REVIEW ARTICLE

The Medial Temporal Lobe and Schizophrenia

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INTRODUCTION

Over a century has now elapsed since the search for a neuroanatomical basis of schizophrenia began. In 1897, Alzheimer reported cortical cell loss and gliosis in patients with schizophrenia (1). Other reports of histological abnormalities in the brains of schizophrenics soon followed (2-5). In 1871, Hecker found that the ventricles of schizophrenic patients were enlarged (6), a finding that was later corroborated by other postmortem and by pneumoencephalographic studies (4,7,8). However, the initial excitement of having found a possible organic basis for psychosis was soon replaced by skepticism when later workers could not confirm the earlier reports (9-11). In 1924, Dunlap concluded that there were no abnormalities in the brains of schizophrenic patients that could not also be seen in the brains of normal controls (9). The search for a neuroanatomical basis for schizophrenia seemed over in 1972 when Plum, in a review of the data to date, declared that "schizophrenia is the graveyard of neuropathologists" (12). Further, in 1976, Corsellis reviewed contemporary histological data and concluded that there was as yet no "convincing substrate for the subtle, and often reversible, mental aberrations that go to make up functional psychosis" (13). Nevertheless, in the same year that Corsellis reached this conclusion, Johnstone and colleagues used computed tomography (CT) to demonstrate enlargement of the lateral ventricles in a group of chronic schizophrenics (14). This study confirmed previous pneumoencephalographic findings of enlarged ventricles in schizophrenics (7,8), renewed interest in a pathophysiological basis for schizophrenia, and started a new generation of imaging studies of psychosis.

Over one hundred CT studies on schizophrenia have now been conducted, with 75% of these reporting enlarged lateral ventricles in schizophrenic patients (for reviews see (15,16)). The findings of enlarged ventricles from the CT studies led researchers to wonder whether there was a corresponding loss of tissue matter in the brains of schizophrenics that is diffusely distributed or localized to certain structures. To answer this question, new postmortem studies and *in vivo* magnetic resonance imaging (MRI) studies have been conducted. This paper is a critical review of the evidence that has been obtained through these methods in the area of the medial temporal lobe, focussing on recent data. Findings from several medial temporal lobe structures including the hippocampus, amygdala, parahippocampal gyrus, and entorhinal cortex will be discussed. The current review will also examine the possible association between deficits on neuropsychological tests of temporal lobe function and the underlying structural abnormalities those deficits are assumed to reflect. Lastly, the neuropsychological and structural data that has been acquired in relatives of schizophrenic patients will be examined.

EVIDENCE FROM POSTMORTEM STUDIES

Four different approaches to the study of postmortem tissue have been adopted. These include the study of cell cytoarchitecture (orientation of cell), the classic neuropathological examination, volumetric and area measurements, and the quantification of cell number (Table 1).

Cell Cytoarchitecture

Cellular disarray has been found in the hippocampus (17-19) and the parahippocampal/entorhinal region

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Table 1. Postmortem studies of limbic system structures in schizophrenia.

