

MAGNETIC RESONANCE IMAGING

IN SCHIZOPHRENIA

by

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ABSTRACT

This work aimed to detect cerebral abnormalities in schizophrenia affecting the volume or T_1 relaxation time of specific anatomical structures.

Sixty-seven schizophrenics under fifty years of age, recruited from admissions to two teaching hospitals, underwent nuclear magnetic resonance scanning at 0.5 Tesla along with thirty-six matched healthy controls. Twenty coronal and twenty-four transverse contiguous slices were obtained and subsequently viewed blind to group status.

Methods of adequate validity and reliability were developed to estimate volumes of the cerebrum, cortex, sulcal fluid, temporal lobes and lateral ventricles, and to measure T_1 times in the centrum semiovale and basal ganglia.

Volumetric data from forty-eight patients revealed a significant increase in sulcal fluid and diffuse reduction in cerebral volume compared to thirty-four controls, using multiple regression to adjust for intracranial volume,. This was primarily due to reduction in cortical rather than subcortical tissue. Patients also had a decreased right temporal lobe volume. These changes bore no close relationship to clinical variables.

Factors that influence T_1 times in normal subjects were identified, through the additional serial scanning of two healthy males, before comparing the patient and control groups. No group difference in either the white matter or basal ganglia T_1 times were found. An animal model was used to assess the effect of neuroleptic drugs on T_1 values over four weeks, and no sustained alteration was seen.

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INTRODUCTION

Structural imaging in schizophrenia had, until the advent of magnetic resonance imaging (MRI), been dominated by the controversy over the presence and possible significance of lateral ventricular enlargement. The study by Johnstone et al (1976), showing a clear increase in the ventricular size of 17 chronically institutionalised male patients, formed an important landmark in this area, and the reasons why it was crucial deserve consideration. As a neuro-imaging result it was not entirely new, having been reported in 18 out of 19 chronic schizophrenics by Jacobi & Winkler (1927) using pneumo-encephalography (PEG). Indeed ventricular enlargement had received comment from a pathologist almost 100 years ago in a single post mortem on a patient with hebephrenia (Hecker 1871). The importance lay more in using the technique of computerised tomography (CT) to demonstrate it, since CT promised access to cerebral structure in a safe and convenient way that would allow research on such patients to become a practical reality. From this vantage point, the existence of structural abnormality in schizophrenia soon became widely accepted, and consequently a major re-evaluation of its aetiology occurred. This attempted to replace the previous division between functional and organic psychoses with more interactive concepts about the brain and the psychological experiences that define this condition. Clearly an understanding of schizophrenia had to involve some appreciation of cerebral structure and function.

However, the repercussions of this work did not stop at this point, since it became apparent that similar structural abnormalities were observed in other psychoses, and that within schizophrenia they were diffuse, variable across individuals and more often

than not showed little association with important clinical features. The need for a much more substantial research undertaking became apparent, and one that had broad implications for much of psychiatry. This was pursued with mounting enthusiasm as new techniques in neuroimaging - magnetic resonance imaging, positron emission tomography, and single photon emission tomography - coincided with the emergence of powerful analytic methods in, for example, neurochemistry and molecular biology.

In consequence, a more reductionist approach rapidly gained greater acceptability within psychiatric research as a whole, but in many respects schizophrenia stands out as the clearest example of this change. This heralded the astonishing expansion of the neurosciences, and provided the challenge as to whether such an approach could trace links that connected the genome right through to aspects of subjective mental experience, thereby combining scientific curiosity with potentially immense therapeutic benefit. Neuro-imaging research into schizophrenia provides details about only one part of an undoubtedly large picture, but its claim for further attention nonetheless remains clear.

The advantages of MRI over CT for structural imaging were apparent soon after its introduction to clinical research six or seven years ago. Finer detail in terms of spatial resolution and tissue discrimination, imaging in any plane rather than just the transverse one, and absence of artefact in the image caused by the skull were usefully combined with a high degree of safety that permitted repeat scanning as required. The present study was therefore undertaken to see if these aspects of MRI could be translated into fresh insights about brain structure in schizophrenia. As exemplified by Johnstone et al (1976), it is often the incorporation of a new technology giving a sudden change of emphasis that takes important ideas, which in retrospect were

waiting in the wings, and moves them to the centre of the stage. It was our hope that the use of MRI as opposed to CT might accomplish a further such shift.

The aims of this work included the identification of any focal lesions in grey or white matter, the volumetric measurement of different anatomical structures, and the possible identification of diffuse tissue abnormalities. It was seen as advantageous to acquire all these different measurements from the same sample, in order that they could then be compared within individuals if necessary. In view of recent neuro-pathological findings the structures of particular interest were the temporal lobes and hippocampal region. Volumes that had not previously been examined quantitatively, such as the cortex and Sylvian fissures, were to be included through the use of image analysis computer programs. Care was to be taken in avoiding the technical weaknesses of earlier MRI studies.

The control group was to be formed of healthy subjects, the first step being to see what distinguished schizophrenics from normal individuals, with the intention of later including a psychiatric control group if the specificity of any abnormality required clarification. Attention was to be devoted to the controls in order to understand more clearly those factors that influenced the normal range of values. Adequate sample size was also regarded as essential if the study was to achieve a respectable level of statistical power. Any detected abnormalities might then be found to bear upon relevant clinical characteristics, in particular those that implicated aetiology or outcome. In this respect, possible differences according to genetic liability were to be contrasted by only including those patients with a family history of schizophrenia or those with a definite absence of any psychotic or major affective disorder in their immediate relatives. Patients with both acute and chronic illness were included, to

appreciate which structural changes varied with duration of illness, and only cases with typical schizophrenia examined so that results could be generalized to the wider population.

This thesis therefore introduces MRI in schizophrenia through an overview of the CT literature, recent neuropathological findings and functional neuroimaging, followed by a more detailed review of MRI studies to date. Next the technique of MRI is described in some detail, in order to highlight some of the methodological problems encountered, before eventually presenting the main study itself.

LITERATURE REVIEW

CHAPTER 1 BACKGROUND RESEARCH RELEVANT TO MRI IN SCHIZOPHRENIA

1. ESTABLISHING THE PRESENCE OF STRUCTURAL CHANGES IN THE BRAIN : PEG AND CT STUDIES

Lempke (1935), following on from Jacobi & Winkler (1927) in the use of PEG, recorded the presence of lateral ventricular enlargement in a larger sample of 100 schizophrenics and related it to poor outcome and personality disintegration. This was confirmed in a more refined study by Huber (1957), where two thirds out of 190 schizophrenics had enlarged ventricles, and a classic PEG study by Haug (1962) on 101 patients where 58% had abnormalities that consisted largely of diffuse symmetrical ventricular enlargement. In both these studies, the extent of the changes was related to the severity of dementia and personality disintegration shown.

However, neuropathologists repeatedly failed to find any substrate for these abnormalities, and an impasse seemed to have been reached by the time of the First International Congress of Neuropathology in 1952. At this point, the case for continued neuropathological inquiry rested mainly on these PEG findings, although it was supported by the known genetic contribution to aetiology and a strong neuroscientific tradition in European psychiatry. During the late 1950's and throughout the 1960's, although the prevailing opinion about schizophrenia centred on sociological and psychological factors, there emerged an interest in the neurodevelopmental aspects of various psychiatric disorders, both in children

(Pasamanick 1960) and in adults (Fish 1957). The latter study was the first of several "high risk" samples which intended to gather prospective information on the children of schizophrenic parents until they had passed the age of risk for developing the condition themselves. Also a spate of studies suggested that obstetric difficulties attended the birth of people who later developed schizophrenia (Lane & Albee 1966; Pollack et al 1966, 1968; Woerner et al 1971, 1973). At the same time, improved agreement about the diagnostic criteria for schizophrenia occurred, partly as a consequence of the International Pilot Study of Schizophrenia (World Health Organization 1973).

In this setting, the findings of Johnstone et al (1976), where almost complete separation was obtained between the ventricular size of schizophrenic patients and controls, confirmed the previous PEG results and gave renewed impetus to exploring any possible cerebral pathology. Their finding that poor cognitive function was related to ventricular enlargement also offered hope of a better understanding of important clinical features. There ensued numerous attempts at replication, excluding any patients with suspected organic damage, of which most were positive although one early failure by Jernigan et al (1982) was notable for its sound methodology. The most frequent measure of structural abnormality was the cross-sectional area of the lateral ventricles at their largest expressed as a ratio to the intra-cranial area on the same slice, the ventricular-brain ratio (VBR). Essentially the mean VBR of a schizophrenic group was found to be significantly greater than that of healthy controls. However reports also appeared of widened cortical sulci, enlargement of the third and fourth ventricles, and cerebellar atrophy (Shelton & Weinberger 1986; Iacono et al 1988; Pfefferbaum et al 1988). The methodological pitfalls were most thoroughly

explored with VBR (Jacobson et al 1985), and it is to this measure that greatest confidence can be ascribed.

It became clear that, in mixed samples, there was substantial overlap in VBR between schizophrenic and affective psychoses (Nasrallah et al 1982; Weinberger et al 1982; Rieder et al 1983; Pearlson et al 1985), and also between such patients generally and healthy controls (Nyback et al 1982; Weinberger et al 1982; Kemali et al 1987; Iacono et al 1988). This overlap might, to some extent, depend on the the sampling procedure of controls (Raz et al 1988; Smith et al 1988), but it is now certain that a wide scatter of values is intrinsic to all groups. The proportion of schizophrenic cases deemed to have such a structural abnormality varied from one sample to another, but appeared to be about a quarter to a third overall. Taking into consideration the numerous studies to date, the finding of increased mean VBR in schizophrenia can be regarded as robust.

2. ASSOCIATIONS OF AN INCREASED VBR

The importance of establishing abnormal cerebral structure in schizophrenia cannot be overemphasised, but the clinical phenomena that related to an increased VBR proved difficult to pinpoint. Cognitive impairment, negative symptoms, and poorer outcome were each related to a large VBR in a number of studies (Pearlson et al 1985; Goetz & van Kammen 1986; Shelton & Weinberger 1986; Kemali et al 1987; Goldberg et al 1988; Keilp et al 1988; Lawson et al 1988), but opposing findings were not uncommon (Nasrallah et al 1983a; Owens et al 1985; Losonczy et al 1986; Farmer et al 1987; Serban et al 1989). One can note that the striking results of the initial study by Johnstone et al (1976) were obtained from long stay male patients showing clear cognitive impairment. This non-specificity in respect of clinical phenomena is partly explicable by the intrinsically wide scatter of VBR across different individuals, unrelated to any pathology. The relationship of increased VBR with poor outcome is the most consistent of the clinical associations observed so far, with Huber (1975) in particular conducting a unique 20 year clinical follow up on his own PEG sample to find that initial ventricular enlargement predicted subsequent poor outcome.

