matter integrity in schizophrenic patients compared to controls. Finally, Foong and colleagues (2000b) reported decreased anisotropy in the splenium of the corpus callosum in patients with schizophrenia. Fig. 6 shows an example of MR diffusion tensor imaging which highlights the corpus callosum fibers. These fibers appear as a dense array of tensors that indicate white matter fiber tracts.

DTI may also be combined with magnetization transfer imaging, which makes possible the indirect estimation of protons bound to myelin and cell membranes of white matter (e.g. Foong et al., 2000a). The magnetization transfer ratio (MTR), which reflects the exchange of magnetization between bound protons and free water, is thought to index myelin and axonal integrity. Thus MTR, in combination with DTI, can help to address further specific white matter anomalies which will likely lead to a new understanding of disrupted connectivity in schizophrenia.

Last, and perhaps the greatest recent advance in MRI technology, is functional MRI. One of the most important changes in the last few years has been to move from examining isolated brain regions to examining interconnected neural networks which are likely

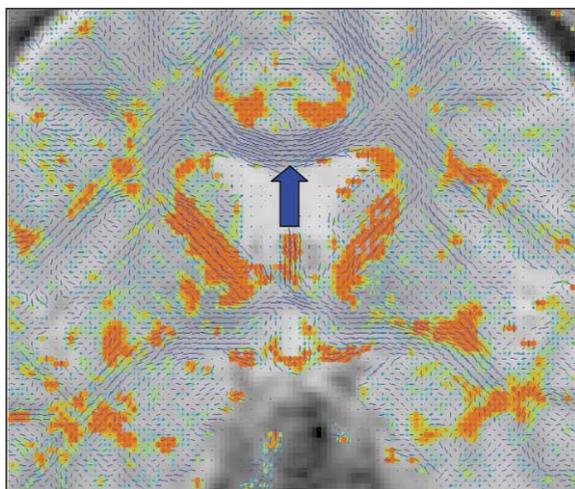


Fig. 6. MR brain diffusion tensor image map of a normal control subject. The diffusion tensor map is displayed as eigenvectors with the blue lines representing the direction of the in-plane components of each eigenvector which correspond to the largest eigenvalue. Note the orientation of the fibers in the corpus callosum which can be readily appreciated. In gray matter, where spherical diffusion is predominant, the eigenvectors points in a random direction. The displayed lines corresponding to the largest eigenvectors are also very short. Harder to visualize are the green and orange colored dots, where the in- and out-of-plane components of the largest eigenvector barely exceed threshold. This figure demonstrates the possibilities that this new technology affords. We call particular attention to the white matter fiber tracts of the corpus callosum, because we think they strongly illustrate the power of this technique in visualizing heretofore unseen fiber tracts in vivo. [Courtesy of Marek Kubicki, M.D., PhD, Clinical Neuroscience Division, Laboratory of Neuroscience, Department of Psychiatry, and Surgical Planning Laboratory, Department of Radiology, Harvard Medical School.]

impaired in schizophrenia (e.g. Andreasen, 1997, 2000; Weinberger, 1996; Weinberger et al., 1996). This move has been significant with the advent of fMRI technology which affords the opportunity to evaluate both brain structure and function more closely. And indeed, many laboratories are developing fMRI technology, which is rapidly changing and evolving, and which has already led to a wealth of new information concerning brain structure and function. [See review by Weinberger et al. (1996)]. fMRI is particularly useful when there is a simultaneous focus on understanding the relationship between normal cognition and functional and neuroanatomical connections. The next decade will likely witness an explosion of new research

from interdisciplinary teams of physicists, cognitive neuroscientists, neuroscientists, psychologists, and psychiatrists, which will likely lead to a greater understanding of the brain mechanisms responsible for observed structural abnormalities in schizophrenia.

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