Authors	Year	Sample	Comment
Scheibel and Kovelman (17)	1981	8 patients	Pyramidal cell disarray in CA1-CA3.
Kovelman and Scheibel (18)	1984	10 patients, 8 controls	Pyramidal cell disarray most pronounced at the CA1-prosubiculum and CA1/CA2 interfaces.
Bogerts et al. (26)	1985	13 patients, 9 controls	i Reduced volume of amygdala, hippocampus and PHG. ii. Only left hemisphere studied.
Falkai and Bogerts (27)	1986	13 patients, 11 controls	i. Reduced left hippocampal volume. ii. Reduced number of pyramidal cells in CA1-CA4.
Jackob and Beckmann (20)	1986	64 patients, 10 controls	i. Abnormal sulcogyral pattern in left temporal lobe ii. Heterotopic neurons in left ENT.
Brown et al. (30)	1986	41 patients, 29 affective disorder	Reduced thickness of left PHG.
Altshuler et al. (22)	1987	7 patients, 6 controls	No significant difference in pyramidal cell disarray.
Colter et al. (31)	1987	17 patients, 11affective disorder	Smaller gyral part of parrahipocampal gyrus.
Falkai et al. (32)	1988	13 patients, 11 controls	Reduced volume of ENT without increased glial cell numbers.
Christison et al. (23)	1989	17 patients, 32 controls	No difference in pyramidal cell size, shape, or orientation.
Jeste and Lohr (28)	1989	13 patients, 16 controls	i. Reduced number of cells in hippocampus. ii. Biggest difference in left CA4.
Altshuler et al. (25)	1990	12 patients, 17 suicides, 10 controls	i. Smaller parahippocampus. ii. No difference in hippocampal volume. iii. Difference in cell shape for both structures in right hemisphere only.
Bogerts et al. (29)	1990	18 patients, 21 controls	Smaller hippocampus.
Heckers et al. (33)	1990	20 patients, 20 controls	No volume reduction in amygdala-hippocampus complex.
Heckers et al. (35)	1990	18 patients, 21 controls	Normal PHG volume.
Benes et al. (24)	1991	14 patients, 9 controls	i. Smaller pyramidal neurons in all sectors of hippocampus. ii. reduced cell number in CA1 only. iii. No cell disarray. iv. No difference in cross sectional area.
Heckers et al. (34)	1991	13 patients,13 controls	i. Tendency toward smaller hippocampal volume. ii. No difference in cell number in hippocampus.
Arnold et al. (21)	1991	6 patients, 16 controls	Aberrant invaginations of the surface, disrupted cortical layers, and heterotopic neurons in entorhinal cortex.
Conrad et al. (19)	1991	11 patients, 7 controls	Bilateral pyramidal cell disarray in CA1/CA2, and CA2/CA3 interfaces.

PHG= Parahippocampal gyrus; **ENT**= Entorhinal cortex

(20,21) of the brains of schizophrenic patients compared with normal controls. Findings of abnormal cellular array have contributed to the adoption, by many researchers, of a neurodevelopmental model of schizophrenia. For example, Kovelman and Scheibel, have suggested that hippocampal pyramidal-cell disorientation in schizophrenia may be due to a prenatal disturbance of neuronal migration in a later phase of cortical development (18). However, not all studies have confirmed the presence of cellular disarray in the hippocampus of schizophrenic patients (22-24). Three factors which may be involved in the variability of findings are thickness of slice, region of hippocampus analyzed (anterior versus posterior), and the patient population under study.

Pyramidal cells are best visualized in slices of approximately 20µm thick since they are about 12 to 20µm in diameter. Studies based on slices greater than 20µm run the risk of neuronal overlap, making delineation of neuronal structure more ambiguous (22). The three studies that found evidence for hippocampal cellular disarray all used slice preparations 20µm in thickness, and found cellular disarray to be most pronounced in the anterior region of the hippocampus (17-19). The two cytoarchitectonic studies that assessed the entorhinal cortex also found abnormalities to be most pronounced anteriorly (20,21). Of the three cytoarchitectonic studies which did not find significant cellular disarray, the first had limited amounts of anterior hippocampal tissue available for study and used 35µm thick slices (22), the second analyzed only the midhippocampus and also used 35µm thick slices (23), and the third study, which used 20µm thick slices, analyzed only the posterior hippocampus (24).

Another difference among the hippocampal studies is the population from which they drew their observations. The three studies that found evidence for hippocampal cellular disarray all studied material from the Los Angeles Veterans Administration Medical Center, where all subjects had a history of multiple hospitalizations and a clear DSM-III diagnosis of chronic schizophrenia (17-19). Conversely, of the three

studies which did not find significant cellular disarray, two used material from the Yakovlev collection where diagnoses of schizophrenia are made retrospectively based on limited case descriptions. For example, Christison et al., were only able to make a diagnosis of schizophrenia based on Research Diagnostic Criteria in half (53%) of the subjects they included as schizophrenics (23). Since it cannot be said with certainty that the material under study was derived from the brains of schizophrenic patients, it is unclear whether the lack of positive findings is due to an absence of cellular disarray or to the subject population from which the material was derived. However, at the same time, since the three positive studies were all from the same laboratory using the same source of brain tissue, the studies can not truly be considered as replicating each other.