More intriguing and resilient results, however, have come from enquiry into the origin and natural history of ventricular enlargement. Given the traditional Kraepelinian position that schizophrenia is a deteriorating condition the initial assumption was that any structural changes would increase with time in each individual. This stance appeared consistent with the tendency for chronic institutionalised samples to show larger mean VBR than those in the earlier stages (Shelton & Weinberger 1986), although VBR enlargement had still been found in outpatients and those with acute illness (Nyback et al 1982; Weinberger et al 1982; Cazullo et al 1989). Yet there was

a failure to correlate VBR with illness duration, which led to questioning whether the increase in VBR perhaps reflected some developmental hypoplasia rather than progressive atrophy. If this were true then ventricular enlargement could be most frequent in chronic samples simply because, as Huber (1975) had found, it reflected a poor prognosis from the outset; yet it would remain static throughout the duration of each individual's illness. The effects of electroconvulsive therapy or neuroleptic medication have not been proven relevant to the interpretation of such data.

It is instructive to look back at the PEG studies, where one finds that lack of progression was the general rule. Lempke (1935) included 6 patients from the earlier sample of Jacobi & Winkler (1927), concluding from their lack of radiological change that a congenital anomaly was responsible, whilst Haug (1962) re-examined 31 of his original 101 patients up to 4.5 years afterwards and noted further enlargement in only 4 cases. Huber (1957) repeated scans in 27 patients up to 5 years later and found further increase in 8 that corresponded with a decline in their clinical state, suggesting that perhaps a small sub-group do show progression. There have also been five CT studies that looked at this question through follow-up and re-scanning of patients over 3-9 years to detect any progressive enlargement (Nasrallah et al 1986a; Illowsky et al 1988; Reveley 1988; Vita et al 1988a; Kemali et al 1989). Although sample size has been smaller than the PEG studies it was again the exception rather than the rule for any such change to occur, with only eight patients in total showing an increase in VBR of over 50%.

If these alterations were indeed static, then they must be present at the clinical onset of schizophrenia. To test this idea eight studies have included patients in their first episode (Benes et al 1982; Weinberger et al 1982; Schultz et al 1983; Woods &

Woolf 1983; Owens et al 1985; Turner et al 1986; Iacono et al 1988; Lieberman et al 1989), and all except two found enlarged lateral ventricles. Benes et al (1982) found no difference from controls, while Iacono et al (1988) found enlargement of the third rather than the lateral ventricular space.

One fact thought to be relevant to these structural abnormalities is the excess of adverse antenatal and perinatal events in people diagnosed schizophrenic in adult life. This is important because it implies that aetiological agents may be operating much earlier in life than was previously thought. Early developmental disturbance is also supported by the epidemiological fact that a birth excess in late winter of approximately 7-15% is seen in schizophrenia, which has so far survived all attempts to dismiss it as artefactual (Bradbury & Miller 1985). Retrospective data on such events remains of dubious validity, although O'Callaghan et al (1990) provide evidence that maternal recall is accurate over several decades, but fortunately several studies also exist where information collected at delivery was still available (Lane & Albee 1966; Woerner et al 1973; McNeil & Kaij 1978; Jacobsen & Kinney 1980; McNeil 1988; Eagles et al 1990). Usually various different events such as pre-eclampsia, perinatal hypoxia or low birthweight have been grouped into some overall measure of "obstetric complications". Although no specificity as to the nature or timing of such events has been identified, there is a surprising consensus that they have an excess frequency in schizophrenic patients.

One of these prospective studies (Silverton et al 1985) has included CT scanning and, although it had only 10 subjects, it revealed a strong association between enlargement of adult VBR and low birth weight ($p=0.001$). However, other groups have produced conflicting results as to whether or not obstetric complications are related to CT

changes, using either retrospective data specifically obtained by maternal interview (DeLisi et al 1986; Hubner et al 1988; Reddy et al 1989) or simply taking routine casenote entries (Owens et al 1985; Pearlson et al 1985; Williams et al 1985; Turner et al 1986; Owen et al 1988). Thus, while the increased frequency of obstetric complications is confirmed, their relationship to CT changes remains uncertain.

3. NEUROPATHOLOGICAL RESEARCH

The incentive for neuropathologists to renew their interest in schizophrenia depended largely on the demonstration of these structural changes by CT scanning. Previous work had concentrated mainly on the neocortex, due to the influence of Kraepelin and the results achieved in Alzheimer's disease, whilst subcortical structures had been neglected as their relevance to higher mental functions lay unappreciated. Building on the work of Papez (1937) and Maclean (1952), the importance of the limbic system in understanding emotion and memory, and its relevance to psychiatric disorders like schizophrenia, had gradually become more apparent during the interim period. It was therefore natural that, once interest was reawakened, it should centre more on limbic structures, situated as they were near the ventricles.

The past five years have witnessed a remarkable surge of interest as new techniques and fresh ideas have been productively pursued. It now appears highly likely that in schizophrenia parts of the limbic system contain fewer neurones, most notably the hippocampus (McLardy 1974; Falkai & Bogerts 1986; Jeste & Lohr 1989) and parahippocampal gyrus (Brown et al 1986; Falkai et al 1988a). This is reflected macroscopically in reduced volume of these two areas (Bogerts 1985; Brown et al 1986; Colter 1987; Altshuler et al 1988; Falkai et al 1988a; Jeste & Lohr 1989; Bogerts et al 1990a) with a corresponding increase in the volume of the temporal horn, particularly on the left (Brown et al 1986; Crow et al 1989). Limbic structures closely related to the hippocampus also reveal abnormalities - notably reduced granule cells in the dentate gyrus (McLardy 1974; Falkai & Bogerts 1986), neuronal abnormalities in the cingulate gyrus (Benes 1986,1987) and reduced volume of both the internal globus pallidum (Bogerts et al 1985; Bogerts et al 1990a) and amygdala

(Bogerts et al 1985). There does not appear to be any consistent abnormality in the thalamic nuclei or corpus striatum (Lesch & Bogerts 1984; Brown et al 1986; Lantos 1988).

Moreover a reduced total brain weight/volume, first described by early pathologists like Southard (1910) and Lewis (1923), has been recently replicated by Brown et al (1986), Pakkenberg (1987) and Bruton et al (1990). Indeed the sulcal prominence repeatedly observed on CT scanning (Shelton & Weinberger 1986; Pfefferbaum et al 1988; Rossi et al 1988a; Stahl et al 1988; Vita et al 1988b; Scottish Schizophrenia Research Group 1989) clearly implied that, provided intracranial volume remained unaltered, there ought to be some measurable loss of brain tissue. The hippocampal and parahippocampal reduction was far too small to account for this, implying that there was some other area(s) additionally involved. Macroscopic focal pathology has been occasionally identified in these post-mortem studies, but does not appear to be either a typical or prominent feature of schizophrenia .

The finding of neuronal loss in the limbic system, and possibly elsewhere, has to be explained in terms of either an acquired or developmental lesion. Gliosis is one of the usual sequelae following neuronal damage (Duchen 1984), and this gliotic response is usually fully established during early postnatal life (Kolb et al 1983; Oyanagi et al 1986). Gliosis, measured using quantitative methods such as glial fibrillary acidic protein (GFAP) immuno-cytochemistry, appears to be absent in schizophrenia (Benes et al 1986; Falkai & Bogerts 1986; Roberts et al 1986, 1987; Stevens et al 1988; Casanova et al 1989), suggestive of some developmental disorder, although this absence of gliosis is not accepted universally (Stevens et al 1982; Stevens et al 1988; Bruton et al 1990).

This line of argument favouring a neurodevelopmental failure appears persuasive, given the non-progressive changes on CT identified at illness onset and the evidence to implicate obstetric complications. Further support comes from two studies that reputedly show disorganization of the customary pyramidal cell arrangement in the CA1/CA2 region of the hippocampus (Scheibel & Kovelman 1981; Kovelman & Scheibel 1984), although failures to replicate this finding have also appeared (Altshuler et al 1987; Christison et al 1989). Jakob & Beckmann (1986), examining the nearby entorhinal cortex of the anterior parahippocampal gyrus, found heterotopic pre-alpha (layer II) neurones that would similarly point to some early disturbance of neuronal migration, and this result has received some confirmation (Falkai et al 1988b).

Following close behind these neuropathological results have been neurochemical studies engaged in disentangling, from the plethora of neurotransmitter systems, those which may show a primary disturbance. Attention is now concentrated in particular on the hippocampus and amygdala. Dopamine still retains a position of active interest, and Reynolds et al (1988) have replicated their earlier finding (Reynolds 1983) that in post-mortem schizophrenic brain it is increased over control levels only in the left amygdala and not the right, but nonetheless interest has moved elsewhere - particularly to the glutamate and γ -aminobutyric acid (GABA) systems.

Reynolds & Czudek (1990) reported bilateral reductions in GABA uptake sites of the hippocampus, particularly on the left where it correlated with amygdalar dopamine levels, and Deakin et al (1990) have confirmed this loss of GABA uptake sites in the hippocampus. Deakin et al (1988) also reported amygdalar asymmetry in the glutamate system, with reduced aspartate uptake on the left; the same system shows

hippocampal asymmetry in having reduced kainate receptors and D-aspartate uptake sites, again on the left side (Kerwin 1988, 1990; Deakin et al 1990). Such results continue to sustain the idea that schizophrenia is peculiarly associated with left hemisphere dysfunction, originally proposed by Flor-Henry (1969)

Cholecystokinin, a peptide neurotransmitter that is often localised in the same neurones as dopamine, apparently shows a substantial loss from the hippocampus of post-mortem schizophrenic brain (Ferrier et al 1983; Farmery et al 1985) although one negative study appears to contradict this result (Kerwin 1990).

So far the existence of neuropathological abnormalities has been almost solely restricted to the temporal lobes, despite additional evidence in schizophrenia strongly suggestive of frontal lobe disorder. This includes the presence of abnormal smooth pursuit eye movements (Holzman et al 1984), controlled to a large degree by frontal areas of cortex, and impairment on psychological tests that are relatively specific for frontal lobe performance (Goldberg et al 1989; Williamson et al 1989), as for example in the Wisconsin Card Sort Test. Some frontal lobe syndromes also bear a clinical resemblance to the negative symptoms of schizophrenia. The only consistent neuropathological finding described in the frontal lobes has been a glutamatergic system abnormality, involving increased kainate receptors (Nishikawa et al 1983; Deakin 1988; Toru et al 1988) and reduced N-methyl-D-aspartate receptors (Kornhuber 1989). It is of note that there is reciprocal control exerted between the dopamine and glutamatergic systems, so that this frontal glutamatergic abnormality may be related to distant dysfunction in the mesolimbic dopamine system.

4. FUNCTIONAL NEURO-IMAGING

Based on the premiss that mental phenomena relate somehow to brain function, the goal of structural imaging must eventually be to move from a morphological brain abnormality through to its functional consequences. There are three different techniques used in functional imaging, which will be briefly described before moving on to the results obtained with them.