Neuropathological Examination

The classic neuropathological examination involves the quantitative measurement of cell size and shape. Investigation of these parameters have only been documented in the hippocampus and parahippocampal gyrus. No conclusions can be drawn since these studies are few and contradictory. Of the two studies assessing the shape of pyramidal cells, one found pyramidal cell shape differences (25), whereas the other found no such differences between schizophrenic patients and normal controls (23). To the current authors' knowledge, only one group has looked at the size of pyramidal neurons. Schizophrenic patients were reported to have reduced neuronal-cell size in all four subfields of the posterior hippocampus (24).

Volumetric and Area Measurements

Reductions in tissue volume of the hippocampal-amygdala complex (26-29), parahippocampal gyrus (25,26,30,31), and entorhinal cortex (32) have all been found in schizophrenic patients in relation to normal controls. When differences are found, these structures are reported to be 20 to 40% smaller in schizophrenic patients. However, a number of studies have reported a lack of volumetric differences in the area of the hippocampus (23-25,33,34) and parahippocampal gyrus (35).

One factor, which may have contributed to the variability of findings, is that different studies often measured and analyzed different subfields of a common structure. For example, Jeste and Lohr found a significant decrease in cell volume only in sector CA4 of the hippocampus (28), while the negative findings reported by Christison et al. are based on the examination of only the CA1 sector of the hippocampus (23). Nevertheless, there is no simple explanation to unite all the discrepant findings since some researchers have found reduced cell volume in all four subfields (CA1-CA4) of the hippocampus (27), whereas others have found that none of the four hippocampal subfields are reduced in volume (34).

Pyramidal Cell Quantification and Density Measurements

Whereas estimates of tissue volume can be skewed by shrinkage during the staining procedure, quantification of the total number of cells is less affected. Reductions in cell number or cell density have been found in the hippocampus (24,27,28) and in the entorhinal region of the parahippocampal gyrus (32), and are most often found to be lateralized to the left. These structures have been reported to contain 20 to 40% fewer cells than those of controls. However, one group did not find significantly reduced cell numbers or density in the hippocampus (34).

Interestingly, Benes and colleagues found 24% fewer neurons in sector CA1 of schizophrenic patients without mood disturbance compared with the number of CA1 neurons in both normal controls and schizophrenic patients with mood disturbance (schizoaffective) (24). Moreover, schizoaffective patients had 36.6% fewer neurons in sector CA3 than did normal controls or schizophrenic patients without mood disturbance. Thus, the location (CA1 or CA3) of pathological change may affect the presence or absence of mood disturbance. This exemplifies the potential importance of differentiating subgroups of schizophrenic patients when investigating the neuropathological substrates of a heterogeneous disease like schizophrenia.

Summary of Postmortem Evidence

Postmortem analyses of medial temporal lobe structures in the brains of schizophrenic patients have yielded conflicting results. Methodological differences between studies are probably at the heart of much of this variability. Lack of sex matching, lack of blind quantification, volume estimations of brain regions based on incomplete hemispheres, and area measurements in one plane only, are all methodological shortcomings capable of introducing variability into the results (36,37). Other sources of error include history of drug use that affect brain structures, time to fixation following death, postmortem shrinkage or swelling of brain tissue, and neuronal atrophy from other complications (for example, vascular disease). Of the six studies assessing the cytoarchitectonics of the hippocampi of schizophrenic patients, three found evidence for cellular disarray and three did not. Cytoarchitectonic

abnormalities occurring in the entorhinal region of the parahippocampal gyrus have now been documented by two separate groups of researchers, and this finding has yet to be challenged. Four of the nine studies which estimated hippocampal volume or area found this structure to be reduced in schizophrenic patients, whereas four of the five studies assessing parahippocampal volume or area reductions found this area to be smaller. Further, the only study to directly assess the entorhinal cortex also found this structure to be smaller. It would seem that anomalies of the parahippocampal gyrus and entorhinal cortex are more consistently found than anomalies occurring in the hippocampus. Furthermore, of the studies that found abnormalities in the hippocampus, the most reliable finding is a reduction in cell number. Three of the four studies looking at this variable found a reduced number of pyramidal neurons in this structure. Thus, the finding that hippocampi of schizophrenic patients contain fewer neurons seems relatively robust, while post-mortem volumetric measurements of the same structure yield less consensus.