The oldest is the ^{133}Xe inhalation technique, where ^{133}Xe carried in the blood was detected by means of a static gamma camera and cortical blood flow measured. This provides useful information about cerebral function since it is known that regional blood flow to the cortex relates closely to cortical neuronal activity (Kety 1985). This inhalation technique is insufficient for acquiring three dimensional information, as the ^{133}Xe remains within the vascular compartment and passes rapidly through the brain. More recently, however, γ -emitting substances have been developed that pass from the blood into cerebral tissue where they persist and allow the entire brain to be imaged. By detecting γ -rays tomographically the technique of single photon emission tomography (SPET) has been developed to produce such three dimensional images. The third method available for functional imaging has been positron emission tomography (PET), where positron emitting substances are used instead of γ -emitters. Again a tomographic method is employed to acquire three dimensional images but, because of the physics of positron behaviour, it has the advantage over SPET of superior spatial resolution. Using radiolabelled glucose or ^{15}O allows metabolic rates to be calculated by PET scanning, and this capacity to yield absolute rather than just relative metabolic rates is another advantage it possesses over SPET. Since positron

and γ -emitter studies are fundamentally different techniques any congruent results obtained from both would be difficult to dismiss as machine artefact.

Ingvar & Franzen (1974) were the first to report a functional imaging abnormality in schizophrenia, using the ^{133}Xe inhalation technique to record regional blood flow. In normal subjects there was a relatively greater flow to the prefrontal cortex, whereas in patients this relative excess was attenuated (a "hypofrontal" pattern). This finding was ignored for almost a decade but has since been well replicated, not only with ^{133}Xe inhalation (Chabrol et al 1986; Guenther et al 1986; Weinberger et al 1986; Geraud et al 1987; Berman et al 1989), but also more recently by both SPET (Raese et al 1989; Sagawa et al 1990; Vita et al 1990) and PET (Jernigan et al 1985; Wolkin et al 1985; Cohen et al 1987; Volkow et al 1987; Weinberger et al 1988; Wolkin et al 1988; Buchsbaum et al 1989).

Indeed, hypofrontality is the only well substantiated abnormality on functional imaging in schizophrenia and, in contrast to the neuropathological data, this fits comfortably with other evidence for frontal lobe dysfunction. Studies that report this finding tend to activate the frontal cortex with specific cognitive tasks, such as the Wisconsin Card Sort Test, rather than measure a simple resting state (Weinberger et al 1986; Cohen et al 1987; Duara et al 1987; Volkow et al 1987). A clinical association between the degree of hypofrontality and both negative symptom severity (Ingvar & Franzen 1974; Volkow et al 1987; Wiesel et al 1987) and long duration of illness (Sheppard et al 1983; Widen et al 1983) has been noted. It also seems to vary with the severity of positive symptoms, such as hallucinations and delusions, as well as negative ones (Hawton et al 1990; Paulman et al 1990).

The question naturally arises whether or not this is just a drug-induced phenomenon. In drug naive patients hypofrontality has been demonstrated by ^{133}Xe (Guenther et al 1986; Geraud et al 1987) but not so frequently on PET (Sheppard et al 1983; Early et al 1987; Cleghorn et al 1989). Anxiety increases resting cortical metabolic rate on PET (Gur et al 1987; Volkow et al 1987), so these negative results may be partly due to examining acute patients who are over aroused by psychotic experiences. Indeed, chronic patients who showed a hypofrontal pattern in remission have been seen to lose this if re-scanned during an acute relapse (Geraud et al 1987; Warkentin et al 1990). Antipsychotic drugs are an improbable explanation for a hypofrontal abnormality since serial studies before and during treatment show increased prefrontal flow after starting medication (Wolkin et al 1985; Berman et al 1986; Volkow et al 1986; Buchsbaum et al 1987). Despite an initial finding of increased D_2 receptor density in drug naive patients (Wong et al 1986), it has subsequently been reported that such patients have normal D_2 receptor density (Farde et al 1987, 1990; Martinot et al 1990).

Reduced cerebral blood flow is also seen in unipolar and bipolar affective disorders (Guenther et al 1986; Baxter et al 1989; Sackheim et al 1990), but whether a hypofrontal pattern is seen to the same degree as in schizophrenia remains controversial (Baxter et al 1989; Buchsbaum et al 1989).

A few studies have attempted to relate the degree of hypofrontality to structural abnormalities in the same patients. Increased VBR on CT has been found to associate with it (Berman et al 1987; Smeraldi et al 1987; Vita et al 1990), but not all studies confirm this relationship (Wiesel et al 1987; Wolkin et al 1988). Broadly speaking, the results from neuropathology and functional neuro-imaging show an intriguing split between purely functional deficits in the frontal cortex and structural ones in the

subcortical limbic system of the temporal lobe. Neurotransmitter abnormalities seem to side mostly with the latter. The one slight reconciliation on offer is that CT abnormalities do include sulcal enlargement over the frontal lobes, as well as other cortical areas, suggestive of some structural change in the underlying brain. The results that have accrued from MRI will therefore be reviewed, to see if further light can be thrown on the extent and significance of these changes.

CHAPTER 3 MAGNETIC RESONANCE IMAGING IN SCHIZOPHRENIA

1. GENERAL INTRODUCTION

This review will cover all work that deals with MRI in adults or adolescents with schizophrenia. Clinically there are some similarities between infantile autism and schizophrenia, but MRI in autism has been largely devoted to cerebellar and brainstem abnormalities not so far detected in schizophrenia (Courchesne et al 1988; Gaffney et al 1988; Garber et al 1989a) so they will not be discussed further. Neither will results from patients with dementia, since they are dominated by pathological effects that have little relevance to schizophrenia. Localized spectroscopy has so far only generated two preliminary reports in schizophrenia (Keshavan et al 1989; O'Callaghan et al 1989). The only other psychiatric patients with any body of MRI research are those with affective disorders, and these results will be compared where possible to those of schizophrenics. On the whole, MRI studies are concerned with distinguishing schizophrenics from healthy controls, and the issue of which changes are specific to schizophrenia, as opposed to affective psychoses, or other psychiatric disorders, has only been approached in two studies so far (Hauser et al 1989; Johnstone et al 1989a).

The majority of studies have concentrated on structural measurements rather than relaxation times or signal intensity. In most cases these have been acquired by tracing manually around certain structures, on either films or at a computer console, and then

using a planimeter or the computer to calculate the enclosed area. Such techniques are familiar from previous methods used in CT imaging. However, the use of computers to undertake such tasks is now starting to make its presence felt, particularly as volumetric measurements require the analysis of many slices instead of just one. Surprisingly, a systematic and detailed visual assessment has only been given for two samples (Johnstone et al 1986; Waddington et al 1990); the results, coupled with the notable absence of visible lesions mentioned in other studies, has reinforced post-mortem findings that macroscopic focal pathology is not characteristic of schizophrenia, although it can be seen in a minority of cases (Bruton et al 1990).

The measurement of relaxation times or signal intensity is usually straightforward, made by outlining a small part of an image that contains the relevant tissue and simply recording its mean value.

As with many new technologies introduced into psychiatric research, the initial studies were generally carried out with small samples and poor quantification, in a hurried attempt to reveal any obvious abnormality. As this hope receded so awareness of the necessity for careful methodology has again become apparent. In most studies the need is acknowledged for careful matching of controls to patients, excluding unsuitable subjects and measuring blind to diagnosis, but the technical errors that may be encountered in MRI measurements appear to be widely omitted from consideration. These will be discussed later, after the principles of MRI have been outlined. However, the review is prefaced by a brief discussion of two additional areas of methodological concern, unrelated to the technique of MRI. These involve the definition of normal values for any particular measurement, and the use of statistical inference in such a way that valid conclusions can be drawn.

Normal values

An important concern at the present time is to define the range of normal variation in the general population for each particular measurement. This involves the identification of factors such as age, gender or height having a major influence upon the characteristics being measured, and avoiding distortion from an inappropriate selection procedure such as including medically screened healthy controls. One of the lessons from CT research into schizophrenia has been that control groups need to be carefully studied if any differences between them and the patients is to be reliably demonstrated and understood. The small number of controls in some studies often precludes any accurate estimate of the normal distribution, and details of how controls as well as patients were sampled, and the exclusion criteria applied, are often too sparsely described to allow evaluation of possible selection bias.

In the absence of such normative data it is clearly essential to either match controls and patients for variables that are assumed to be important or else allow for them in the analysis. Such variables have usually included age and sex, occasionally handedness, and more recently social or educational level. The latter is problematic in that premorbid social and educational level are often impossible to gauge given the insidious onset of symptoms during adolescence, and the childhood social and cognitive impairments that precede schizophrenia more commonly than in the general population; a more appropriate matching might be on parental social/educational level. Some variables such as alcohol intake or racial group, that may have an important influence, are infrequently mentioned. A few studies included subjects over the age of 50 years which may introduce the effects of ageing into measurements (Matthew et al 1985a; Besson et al 1987a; Hauser et al 1989).

Statistical analysis

With a large number of structures available to measure in several different ways there is often a large data set to handle, and certain difficulties are commonly encountered in this area. The situation is compounded if there is no clear hypothesis about how patients and controls will differ on each variable.

This usually leads to one of two approaches. The first is to compare the two groups on each measurement separately, which involves an increased risk of falsely regarding a finding as significant (type I error) unless a reduction is made in the significance level, as in the Bonferroni correction (Grove & Andreasen 1982). Such a correction is desirable but does increase the opposite risk of missing a genuine difference (type II error), particularly if the sample size is small. To alert one to this possibility, the 95% confidence limits for each comparison may be useful. The most frequent weakness is that results have been reported as "significant" without correction for multiple testing, and negative results rarely include any confidence limits to assess their degree of certainty.

The second approach is to enter all the measurements into a multivariate procedure, such as a multivariate analysis of variance (MANOVA) or a multiple regression, and make one overall group comparison. There are, however, certain assumptions about the data that underlie such procedures, the most common of which are that (a) each variable is normally distributed with any two variables having a bivariate normal distribution and (b) that they share similar variances. Multivariate tests are often sensitive to the influence of extreme values. Deviation from these assumptions does not automatically invalidate a procedure, but tolerance to such deviations will vary according to the test employed and the assumption in question. Given this situation

the use of a multivariate procedure should be accompanied by some evidence that the data has been examined with its validity in mind. Again most of the studies reviewed here do not acknowledge this need, even to the extent of showing that the data was parametric, which weakens the strength of their conclusions. Another limitation on multivariate procedures is that of sample size in relation to the number of variables being examined. There should usually be at least three times as many subjects as variables, which is a requirement met by most but not all studies.

In general it would seem appropriate to use a single multivariate analysis in preference to several univariate tests, particularly if variables relate to the same structure. If multiple testing is made without a previous multivariate procedure then a corrected significance level is indicated, with confidence limits given as appropriate. Problems can often be avoided by adequate sample size and parsimony with the number of variables measured in the first place.

The structural abnormalities addressed by MRI can be placed into the broad anatomical categories of the cerebrum, the temporal lobes and their associated limbic structures, the frontal lobes, the midsagittal corpus callosum, and the ventricular system.

2. ASSESSMENT OF CEREBRAL SIZE

A question mark has lingered for many years over whether or not the entire cerebrum is of normal size in schizophrenia, and neuro-imaging has offered an alternative approach to post-mortem work in the search for an answer. Evidence from the latter that the brain is indeed smaller than average (Brown et al 1986; Pakkenberg et al 1987; Bruton et al 1990) suggests there is a 4-8% reduction in brain weight. Most CT studies have, in general, omitted to report this measure in favour of area ratios, but two recent reports (Johnstone et al 1989b; Pearlson et al 1989) have commented on reduced cerebral area. Care should be taken to distinguish cerebral from intracranial size, as the erroneous implication that they are equivalent only serves to confuse discussion about any abnormality of cerebral size. On CT scans intracranial area is a far more accessible measurement than cerebral area, whereas the standard MRI measurement in schizophrenia appears to be cerebral area or volume. The one exception in MRI has been Andreasen et al (1986,1990), who reported both intracranial and cerebral areas.

Most MRI studies have taken cerebral area on a single slice as an acceptable measurement of its overall size, an assumption that has received less criticism than it perhaps deserves. From such area measurements there appears to be little support that cerebral size is reduced in schizophrenia (Tables 1 and 2), with eight out of nine studies reporting no significant difference (Smith et al 1987a; DeMeyer et al 1988; Coffman et al 1989; Hauser et al 1989; Johnstone et al 1989a; Stratta et al 1989; Andreasen et al 1990; Rossi et al 1990), but if the effect is small it may not be easily detected on single slice images. None of these studies give confidence limits for their negative findings, which would be of great assistance in knowing how large a

difference could be excluded. The remaining study (Andreasen et al 1986) showed a decrease, and the controversy that arose over this result led to several unsuccessful attempts at replication, both on CT (DeLisi et al 1987; Reveley & Reveley 1987) and MRI (Smith et al 1987a). The latter used transverse and coronal cuts as well as the mid sagittal one and indeed the trend of their findings was in the opposite direction.

Only two MRI studies have assessed cerebral volume rather than area (Kelsoe et al 1988; Nasrallah et al 1990). The first of these showed no significant reduction in schizophrenia, but the sample size was small and the occipital pole was omitted from the scanned volume. The second has shown a significant reduction in cerebral volume of the order of 5-10% but remains only a preliminary analysis. In general one can conclude that a substantial reduction appears unlikely but has not yet been satisfactorily disproved, while a minor decrease seems credible but may have to await support from more accurate volumetric data.

The results from Andreasen et al (1986,1990) are of interest because, despite sample sizes of 38 schizophrenic patients and 49 healthy controls in the first study and 54 patients and 47 controls in the second, this group completely failed to replicate their result of reduced cerebral and frontal areas on the mid-sagittal slice. Their data reveal that for mean intracranial area the two control groups were identical (157.6 cm³) while the patients were spread on either side of this value. For cerebral area the difference between the patients and controls in the first study is almost exactly reversed in the second. Overall it suggests that there are unexplained sources of variance in these two measures but no consistent difference between patients and controls.

It is instructive to compare these two studies further to see if these sources of variance can be identified. In both cases subjects were excluded if there was any neurological illness or substance abuse; all subjects except one were Caucasian. Patients were taken from consecutive admissions to two hospitals and were mostly young, single, unemployed men with a chronic pattern of illness. There appeared to be no major differences in the selection of patients or their clinical features. In the first sample no-one was included if they had an intelligence quotient under 70, while in the second the cut-off was set at 80. Deliberate selection was made in the first sample for some left handed patients, of which 7 (18%) were obtained, and similarly in the controls where 19 (39%) were sinistral; by contrast in the second sample five patients and none of the controls were sinistral. Controls, in the first sample, were drawn from hospital staff (doctors, nurses and radiology technicians), and in the second from the general population with deliberate matching for educational ability. Subjects appear to have been similarly scanned, except that for the first control group there was only a single mid-sagittal scan performed which therefore limited their analysis to this one slice. It was projected onto a screen for conducting planimetry of the intracranial area, entire cerebrum and frontal lobe. Four raters achieved a reliability of $r > 0.9$ for the cerebral and intracranial areas and $r > 0.8$ for the frontal lobe; ratings were made blind to diagnosis.

Differences between the studies are therefore apparent in terms of the handedness and socio-educational level of the controls, but these do not provide much help in understanding the wider variance in cerebral and intracranial areas shown by the patients. One conclusion, therefore, is that sufficient variance from unknown sources exists in these anatomical measurements to engender caution in interpreting significant results from even moderately large samples. Group differences may relate not to the

presence or absence of schizophrenia but to the influence of some unknown variable. This emphasis on the importance of adequate sample size echoes previous CT work. Unfortunately, neither a frequency distribution or scattergram display of these results were provided; this would have given some indication about departures from normality in their data. Such information also might have clarified the other substantial difference between the two studies, which was the statistical analysis. The first involved an analysis of variance according to sex and diagnosis for each of the area measures. This was followed by multiple regression to reduce the confounding effects not only of sex ($p < 0.005$) but also of height and weight. The second negative study simply used multiple t-tests.

No correlations appears to exist between cerebral size and severity of psychotic symptoms (Andreasen et al 1986), social function (Johnstone et al 1989a), or a history of obstetric complications (DeLisi et al 1988a). There is a suggestion that familial schizophrenics might have a smaller cerebral area compared to the non-familial (Schwarzkopf et al 1989), but an early finding that cerebral area might relate to negative symptom severity (Andreasen et al 1986) has not since been substantiated (Nasrallah et al 1988). It is also unclear whether cognitive function is related at all to cerebral area (DeMeyer et al 1988; Johnstone et al 1989a; Coffman et al 1990); if so it may be an indirect association, possibly mediated through the effects of social class and nutrition (Hooton 1939; Pearlson et al 1989).

3. ASSESSMENT OF THE TEMPORAL LOBE STRUCTURES

a) The temporal lobes

More consistent and interesting results have emerged from examining the size of the temporal lobe, and the contention that this region is reduced in volume now appears to be supported by MRI as well as neuropathology (Tables 1 and 2). For volumetric measurements the use of contiguous slices in the coronal plane to cover the entire lobe is now the accepted method (Kelsoe et al 1988; Suddath et al 1989; Bogerts et al 1990b), although some discrepancy about defining the temporal lobe's posterior boundary clearly exists. Landmarks used for this purpose are the posterior tip of the Sylvian fissure (Suddath et al 1989), the point where temporal white matter converges on the thalamus and lateral ventricle (Kelsoe et al 1988), the ascent of the fornix around the pulvinar (Bogerts et al 1990b) or an external reference point such as the internal auditory canal (DeLisi et al 1990); the use of these various reference points is undoubtedly a source of variance.

Area measurements, usually employing manual planimetry, can avoid this difficulty if an anterior slice is chosen, but area differences may not truly reflect changes in volume. Most commonly the slice that shows the temporal lobe at its maximum area is taken (Johnstone et al 1989a; Rossi et al 1990), but the rationale for this is not clear and it does not relate to standard anatomical landmarks.

The angle at which the images cut across the temporal lobe is also relevant, since it affects not only area measurements but also the volume included at the posterior boundary. This is particularly true if landmarks external to the temporal lobe, such

as the internal auditory canal, are used to define this boundary. Similar comments apply to measuring the temporal horn and hippocampus, occupying the posterior part of the temporal lobe.

If one focuses purely on those results derived from a volumetric approach then three studies find a reduction in temporal lobe volume (Suddath et al 1989; Bogerts et al 1990b; DeLisi et al 1990) and two do not (Kelsoe et al 1988; Nasrallah et al 1990), although Bogerts et al (1990b) only observed this effect in males. However, if studies that use area measurements from one or two slices are then examined the consensus appears to swing firmly towards finding a reduction of temporal lobe size (DeLisi et al 1988b, 1990; Coffman et al 1989; Johnstone et al 1989a; Rossi et al 1990). One study also included patients with affective disorder, as well as schizophrenia, in whom there was no difference in temporal lobe area compared to controls, suggesting that this reduction may be relatively specific to schizophrenia (Johnstone et al 1989a).

In many cases this reduction is bilateral (DeLisi et al 1988b, 1990; Suddath et al 1989; Rossi et al 1990) but, given the neuropathological evidence, the question remains whether the left hemisphere is perhaps affected more than the right. This can be answered either by comparing each side separately across patients and controls, or by looking for an asymmetry in the patients that is absent in the controls, and the two methods give conflicting results. The former approach suggests the reduction is indeed more marked on the left (Coffman et al 1989; Johnstone et al 1989a; DeLisi et al 1990; Rossi et al 1990), with only one report finding it more prominent on the right (Bogerts et al 1990b). The latter approach has to allow for a degree of normal asymmetry, whereby the right temporal lobe is slightly larger than the left in healthy controls (Jack et al 1989; Suddath et al 1989; Rossi et al 1990), but if this is done the

reduction in schizophrenics shows no left-sided emphasis (Coffman et al 1989; Johnstone et al 1989a; Suddath et al 1989; DeLisi et al 1990). One can conclude, as far as macroscopic appearances go, that the underlying pathology may have a slight preference for the left side, but not to a marked degree.

The clinical correlations of such temporal lobe changes remain uncertain. DeLisi et al (1990) examined patients in their first episode as well as those of many years duration and found that the reduced volume on the left, but not the right, was related to chronicity of illness. As with the greater VBR seen in more chronic patients on CT scans, this does not necessarily imply that there is a progressive atrophy during the illness, since it may be that those patients destined for a chronic course have reduced temporal lobe volume from the outset. Only follow-up studies will answer this question satisfactorily. No correlation has been found between impairment of cognitive performance and temporal lobe size (Johnstone et al 1989a; DeLisi et al 1990), but other clinical associations have not been explored.

The study by Suddath et al (1989) deserves further attention, despite a small sample of only 15 patients, because of the image analysis software adopted to distinguish grey and white matter within the temporal lobe. They were able to note that decreased temporal lobe volume primarily arose from a 20% loss of grey matter volume. It may be critical to achieve such tissue discrimination if only grey matter is affected, otherwise changes will be obscured by including normal volumes of white matter. For the same reason it may be desirable to separate limbic cortex from neocortex in the temporal lobe, given that neuro-pathological data suggest the former is particularly affected. Their software is poorly described in terms of its actual operation (Loats et al 1986), so the reliability of these findings remains to be confirmed.