EVIDENCE FROM MAGNETIC RESONANCE IMAGING STUDIES

Advantages of using Magnetic Resonance Imaging

Although the ability of MRI to define and measure structures remains inferior to that of postmortem examination, it nevertheless provides particular advantages not offered by either postmortem analysis or CT (Table 2). MRI technology has allowed for the first time the possibility of obtaining high resolution pictures of the living brain. One advantage of *in vivo* analyses is that a clear DSM diagnosis of schizophrenia can be established for subjects prior to scanning. Another advantage of MRI over postmortem techniques is that it avoids problems associated with the preservation and preparation of materials such as the shrinkage of tissue during the staining procedure. Moreover, since schizophrenia is a non-fatal disease with onset generally early in life, brains acquired after death will most likely have been obtained from patients who had been ill for many years or who had committed suicide. In these cases, the neuropathological features of schizophrenia might be obscured by the effects of aging, neuroleptic medications, neuronal atrophy due to other neurological conditions or finally, depression. Non-invasive neuroimaging tools offer the possibility of studying an intact brain. However, not all *in vivo* brain imaging tools offer the same advantages. MRI offers the following advantages over CT: the ability to differentiate gray and white matter, making it easier measure the size of cortical and subcortical structures, as well as lack of radiation exposure, permitting multiple scans of the same individual.

Magnetic Resonance Imaging Studies

Increased size of the lateral ventricles was one of the earliest and most consistent results found in both MRI (38,39) and CT (14,40,41) studies of schizophrenia. Lateral ventricular volume is normally about 2% (15ml) of the total volume of the brain (794ml). In schizophrenia, ventricular volume increases to 3% (25ml) of the total brain volume. Thus, the ventricular enlargement seen in schizophrenic patients is thought to represent a loss of approximately 10ml of brain tissue, which is minute in comparison with the total brain volume. Loss of tissue would be very difficult to localize unless it represented a significant reduction in certain areas, as opposed to more subtle, widespread reduction. The candidate regions were narrowed by a standardized, quantitative postmortem study that reported the temporal horns of the lateral ventricles to be enlarged by 97% (30). This study, as well as other postmortem studies reporting volume loss in limbic structures (reviewed above), led to a profusion of neuroimaging studies trying to assess whether the volume of lost tissue could be localized to medial temporal lobe structures.

Of the 23 neuroimaging studies reviewed, 12 found volume reductions of the amygdala-hippocampal complex and parahippocampal gyrus in schizophrenic patients (39,42-52), whereas 11 other studies were unable to find any significant differences in the volume of mesolimbic structures (38,53-62) (Table 2).

Shenton has pointed out that some of the variability among studies might be accounted for by individual differences in quality of the MRI scanners (63). Scanners vary according to many parameters including thickness of slice and image resolution. The resolution of MRI scans is partially determined by the strength of the scanner's magnetic field, expressed in teslas, with higher field strengths leading to thinner slices and a greater resolution. Estimation of a structure's volume is derived by summing the area measurements of individual slices. Higher quality scanners produce a larger number of thin slices. Therefore, increased resolution of the measurements leads to an increased probability of finding subtle differences in small, irregularly shaped structures. When measuring limbic structures, such as the amygdala-hippocampus complex, 1cm thick slices, offered by a low quality MRI, would permit only three to four slices in which to perform area measurements. In contrast, newer

Table 2. Magnetic resonance imaging studies in schizophrenia.