This same group (Suddath et al 1990) has also provided some other data of great interest since it derives from 15 pairs of monozygotic (MZ) twins discordant for schizophrenia according to DSM III criteria (American Psychiatric Association 1980). Coronal slices of 5 mm thickness were obtained on a 1.5 T scanner, and area measurements again summed over slices to yield volume estimates, using the same image analysis system as for their singleton study. The affected twins showed a significantly smaller volume of grey matter in the left temporal lobe, using a paired t-test ($p < 0.002$), which was not evident in the right temporal lobe. This very similar result using the powerful discordant MZ twin strategy gives strong support for the validity of a grey matter decrease in the temporal lobe, and again emphasizes the asymmetry of this change.

The use of computers to alter the appearance of an image and undertake automated measurement, broadly termed "image processing", is also an important source of difference between studies. This can be illustrated by the two studies of Kelsoe et al (1988) and Suddath et al (1989), since they reached conflicting conclusions about changes in temporal lobe volume using the same sequences on very similar subjects; indeed seven patients and ten controls were common to the two studies since they originated from the same research group. The main difference lay in the image analysis of the latter group, which permitted a more detailed separation of the temporal lobe from surrounding CSF than can be achieved by manual planimetry. This increase in accuracy of computerised edge detection over manual planimetry seems the most likely explanation why only this group found a significant difference between patients and controls. The only other apparent difference was the definition employed for the arbitrary posterior boundary of the temporal lobe. What is also clear from these two studies is that image processing made a ready separation of the grey

and white matter that would not have been practical using manual planimetry, so that only the latter study was able to detect the substantial reduction in grey matter volume.

Although various methodological criticisms can be directed against most of the studies that found reduced temporal lobe size they do not generally involve any systematic bias, and this finding is highly unlikely to be completely artefactual. With the exception of enlarged VBR, a reduction in temporal lobe volume can so far be accepted as the most consistent structural imaging abnormality seen in schizophrenia, possibly affecting the left side more than the right and the grey matter more than the white.

b) The hippocampus/amygdala

Four studies have included the hippocampus/amygdala complex in their analyses, including one MZ twin sample (DeLisi et al 1988a; Kelsoe et al 1988; Bogerts et al 1990b; Suddath et al 1990). In the latter study (Suddath et al 1990), the affected twin could be distinguished in 13/15 of the discordant pairs on the basis of blindly rated reductions in hippocampal size, particularly the anterior hippocampus. These highly significant changes were bilateral, of the order of 10% in magnitude, and were unrelated to clinical variables such as age of onset, duration of illness or amount of neuroleptic medication received. There was a conspicuous lack of focal lesions, or areas of high signal such as one would observe in hippocampal sclerosis. This was a powerful study, but such a sample was unique and there always remains uncertainty over how far the results of a twin study can be generalized to singletons.

At present the over-riding problem with data about these structures lies in the difficulty of their accurate delineation, particularly the anterior hippocampus and amygdala. Images need to focus down on these limbic structures, and should generate volumetric measurements from slices thin enough to achieve the requisite spatial resolution. With the ability to take oblique slices it is now becoming possible to define temporal lobe structures much more sharply by angling slices to cut across the temporal lobe axis exactly.

It is of note that, of the three singleton studies designed to look specifically at the medial temporal structures, the only one which met these requirements was also the only one to give a clearly positive finding (Bogerts et al 1990b). They used 63 contiguous 3 mm coronal slices on a 1.0 T system, with a pixel size of 1.0 x 0.6 mm., and included a computer correction for partial volume artefact. Furthermore they validated their MRI measurements in controls against age and sex matched post-mortem samples sectioned in the same plane. Both inter-rater and test-retest reliability on measurements of the temporal horn and hippocampus/amygdala were high ($r > 0.85$). They found the hippocampus to be significantly smaller in male schizophrenics but not females, and this amounted to a 9% bilateral reduction in volume. There was a lack of correlation within each individual between the volume of the hippocampus/amygdala and the temporal horn, suggesting the latter may not just be a reflection of the former.

Any clinical associations of an alteration in the hippocampus or amygdala have yet to be brought to light. Apart from the negative findings of Suddath et al (1990) mentioned above, the only other relevant result has come from DeLisi et al (1988a). They noted a significant area reduction if the hippocampus and amygdala were

combined as a single measurement with the parahippocampal gyrus, and raised the question whether obstetric difficulties might explain smaller size of these structures but could find no such relationship.

c) The temporal horn

Interest in the temporal horn arises mainly from its proximity to the medial limbic structures, changes in which might cause temporal horn enlargement. Such an increase was observed at post-mortem by Crow et al (1989), but again there is difficulty detecting changes by MRI in such a small structure, particularly if area rather than volume measurements are taken. Being a narrow ribbon-like structure it is especially prone to partial volume artefact.

Four MRI studies have attempted such measurements (DeLisi et al 1988b, 1990; Johnstone et al 1989a; Bogerts et al 1990b), of which only two were volumetric (Bogerts et al 1990b; DeLisi et al 1990). The twin study mentioned above did not include measurements of the temporal horn (Suddath et al 1990). Bogerts et al (1990b) found the left temporal horn significantly enlarged, most notably in women and more anteriorly, but the left LV body and left occipital horn were also significantly enlarged (DeGreef et al 1990). The other three studies found no such change in temporal horn size. This discrepancy is not easily explicable by different sample selection, since Bogerts et al (1990b) looked at first episode patients whilst the negative studies were of more chronic groups, and probably arises from the difficulties in accurate measurement.

In regard to clinical associations, Bogerts et al (1990b) further commented that temporal horn volume correlated with both positive and negative symptom severity, which was a little surprising in view of the absent correlation between the temporal horn and hippocampal volumes. For the time being the question of temporal horn enlargement and its significance remains unresolved.

4. ASSESSMENT OF FRONTAL LOBE SIZE

Frontal lobe size has generally been found to be similar in schizophrenics and controls (Smith et al 1987a; Kelsoe et al 1988; Coffman et al 1989; Suddath et al 1989; Uematsu et al 1989; Andreasen et al 1990; Rossi et al 1990), but sufficient dissenting voices exist (Tables 1 and 2) for the issue to still remain open (Andreasen et al 1986; DeMeyer et al 1988; Stratta et al 1989).

Much of this research was influenced by the early report from Andreasen et al (1986), using a single mid-sagittal slice, of frontal area reduction in schizophrenia, particularly marked in males. This was considered important both because of the frontal metabolic changes being shown at that time by functional neuro-imaging, and also the clinical parallels drawn between negative symptoms and those of frontal lobe lesions. In this particular study, though, negative symptom severity was associated with cerebral but not frontal area reduction, and the case for relating structure to function was further weakened by absent correlation between frontal area and performance on frontal lobe cognitive tasks. Attempts by other groups to replicate this frontal area decrease were unsuccessful (Smith et al 1987a; Uematsu et al 1989), and no association between frontal lobe size and negative symptoms has since come to light. It is worth noting the possibility that smaller frontal areas may just be restricted to the sub-group of familial schizophrenics (Schwartzkopf et al 1989).

Later, Andreasen et al (1990) failed to replicate their earlier result, which provoked further controversy. It appeared primarily due to differences in frontal area between the two control groups, unlike the differences in cerebral area which, as discussed above, arose from greater variance in the two patient samples. This might be

explained by differences in their social background since controls in the earlier study were drawn from hospital staff and had achieved much higher educational goals, whilst controls in the later study were selected from the general population to be of similar ability to the patients. In controls there was a moderate correlation of frontal lobe area with educational level ($r=0.31$, $p=0.04$), but not with cognitive abilities; the latter is also noted by DeMeyer et al (1988).

The other two studies that note reduced frontal lobe area both use measures in the transverse plane. Stratta et al (1989) employed linear measurements and an unconvincing statistical analysis, while DeMeyer et al (1988) only found a difference on one of the two slices examined. Both these groups comment on the left frontal lobe being smaller than the right in the patient group, but this asymmetry is a normal phenomenon and not significantly greater in the patients than controls.

Volumetric measurements face the difficulty that, as with the temporal lobe, the frontal lobe has no agreed subcortical boundary. Nonetheless if frontal lobe size is to be measured at all a consistent, if arbitrary, boundary to permit volume estimation seems preferable to any single slice area measurement. Such volumetric measurements, so far, have not shown any difference between patients and controls (Kelsoe et al 1988; Suddath et al 1989).

5. ASSESSMENT OF OTHER STRUCTURES

a) Corpus callosum and septum pellucidum

These two structures are closely related since the septum pellucidum lies between the lateral ventricles, the roof of which is formed by the corpus callosum. In both cases they have to be measured by area rather than volume, because the septum is very thin and the corpus callosum has no clear lateral edges. Results from such midline measurements are summarized separately in Table 3.

Of eight studies that have examined the corpus callosum, the consensus weighs universally against any abnormality in its area; a report to the contrary by Galluci et al (1987) was later withdrawn as the sample was enlarged (Stratta et al 1989). Not surprisingly, there has been a similar failure to relate callosal area to clinical variables such as symptom or illness severity, age of onset, or family history of schizophrenia (Matthew et al 1985a; Uematsu et al 1988).

With regard to callosal width, an early result by Nasrallah et al (1986b) suggested that, after matching for the effects of gender and handedness, callosal width was greater in right-handed female patients, although only small sub-groups were then being compared. Weak support for this result came from one post mortem report of anterior callosal thickening in schizophrenia (Bigelow et al 1983). Hauser et al (1989) analysed the data collected by DeLisi et al (1988b) to try and replicate these results. With 24 patients matched to an equal number of controls for sex and handedness, they repeated their technique and recorded 11 different measurements from the mid-sagittal slice. Each of these was entered into an ANOVA as the dependent variable, with

gender and diagnosis as the independent variables. The only diagnostic group difference of significance was found in the same category of dextral females which Nasrallah et al (1986b) had noted to be different. However the difference was in the opposite direction, the explanation for which is not at all obvious.

Similarly, with callosal length and the callosal-brain area ratio, four studies find no abnormality in the patient group compared to healthy controls. Those few studies that do note such a difference are either inconsistent (Stratta et al 1989; Uematsu et al 1989) or isolated findings (Matthew et al 1985a) that did not follow from any stated hypothesis. Hauser et al (1989) had noted that patients with affective disorder had shorter callosal length than either schizophrenics or controls, but there has been no confirmation of this result.

In fact the only replicated abnormality comes from two analyses of the septum pellucidum (Matthew et al 1985a; Uematsu et al 1989). Both detected an increased area in the patient group, but this is most likely a concomitant of lateral ventricular enlargement in view of the close relationship between these two structures. Until it is shown to be an independent abnormality it is a finding that has few implications of interest; unfortunately neither study provided data to test whether or not this was the case.

b) Ventricular size

Several MRI studies replicate the well-established bilateral enlargement of VBR seen with CT scans (Kelsoe et al 1988; Suddath et al 1989; Andreasen et al 1990; DeLisi et al 1990; Suddath et al 1990). In these studies the ability of MRI to use coronal

rather than transverse slices, which reduces the substantial partial volume artefact often present on CT images, and to estimate ventricular volume rather than area, consolidates the validity of this finding. Although two studies (Kelsoe et al 1988; DeLisi et al 1990) found it to be more prominent on the left side, which would accord with the asymmetrical temporal lobe decrease suggested above, this may simply reflect the normal LV asymmetry seen in the general population where the left lateral ventricle is slightly larger than the right.

There has been no clear proof yet that this enlargement is localized to any particular part of the lateral ventricles. Kelsoe et al (1988) made an attempt to subdivide them, with each coronal slice referenced to the most anterior part of the frontal horn. The posterior part was found, by this method, to be more enlarged than the anterior but it must be questioned whether this was artefactual or not. If there was a generalized increase in the ventricular volume then, with the slices referenced to its anterior end, a larger ventricular system will tend to compare its broader trigone area with the more pointed occipital horn of a smaller system. Posterior differences by this method may therefore reflect only a generalized enlargement rather than a local one. A repetition of their procedure using a posterior reference slice rather than an anterior one might have resolved this particular issue, but was not performed. Crow et al (1989) reported a similar posterior emphasis using post-mortem material, but Andreasen et al (1990), using a reference slice that passed through the optic chiasm, found the opposing effect of ventricular enlargement being more obvious in the anterior horn.

The findings of Andreasen et al (1990) strongly pointed to the fact that lateral ventricular enlargement is a feature of schizophrenia in men rather than in women, which would fit the fact that patients with poorer outcome, who tend to have greater



VBR, are predominantly male. This gender difference echoes the reduction of hippocampal volume that Bogerts et al (1990b) saw in male but not female patients.

With regard to other parts of the ventricular system, the discordant MZ twin strategy has provided compelling evidence of third ventricular enlargement, with 13/15 pairs showing it to be greater in the affected twin (Suddath et al 1990). Kelsoe et al (1988) substantiate this result, with the anterior part of the third ventricle being enlarged in area by 73% in the patient group, although the real magnitude of this difference was small (0.83 and 0.48 cm² for patients and controls respectively). On the other hand third ventricular size appeared normal in three other schizophrenic samples (Smith et al 1987b; Andreasen et al 1990; DeLisi et al 1990). The reason why some studies have missed this effect is probably because, in addition to its small size, there can be a technical problem in measuring the third ventricle. As the thalami and hypothalami move with the systolic pressure wave, pumping CSF through the foramina of Monro, the flow can markedly alter the CSF signal intensity and may make the third ventricle more difficult to define (Quencer et al 1990).

Fourth ventricular area has been assessed from the mid-sagittal slice in only two studies and neither found any abnormality (Matthew et al 1985b; Stratta et al 1989).

6. RELAXATION TIMES AND SIGNAL INTENSITY

These measurements can provide quantitative evidence, which may not be apparent from structural measurements or simply looking at a scan, of a diffuse tissue abnormality. It is in this fact that their importance lies. There is considerable scope for spurious results when using these MRI parameters, so it becomes essential to look both for replication of results and strict methodology (see Table 4). It is perhaps partly due to these technical pitfalls that relatively few investigations have included such measurements.

a) A general increase in signal intensity

Both Smith et al (1987b) and Kelsoe et al (1988) described an small increase in chronic schizophrenic patients of T_1 -weighted intensity values over all areas of white and grey matter examined. It should be noted, though, that Kelsoe et al (1988) used raters that were not blind to diagnosis, whilst the study of Smith et al (1987b) had severe methodological weaknesses that are illustrative of some of the points mentioned earlier. Firstly, there was a major scanner upgrade midway through sample collection, which severely compromised their data since the latter half had significantly lower intensity values. Secondly, when individuals were re-scanned later the same day, it was apparent that there was considerable variation in values, the source of which was not identified but which they assumed the use of a phantom would correct; signal non-uniformity was not measured. Thirdly, the sample was small in having only 16 patients and 13 controls, and the patient sex ratio was clearly atypical of most schizophrenic samples in being 83% female, while it was 57% for controls. Significance levels were uncorrected for the large number of comparisons made.

Their finding on the IR sequence was conspicuously absent on the SE sequence, which was similarly T_1 -weighted and should therefore have shown similar changes. For all these reasons grave doubt hangs over their results, and furthermore such a T_1 effect was not detected by Besson et al (1987a), using the superior method of T_1 relaxation time measurement in a similarly chronic group.

Johnstone et al (1986) specifically examined for peri-ventricular signal increase in schizophrenics experiencing an acute relapse, reasoning that ventricular enlargement might arise from some local pathology such as an inflammatory reaction that would cause a signal increase due to the presence of oedema. However no abnormality was observed on visual assessment.

b) Elevated relaxation times in the basal ganglia

One positive abnormality in relaxation times that has been replicated is an elevation of T_1 times in the basal ganglia. Both Fujimoto et al (1985) and Besson et al (1987a) found an increase in the putamen/globus pallidus. This abnormality was given added importance by the latter group being able to relate basal ganglia T_1 values to the severity of tardive dyskinesia. The fact that in each study these extensive changes were bilateral makes it seem less likely they were due to scanner artefact. Partial volume artefact is also an implausible explanation for the T_1 elevation since the putamen is adjacent to white matter which has a lower T_1 relaxation time. Still, there is a paucity of methodological detail in both studies with regard to control data, scanner stability, measurement technique and reliability that must make acceptance of this result only provisional. Andreasen et al (1989) noted a T_1 elevation of the left

putamen but not the right in a small sample of six schizophrenics compared to six controls.

These studies were performed with patients on medication, and clearly the effects of D_2 antagonist anti-psychotic drugs on relaxation times needs to be examined since they will be most abundant in the basal ganglia. Longstanding interest in the dopamine rich basal ganglia as a possible site of disorder in schizophrenia, arising from clinical features like catatonia and tardive dyskinesia along with the dopamine antagonism of antipsychotic drugs, make it surprising that the above T_1 changes have not been pursued further. Neuro-pathological findings suggest that there may be a reduction of volume in the internal portion of the globus pallius (Bogerts et al 1985, 1990a).

c) Abnormalities in cortical grey matter

Given the evidence from structural measurements that the grey matter of the temporal lobe is perhaps preferentially reduced in schizophrenia there is considerable interest in whether or not a diffuse change could be picked up using relaxation times or signal intensity. However partial volume artefact is a particularly common problem when trying to record grey matter measurements, since sulcal fluid with its long T_1 and T_2 times is often inadvertently included, and this will be reflected in unstable readings. This is more difficult to avoid when using a single slice rather than multislice technique since adjacent slices cannot be examined, although Andreasen et al (1989) report acceptable reliability with this approach. This group found a T_2 elevation in the left dorsolateral grey matter of the frontal lobe, but as noted above the sample size was extremely small.

Two groups have reported abnormalities in the signal intensity of temporal lobe grey matter (Smith et al 1987b; Rossi et al 1988b), but both studies have deficiencies that must limit any conclusions drawn from them. They are also contradictory insofar as the former finds a bilateral increase compared to controls, whilst the latter reports a right-sided decrease.

The study of Rossi et al (1988b) had essentially negative findings with no differences between patients and controls but, from over 150 parametric tests conducted without adjustment to the significance level, one of the results extracted as significant was that patients had lower values in the right temporal grey matter relative to their left side. This asymmetry amounted to only 4% of the mean intensity value and, while it achieved the 0.5% level of significance on a paired t-test, it is clearly within the range of ordinary scanner and measurement variation. The sample size included only 12 patients and 12 controls, and the problem of partial volume artefact in their measurements was not considered. The difficulties encountered by Smith et al (1987b) have been discussed already.

d) Abnormalities in white matter

Diffuse pathology in white matter that appears normal to the human eye has been successfully identified using relaxation times in multiple sclerosis (Miller et al 1989), dementia (Christie et al 1988), and possibly obsessive compulsive disorder (Garber et al 1989b). In regard to the T_1 time of normal appearing white matter in these disorders, the difference between patients and controls ranged from 13-17 msec.

Despite this success, there has been little sustained attention paid to possible white matter abnormalities in schizophrenia. Besson et al (1987a) made the observation that higher T_1 values in temporal lobe white matter were related to the severity of psychotic symptoms, and an increased white matter T_1 in the left temporal lobe of epileptics with psychosis was reported to be related to the presence of auditory hallucinations (Conlon et al 1990). Andreasen et al (1989) found elevated T_2 values in left temporal white matter but did not relate this to any clinical features. Fujimoto et al (1985) suggested a possible decrease in frontal white matter T_1 values but this finding, like that of Besson et al (1987a) was not explored further or included in any initial hypotheses so it remains speculative. In bipolar and unipolar affective disorders there have also been reports of a T_1 increase in frontal white matter (Rangel Guerra et al 1983; Dolan et al 1990). Since the presence of gliosis would be expected to increase the T_1 time of white matter (Barnes et al 1988a) the above findings in schizophrenia warrant further investigation.

7. SUMMARY OF MRI FINDINGS IN SCHIZOPHRENIA

The main MRI findings can be briefly summarized as follows.

1. There is strong evidence for reduced volume of the temporal lobes, probably affecting the grey rather than white matter and possibly more obvious on the left side.
2. A reduction in hippocampal volume is also likely, given the MZ twin data in conjunction with neuropathological findings.
3. Enlargement of the lateral ventricles has been confirmed volumetrically, and although there is tentative evidence for an increased area of the septum pellucidum this is most probably a simple accompaniment of such ventricular enlargement.
4. It is unlikely that there is any major reduction in size of the frontal lobe or cerebrum, although a minor decrease remains quite possible.
5. Discrete lesions, which might have indicated gliosis from antecedent cerebral insults, appear to be no commoner in schizophrenics than in controls.
6. Two studies suggest that there is an increase of relaxation times in the basal ganglia, but even if confirmed this has yet to be proved more than just an effect of antipsychotic medication.
7. Clinical correlations remain preliminary but may include a relationship between smaller temporal lobe size and chronicity of illness. Important questions regarding the

size of the temporal horns and limbic structures require more detailed examination before any conclusions can be drawn. The specificity to schizophrenia of the reduction in temporal lobe and hippocampal volume needs to be answered by greater use of psychiatric as well as healthy controls.

PRINCIPLES OF MAGNETIC
RESONANCE IMAGING

1. THE NUCLEAR MAGNETIC RESONANCE SIGNAL

Nuclear magnetic resonance (NMR) was first observed by Rabi in 1939 when a beam of hydrogen molecules in a magnetic field absorbed radiofrequency energy at a sharply defined frequency. A similar discovery using solid materials was made independently by Bloch (1946) and Purcell et al (1946). Only later was use made of the resonance frequency to provide information about the chemical environment of resonating nuclei, which provides the basis for NMR spectroscopy. Nuclear magnetic resonance phenomena are most accurately described by quantum mechanics, but classical physics provides a useful approximation for systems larger than the molecular level.