Authors	Year	Sample	Imaging Parameters	Comment
DeLisi et al. (53)	1988	24 patients, 18 controls	0.5 tesla scanner, 1 cm coronal slice	All limbic areas smaller than in controls but did not reach significance
Kelsoe et al. (38)	1988	24 patients, 14 controls	0.5 tesla scanner, 1 cm coronal slice	Normal amygdala-HIPP complex
Suddath et al. (42)	1989	17 patients, 17 controls	0.5 tesla scanner, 1 cm coronal slice	Smaller amygdala and anterior HIPP
Barta et al. (43)	1990	15 patients, 15 controls	1.5 tesla scanner, 3 mm coronal slice	Smaller amygdala on left
Bogerts et al. (61)	1990	34 patients, 25 controls	1.0 tesla scanner, 3.1 mm coronal slice	Normal HIPP
Suddath et al. (39)	1990	15 patients, 15 controls	1.5 tesla scanner, 5 mm coronal slice	Monozygotic discordant twins: Smaller HIPP in affected twin as compared to normal twin
Dauphinais (54)	1990	28 patients, 28 controls	0.5 tesla scanner, 1 cm coronal slice	Normal HIPP-amygdala complex
DeLisi et al. (55)	1991	45 patients, 20 controls	1.5 tesla scanner, 5 mm coronal slice	No significant difference in amygdala, HIPP or PHG after controlling for total brain volume
Jernigan et al. (44)	1991	42 patients, 24 controls	1.5 tesla scanner, 5 mm coronal slice	Smaller HIPP, amygdala, and PHG
Young et al. (56)	1991	31 patients, 33 controls	0.08 tesla scanner, 1 cm coronal slice	Normal HIPP-amygdala complex
Shenton et al. (45)	1992	15 patients, 15 controls	1.5 tesla scanner, 3 mm coronal slice	Smaller HIPP, amygdala, and PHG on left
Swayze et al. (57)	1992	54 patients, 48 bipolar, 47 normal	0.5 tesla scanner, 1 cm coronal slice	Normal HIPP-amygdala complex
Breier et al. (46)	1992	44 patients, 29 controls	1.5 tesla scanner, 3 mm coronal slice	Smaller amygdala- HIPP complex
Bogerts et al. (47)	1993	19 patients, 18 controls	1.0 tesla scanner, 3.1 mm coronal slice	Smaller amygdala- HIPP complex
McCarley et al. (48)	1993	15 patients, 14 controls	1.5 tesla scanner, 3 mm coronal slice	Smaller amygdala, PHG, and left anterior HIPP
Colombo et al. (58)	1993	18 patients, 18 controls	0.5 tesla scanner, 5 mm coronal slice	Normal HIPP
Rossi et al. (49)	1994	19 patients, 14 controls	0.25 tesla scanner, 3 mm coronal slice	Smaller amygdala, and left anterior HIPP
Zipursky et al. (59)	1994	22 patients, 20 controls	1.5 tesla scanner, 3 mm coronal slice	Normal HIPP, but only looked at mid. HIPP
Howard et al. (60)	1995	31 patients, 35 controls	1.5 tesla scanner, 5 mm coronal slice	After correcting for age, no difference in limbic structures between delusional disorder, schizophrenics, and controls.
Becker et al. (50)	1996	20 patients, 20 controls	1.5 tesla scanner, 4 mm coronal slice	Smaller posterior HIPP
Barta et al. (51)	1997	11 patients, 8 controls	1.5 tesla scanner, 3 mm coronal slice	Smaller ENT and left HIPP
Barr et al. (52)	1997	32 patients, 42 controls	1 tesla scanner, 3.1 mm coronal slice	Smaller left HIPP
Nasrallah et al. (62)	1997	57 patients, 35 controls	1.5 tesla scanner, 5 mm coronal slice	Normal ENT (only structure measured)

HIPP= Hippocampus; **PHG**= Parahippocampal gyrus; **ENT**= Entorhinal cortex

imaging technology permits researchers to obtain slices as thin as 1mm in thickness. Of the studies that found reduced limbic volumes, 75% used slice thickness of less than 5mm; only 18% of negative studies used slices this thin. This informal observation is supported statistically, as negative studies used, on average, slices twice as thick as positive studies (df = 21, $p = 0.013$). Further, the one negative study that did use 3mm slices (59) only assessed the middle portion of the hippocampus, thereby excluding the portions of this structure where pathological changes have been reported to be greatest in schizophrenia (anterior portion including the amygdala). Thus, the studies that fail to report alterations in limbic structures in schizophrenic patients have tended to use neuroimaging tools with thicker slices and lower magnetic field strength and thus may not have had enough power to detect subtle differences between group.