The first NMR image was produced by Lauterbur (1973), in a method he called zeugmatography, and the current techniques of two dimensional Fourier transform (2DFT) in signal analysis were first put forward by Kumar et al (1975). The following 5 years were largely spent in improving spatial resolution, with the spin warp modification introduced by Edelstein et al (1980). Further changes permitted substantial reduction in the duration of scanning as, for example, with the multislice imaging method proposed by Crooks et al (1982). The biological safety of the technique at conventional field strengths appears to be excellent (Shellock 1987).

Atomic nuclei with odd atomic numbers, such as ^1H , ^{13}C , ^{19}F , ^{23}Na and ^{31}P are called "spins" since they behave as if the positive charge from protons in the nucleus rotates, thereby giving it a magnetic "moment". These magnetic moments will be randomly orientated unless a powerful external magnetic field (B_0) is applied, when they will align along its axis to give an overall magnetic moment (M), which has an equilibrium

value of M_0 . This is proportional to the density of protons (ρ), which for water is approximately $10^{23}/\text{cm}^3$.

If a second smaller field (B_1) is applied perpendicular to B_0 then these nuclei will be displaced away from B_0 and will start to precess around its axis, analagous to a gyroscope displaced in a gravitational field i.e. the spinning axis of each individual nucleus itself circles around the main axis of B_0 . Since the moment M is the sum of these spins then it too will precess, at a constant angle of θ as long as B_1 is applied, with a frequency that is described by the Larmor equation:

$$\omega_0 = \gamma \cdot B_0$$

B_0 = magnetic field (Tesla)

ω = Larmor frequency (radian/sec)

γ = gyromagnetic ratio for that

nucleus (2.68×10^8 rad/T for ^1H)

For ^1H in a 0.05 T field the Larmor, or resonant frequency, will be 21 MHz. The moment M is a vector and can be resolved into a static component parallel to B_0 and a rotating component perpendicular to B_0 . These are termed M_z and M_{xy} respectively, since the direction of the main magnetic field is designated the z axis, and x/y the two orthogonal axes. The rotating component is able to induce a small a.c. voltage in a suitable coil near the sample, which is the NMR signal.

The precession achieved by applying the second smaller magnetic field (B_1) has only a small θ if it is static, but if instead B_1 is rotated at the same Larmor frequency as the vector M then the precession is cumulative, and M spirals out towards a plane that is 90° to B_0 . The rotating B_1 field is achieved by applying to a transmitter coil

surrounding the sample a radiofrequency (r.f.) voltage appropriate for the Larmor frequency. Typical values to achieve a θ of 90° , where the maximum NMR signal is obtained, would be $15\mu\text{T}$ over $800\mu\text{sec}$, and in this case the B_1 pulse is called a 90° pulse, although it is possible for θ to have any value from 0° to 180° .

One isolated nucleus excited in this way would precess indefinitely, but in a block of material there are interactions that cause energy exchange so the system moves back towards the equilibrium position of M_0 after the r.f. pulse ceases. This energy exchange can occur in two ways. The first is between excited nuclei and the surrounding environment other than such nuclei, called the "lattice". The nuclei lose energy to the lattice and so move back to the lower energy state of M_0 parallel, or longitudinal, to B_0 . This is called spin-lattice (longitudinal) relaxation, and the effect is for M_{xy} , the perpendicular component of M that generates the NMR signal, to decrease exponentially towards zero as M alters direction. It has a time constant called the longitudinal relaxation time, or T_1 .

The second exchange is between excited nuclei so that, although they are pointing in the same direction perpendicular (or transverse) to B_0 when they start to precess, there is gradually a loss of phase coherence in that plane as precession frequencies vary. This will again lead to an exponential decrease in the overall moment of M_{xy} , and therefore the NMR signal, even though individual spins are still precessing. It is called spin-spin relaxation and has a time constant of T_2 , sometimes referred to as the transverse relaxation time. The T_2 of solids is usually substantially shorter than their T_1 , but in fluids they tend to be more equal since spin-spin relaxation is slower in fluids. As spin-spin relaxation cannot persist beyond full spin-lattice relaxation it follows, however, that T_1 always exceeds T_2 .

These two relaxation processes usually occur together but it is possible to have longitudinal without transverse relaxation if a 180° pulse is applied. In such a case there can be no overall precession since the moment M lies anti-parallel to M_0 , and consequently no NMR signal produced as individual spins relax from 180° back to 0° .

An NMR signal, oscillating at the Larmor frequency as its amplitude decreases, is called the "free induction decay". In reality this decay is much more rapid than predicted from T_2 since inhomogeneity of the B_0 field causes additional spin-spin dephasing. However the effect of this additional dephasing will cancel itself out if the relative position of spins are repeatedly alternated through 180° in the transverse plane as relaxation occurs. This causes the signal to wax and wane successively, called "spin-echoes", and it is the decay in amplitude of these echoes that has the time constant T_2 . In practice, the free induction decay commences too soon after the r.f. pulse to be adequately measured, and the collected NMR signal is always a spin-echo. Although a T_2 estimate can be obtained from a single spin-echo it is preferable to collect several such spin-echoes if it is to be accurate, and a series of such measurements is termed a multi-echo sequence.

2. IMAGE CONSTRUCTION

An NMR signal elicited in this way from a homogenous block would be the same for each of its volume elements (voxels), and therefore spatially indeterminate. The signal needs to be manipulated so that its position of origin can be specified in three dimensions.

Slice position, along the first axis, can be readily determined by applying a magnetic field gradient (G_{sl}) at the time of the r.f. pulse, so that the Larmor frequency is only matched by a narrow slice of tissue, which then starts to precess. Direction along the remaining two axes, within the slice, then has to be coded into the signal during its evolution. This is achieved by the use of two further orthogonal magnetic field gradients (G_{pe} , G_{ro}) which alter the frequency of precession so that the NMR signal frequency becomes position dependent in the x and y dimensions. To obtain this spatial information for a single image requires many repetitions (usually 128-256) of the excitation/relaxation process, each one with a different G_{pe} (phase encoding) gradient but the same G_{ro} (readout) gradient. These rapidly alternating field gradients use up power in the order of 10 kW per gradient coil, which imposes practical limitations on which sequences are possible, and may create electrical eddy currents in multi-slice imaging that distort the signal.

Applying the G_{pe} and G_{ro} field gradients yields a complicated NMR signal, if amplitude is measured over time. The great advantage of the Fourier transform is to convert this signal into its constituent oscillating frequencies which, as described above, will be position dependent due to the field gradients. Such a transform can be made twice, one for each gradient effect, in order to give two dimensional position.

The "matrix", which is the number of unit areas, or picture elements (pixels), each image is subdivided into, is determined by the number of gradient steps in G_{pe} , along with the range of G_{ro} which is held constant. Common examples would be 256×128 or 256×256 , and the resultant pixel area taken with its depth (slice thickness) decide the volume of each basic unit (voxel). The area of each pixel can be easily related to actual area if the scan's field of view is known. It is possible to alter the plane of the selected slice of tissue simply by deciding which of the three orthogonal field gradients will act as the slice select gradient, G_{st} . Furthermore it is economical of time if the slice select gradient allows several slices that are not adjacent to be examined almost simultaneously, which is termed multi-slice imaging.

Each excitation/relaxation process is designated a "sequence" and details about the different aspects of a sequence provide the core description of any NMR image. In summary, it involves the initial r.f. pulse with one or more subsequent pulses before measurement of the spin-echo signal and then letting the system relax, all the time applying precisely controlled field gradients to spatially locate that signal. The time allowed between the initial r.f. pulse and spin-echo measurement is called the echo time (T_e), while the time for the entire sequence is the relaxation time (T_r) since it mainly comprises time for the system to regain equilibrium. Each sequence repetition conventionally takes in the order of 1-2 seconds, so that 256 repetitions to construct an image will amount to 8-10 minutes.

Alternative techniques to that described above, at present too time consuming or yielding inferior image quality, are available and rapidly becoming realistic options as technology improves. Very fast techniques, such as echo planar imaging in which only one echo need be observed or gradient-echo methods (Hesslink et al 1990), are

one example and three-dimensional imaging is another (Runge et al 1990). Different disciplines will image organs other than the brain, or examine different parameters such as blood flow, and various approaches have evolved to meet such diverse requirements, but these fall outside the scope of this introduction. Imaging nuclei other than ^1H is also of great interest and, other than requiring a considerably higher field strength for the same image quality, is based on the same principles as proton imaging.

3. TISSUE DIFFERENTIATION AND CHOICE OF SEQUENCE

The sequence described above would be termed a "spin-echo" (SE) sequence, but if it were preceded by an inversion of the spins through 180° before the 90° pulse initiates their precession it would be termed an "inversion-recovery" (IR) sequence, although the NMR signal still derives from spin-echo measurement. Such an initial inversion leads to longitudinal relaxation without transverse relaxation and, although no NMR signal occurs as a result, the size of the subsequent NMR signal after the 90° pulse will be heavily influenced by the amount of longitudinal relaxation that took place before it. The signal from such a sequence is therefore dominated by the T_1 of longitudinal relaxation, rather than the T_2 of transverse relaxation that often characterizes a SE sequence. The duration allowed for such longitudinal relaxation is termed the inversion time (T_i) and usually lasts several hundred milliseconds.

The NMR signal intensity (I) for these two broad classes of sequences is given by the Bloch equations, from which it is clear that for both SE and IR sequences the basic parameters that characterize a tissue are ρ , T_1 and T_2 :

$$I_{SE} = K \cdot \rho \cdot e^{-Te/T_2} \cdot (1 - e^{-Tr/T_1}) \quad \text{where} \quad \begin{array}{l} K = \text{a constant} \\ \rho = \text{spin density} \end{array}$$

$$I_{IR} = K \cdot \rho \cdot e^{-Te/T_2} \cdot (1 + e^{-Tr/T_1} - 2 \cdot e^{-Ti/T_1})$$

This signal intensity is then assigned to a grey scale on a computer which is usually 8 bit (256 gradations) or 16 bit (65,536 gradations). The constant K includes arbitrary scale factors, the proton diffusion coefficient and the velocity of any proton flow during the sequence. Proton flow can be largely ignored in structural imaging of the

brain apart from any pulsatile movement that occurs with the cardiac cycle, which shows its effect on the appearance of blood vessels and ventricular cerebrospinal fluid (CSF). Proton density (ρ) will vary from one tissue to another, predominantly according to water content, but greater tissue contrast is obtainable if the relaxation times are used in preference to ρ , as shown by the following typical values in brain images at 0.5T :

| <u>Tissue</u> | <u>% Water content</u> | <u>T₁ (msec.)</u> | <u>T₂ (msec.)</u> |
|---------------|------------------------|------------------------------|------------------------------|
| Fat | - | 300 | 65 |
| White matter | 71 | 400 | 85 |
| Grey matter | 84 | 600 | 100 |
| CSF | ~100 | >2000 | >1500 |

Tissues with longer T₁ also tend to have a longer T₂, and vice versa, since different but closely related aspects of water molecule behaviour influence each relaxation process (Mathur-de Vré 1984). White matter is characterized by shorter relaxation times than grey matter due to its greater lipid content.