SUMMARY OF ABNORMALITIES IN MESOLIMBIC STRUCTURES IN SCHIZOPHRENIA

An interesting feature from the current analysis of postmortem studies was that, despite the general perception that the hippocampus is the limbic structure most often found to be pathological in schizophrenia, abnormalities in both cell cytoarchitecture and volume or area measurements were most consistently and reliably documented to occur in the parahippocampal gyrus and entorhinal cortex. The most reliable finding in the hippocampus was a reduction in pyramidal cell numbers. A more global analysis of the medial temporal lobe literature reveals that 74% (14/19) of the postmortem investigations and 52% (12/23) of the MRI investigations found abnormalities in one or several limbic structures. Interestingly, all studies that reported reduced volume of limbic structures also found increased ventricular volume when it was assessed.

Sixty percent of studies that did not find reduced volume of limbic structures nonetheless reported ventriculomegaly. This could suggest that although these studies were capable of detecting relatively large group differences such as ventriculomegaly, they may not have possessed enough power to localize more subtle differences, or that, while ventriculomegaly occurs relatively reliably in schizophrenic patients, the localization of volume loss may vary according to schizophrenic subtype or other variable.

NEUROPSYCHOLOGICAL CORRELATES OF TEMPORAL LOBE ABNORMALITIES

A central premise of brain-behavior research is that neuropathological abnormalities, such as cerebral tissue loss, are associated with cognitive and behavioral impairments. Neuropsychological tests permit regional predictions as to the location of pathology because they have been validated on groups of patients with known neuropathic insults. Limbic structures (temporo-hippocampal complex) have been strongly associated with long-term memory formation (64), a function which has consistently been shown to be impaired in schizophrenic patients (65-70).

Despite the strong literature implicating an association between temporohippocampal pathology and memory deficits, results from studies directly assessing this link have been confusing. For example, two studies have reported that although the limbic structures of schizophrenic patients did not differ significantly from those of normal controls, verbal memory was significantly worse (55,58). In the study by DeLisi and colleagues, no correlation was found between hippocampal volume and verbal memory, but parahippocampal volume was significantly correlated with verbal memory (55). Two studies have reported that reduced volume of limbic structures predict frontal rather than hippocampal neuropsychological performance in schizophrenia (71,72). Finally, Seidman et al. found that poor memory performance correlated with a reduction in size of the dorsolateral prefrontal cortex (DLPFC), but this study did not assess the volume of limbic structures (73).

One of the surprising features of these data is that hippocampal volume has been consistently reported to be uncorrelated with memory performance in schizophrenia. Instead, parahippocampal gyrus volume reductions were found to be correlated to poor performance on tests of memory, and tests of frontal functioning. Parahippocampal deficits were also more robust than hippocampal deficits in the postmortem analysis. Another surprising feature of these data was that putative tests of frontal function, such as the Wisconsin Card Sorting Test, were found to correlate with the volume of limbic structures, while memory performance was found to correlate with the DLPFC, a frontal lobe structure. Weinberger's postulation that some of the neuropsychological deficits seen in schizophrenic patients can be understood within the context of a deficient neural system, involving both the DLPFC and temporal lobe structures (74), offers a framework in which these results can be understood. Due to the high interconnectivity among the DLPFC and temporal lobe, a discrete lesion to any component of the circuit could lead deficits in frontal or temporal lobe function. It has been proposed that the parahippocampal-entorhinal complex serves as a gateway for reciprocal hippocampal and neocortical projections (75). Therefore, abnormalities in gateway structures of the circuit may be associated with more reliable and generalized neurocognitive deficits.

In summary, there have been many studies separately reporting either volumetric reductions in limbic structures or deficits in neuropsychological tests of temporal lobe function. The few studies that directly correlated these parameters in schizophrenic patients have offered little evidence for a direct association possibly due to the neuropsychological deficits being more accurately reflected by the parahippocampal gating of DLPFC and hippocampal interconnectivity.

USING TEMPORAL LOBE ABNORMALITIES TO AID IN THE IDENTIFICATION OF GENETIC MARKERS OF SCHIZOPHRENIA

Mesolimbic pathology seems to be intimately involved in schizophrenia. However, the discussion so far has not addressed the genetic components of schizophrenia and how the mesolimbic pathology can be used to assess it. Twin, family, and adoption studies have pointed to important genetic contributions to the pathophysiology of schizophrenia (76-80). Unfortunately, the mode of genetic transmission remains unknown. One approach to identifying the schizophrenic gene is to identify biological or behavioral characteristics indicating an increased predisposition to the disease (81). Once identified and validated, behavioral markers can facilitate genetic linkage studies by identifying carriers who do not express the disorder, such as has been done with smooth pursuit eye tracking deficits (82). To be considered a behavioral marker of genetic risk for developing schizophrenia, a characteristic should be present and relatively stable in schizophrenic patients, less common in patients with other psychiatric illnesses, and present (perhaps in a milder form) in relatives of schizophrenic patients (83).

Interestingly, relatives of schizophrenic patients, including children of schizophrenic patients and adult

relatives of schizophrenic patients, show a pattern of neuropsychological deficits similar to that seen in schizophrenic patients themselves (83). For example, relatives have been reported to have verbal learning and memory deficits such as reduced immediate and delayed free recall of stories (84-87), tasks thought to rely heavily on temporal-hippocampal function. Because memory impairments have been reported to occur in both patients and their relatives, it is possible that the temporal lobe structural pathology existing in schizophrenic patients may also be present in attenuated form in relatives. Unfortunately, to the current authors' knowledge, no post-mortem studies of relatives have been conducted. However, three volumetric imaging studies of temporal lobe structures have been conducted in relatives of schizophrenic patients (54,88,89). Two of these used the siblings as control subjects rather than as the study population (54,88), but the other provided preliminary evidence (n = 6) of reduced hippocampal and amygdala volume in unaffected relatives of schizophrenic patients, along with increased ventricular volume (89). Investigations using CT have shown that ventriculomegaly increases in a stepwise, linear fashion with increasing genetic risk for developing schizophrenia (90,91). That is, ventricular enlargement is greater among those with two affected parents compared with those with one affected parent, and greater among those with one affected parent compared with those with normal parents. Therefore, it may be possible to use mesolimbic pathology in the same manner as smooth pursuit eye tracking deficits were used to refine linkage analyses increasing the chance of finding the schizophrenia gene(s).

CONCLUSION

One of the purposes of the present review was to divide previous postmortem and MRI studies into discrete structure-anomaly categories. Because studies often report many findings at once, regrouping the findings into discrete categories offers a clearer perception of the type of anomaly most often found to occur in a specific structure of interest. Using this technique, the neuropathological findings in schizophrenia strongly suggest that schizophrenic patients have increased ventricular volume as well a possible concomitant reduction in the volume of the parahippocampal gyrus and less reliably, the hippocampus proper.

Because relatives share genetic and environmental influences with schizophrenic patients, many may possess both neuropsychological as well as neuropathological characteristics paralleling those found in schizophrenics themselves. Some of the emerging evidence that schizophrenic patients and their relatives show a similar pattern of deficits on neuropsychological tests of temporal lobe function has been briefly presented. It is suggested that future research address whether relatives of schizophrenic patients have medial temporal lobe structural abnormalities and, if so, whether structural pathology in this region may serve as a marker of risk for the disorder. This can be accomplished by integrating neuroimaging studies of relatives with neuropsychological assessments or with other behavioral markers of genetic risk. A better characterization of the anatomical and behavioral profiles of subjects at increased risk for schizophrenia offers the considerable advantage of providing insight into the genetic contributions to brain abnormalities in schizophrenia and of facilitating the genetic linkage studies that may ultimately identify the loci of genes predisposing to schizophrenia.

ACKNOWLEDGMENTS

This work was supported in part by the National Alliance for Research on Schizophrenia and Depression (NARSAD), the Scottish Rite Schizophrenia Research program, and by the Medical Research Council of Canada.

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