Tissue differences in T₁ and T₂ can be given maximum emphasis if the correct T_e and T_r are selected. If T₂ contrast is the main priority then a SE sequence with the appropriate T_e is required, whereas for T₁ contrast either an IR sequence or a short T_r SE sequence is indicated. Contrast in a SE image can be gained, for most tissues, from either T₁ or T₂ differences but not from both together because they have opposing effects on image intensity.

Superior T_1 contrast is obtainable by the use of an IR rather than a SE sequence, through the procedure of inversion rather than T_r manipulation. Tissue contrast in a IR sequence can be twice that of a SE since relaxation occurs through 180° rather than just 90° . To weight T_1 differences in an IR sequence full relaxation is desirable so the T_r is kept long but, as with the T_1 -weighted SE, the T_e is kept short in order to minimize T_2 effects. The advantage of greater contrast is therefore at the cost of longer scanning time due to the added T_1 and long T_r .

A single image that combines T_1 and T_2 contrast is suitable for structural delineation of normal anatomy and pathological structures, but sometimes one wishes to examine an image based solely on T_1 or T_2 values, in order to specify any underlying signal change more precisely. It can be seen from the Bloch equations that it is possible to calculate such values for each pixel if two or more appropriate sequences are made over an identical volume. Such sequences will need to share the same T_e or T_r in order to estimate T_1 or T_2 respectively.

4. SELECTING IMAGES OF OPTIMAL QUALITY

The major criterion of image quality is contrast (C), which is the difference in image intensities between two tissues of interest. This depends most crucially on the intrinsic T_1 and T_2 of the relevant tissues and tailoring the sequence, using the considerations described above, to contrast particular tissues in the desired manner. It also relies, though, on maximizing over the whole image the amount of true signal (S) relative to random signal fluctuation, or noise (N), that occurs throughout the image. The signal-to-noise ratio (SNR) is a basic quantity that, visually, corresponds to the "graininess" of an image. By clearly defining variables that influence the overall SNR it is possible to modify a given sequence to obtain the best possible scan within a given time restraint. It increases with the main field strength (B_0) but, more particularly, it is inversely proportional to the spatial resolution achieved:

$$\text{SNR} \propto \text{pixel area} \cdot \text{slice width} \cdot \sqrt{(\text{matrix size} \times \text{repetition no.})}$$

Noise is random and will tend to cancel out if the signal from each pixel is averaged over several repetitions of the same sequence (number of "excitations"). The SNR is also dependent on careful design of the receiver coil, which needs to be close to the head surface if it is to be maximized, but for given hardware and a standard phantom the SNR on a specific sequence varies only with the spatial resolution and number of excitations. It should be noted that there is a lengthening of T_1 in various tissues as the static field increases, until values eventually approach that of water, so that tissue contrast dependent on T_1 may actually be reduced as B_0 becomes more powerful despite the increase in SNR.

Each sequence will have a limit imposed on the number of slices it can include in one multislice data collection so, for a given slice width, two or more adjacent data collections may be necessary for a sequence to cover the desired brain volume. In practice, because there are constraints on scanning time, the factors that influence SNR have to be juggled against each other and against the sequence's T_r in determining the final tissue contrast. If one wished to make a realistic comparison of two sequences the contrast between two tissues achieved per unit time (the contrast efficiency) would be a more appropriate measurement than contrast considered in isolation.

This can be expressed:

$$\text{Contrast efficiency} = C / \sqrt{(T_r \cdot N_{\text{seq}})}$$

N_{seq} = sequence repetitions needed to
cover the desired volume.

C = contrast.

T_r = relaxation time.

When more than two tissues are to be differentiated from each other then the situation is more complex. Contrast agents, such as gadolinium compounds, act by altering the relaxation times of water protons and change the image intensity in tissue compartments to which they gain access.

5. SOURCES OF ERROR IN IMAGE MEASUREMENTS

The versatility of MRI is accompanied by a correspondingly large source of potential errors, which cannot be regarded as trivial if measurements are to detect changes that may be subtle. Scanners have continued to develop rapidly but careful attention to their daily performance remains an essential prerequisite. This is particularly critical when making direct measurements of image intensity values or relaxation times in order to detect diffuse tissue changes, as opposed to the size of anatomical structures or the counting of obvious lesions. This section therefore gives a brief summary of those factors that most commonly contribute to poor quality of measurements, despite having selected a sequence with adequate contrast and signal-to-noise ratio.

a) Relaxation times and signal intensity

These measurements are simply a question of taking the digital information used to display an image and obtaining a value that is representative of a particular tissue, structure or anatomical region. It follows that they are only possible if the image is available on some electronic medium, such as magnetic tape, that can be displayed by computer, rather than on film. Their advantage is that, by using this digital information, they can quantify changes in appearance that would otherwise have to rely on a purely qualitative visual judgement, and also detect changes that are too subtle for the naked eye. They nearly always involves tracing or outlining a relevant part of the image, called a "region of interest" (ROI), before taking the mean value of the pixels contained within it. For example, with specific structures like the basal ganglia the trace might be formed around their perceived anatomical border, or a small ROI chosen from within them, according to which was thought more valid.

In acquiring such readings there are a number of common problems that arise from the scanner. Signal non-uniformity on each slice is universal to some degree, mainly due to the receiver head coil geometry creating an uneven response. This causes the signal to vary according to its position relative to the head coil, regardless of what is actually being scanned. Relaxation times, calculated from identical points in two or more images, clearly adjust for this effect but this is not the case if the signal intensity from just one sequence is measured. In particular, signal intensity values away from the centre of the image are prone to distortion.

Instability over time that involves a consistent shift is mostly due to adjustments in either the hardware or software. Short term variation of scanner performance over days or weeks is often considerable but usually, being random, involves no consistent shift in values.

In multislice sequences eddy currents (distortions in the gradient field) can accumulate and alter the slice width, which has the effect of introducing slice-to-slice non-uniformity in the signal intensity. However this will only be pronounced with short repetition times and small gaps between sequentially excited slices.

In addition there is a major source of error in measurement, partial volume artefact, that arises when the ROI is situated close to the border between two tissues of different signal intensity. In MRI there are just three major "tissue" compartments inside the skull - cerebrospinal fluid, grey matter and white matter. It happens because, at such a border, more than one tissue can get included in a single voxel. This leads to a signal derived from their combination so that, for example, in measuring cortical grey matter there are likely to be small amounts of sulcal fluid

included, the extent of which will vary according to the cortical surface of each individual. Partial volume artefact is reduced as the spatial resolution of the scanner is improved.

When repeated measurements are made on the same subject there is also the error that can arise if re-positioning is not accurate since the image slices will not be aligned in exactly the same plane. In particular, partial volume artefact will alter according to the image plane.

Provided that patients and controls are scanned concurrently, and relaxation times or signal intensity are measured in a consistent manner, the only likely source of systematic bias from those listed above is partial volume artefact e.g. if patients exhibit more sulcal atrophy then cortical grey matter readings are likely to include a greater proportion of cerebrospinal fluid. However the other effects will all contribute to greater variance in the measurements, thereby reducing the chances of detecting a real difference. Additional sources of variance are likely to arise from intrinsic differences between individuals but these reflect real biological effects rather than scanner artefacts.

Image intensity values are specific to each sequence, so that it is rarely feasible for a group to establish normative values and examine these sources of error for each of the many sequences they wish to use. In contrast, relaxation times are independent of the sequence used and it becomes practical to invest the necessary time in quantifying these effects. By the same token they also provide a more universal scale of measurement for different groups to compare results. The only advantage of image intensity values lies in the shorter time required for their collection.

b) Structural measurements

For structural measurements it is necessary to calculate an anatomical area or volume, and here the critical factor is defining the relevant anatomical border. The traditional method, other than a crude visual rating, has been to trace it by hand and then use a planimeter to calculate the enclosed area. With the advent of digitised images and image processing there are now several different alternatives to select from, which will be discussed later, but essentially the main sources of artefact are those altering the appearance of an anatomical boundary, or distorting the relationship between the area of a pixel and the real area that it represents.

A major problem in deciding where the boundary between two structures lies can be partial volume artefact. As discussed above, this involves the inclusion of two or more tissues in a single voxel, which has the effect of making any edge fuzzier in appearance than it is in reality. Greater slice thickness inevitably means greater partial volume artefact, and this is the main reason for trying to obtain images in thin slices. If, as a consequence of this artefact, it is not possible to trace an anatomical edge then a specific cut-off value in signal intensity between two tissues may be used to provide one. In such cases signal non-uniformity across different slices, as well as within each slice, may become important as the cut-off value will separate the two tissues differently over various parts of the image.

To infer abnormalities in an irregular 3-D structure from a single slice is to invite difficulties in interpretation and replication, given the wide variations in shape, position and symmetry that are often seen in the normal population. It is therefore desirable to estimate the size of an irregular structure by volume, not by area. A

substantial degree of variance in area measurements is likely to arise from small changes in the slice position through such a structure. Area measurements are obviously still appropriate for those structures like the corpus callosum that have no clear boundary except in one specified plane. Contiguous multislice imaging remains the main approach to volumetric measurement until such time as 3-D data collection over large volumes of the brain is quick enough to be practical.

Anatomical shape can vary greatly in each individual so that, even with volumetric measurements, sufficient subjects are required in a sample to define clearly the distribution of its values. This irregularity also means that, in the case of repeated measurements, it is important to achieve a high degree of re-positioning accuracy. Consequently, the reliability of an area or volume measurement is assessed more thoroughly if, instead of being re-measured from only a single scan, it is recorded from repeated scans of the same person.

Subject movement is a frequent problem, usually in the form of mild fidgetiness during a scan, and always contributes to more partial volume artefact. If severe it can also cause displaced "ghost" images in the direction of the phase encoding gradient. Rhythmic movement from the cardiac cycle can be reduced by signal averaging or electrocardiac gating, but is likely to be a particular problem with medial temporal lobe structures lying close to the internal carotid arteries. Narrow parts of the ventricular system, such as the foramina of Munro or the third ventricle, may show fluid turbulence secondary to systolic pulsation which alters the CSF appearance at that point (Quencer et al 1990).

Geometric distortion is the term given to discrepancies between the area of a pixel and the real area it should represent, caused largely by changes in the gradient fields, which needs to be borne in mind if structural measurements are to be valid. Geometric distortion within slices should be routinely recorded if any structural comparisons are involved, particularly when small inter-hemispheric differences within each subject are analysed.

6. IMAGE PROCESSING

In MRI, as in CT, the overall appearance of an image is composed of many pixels, each of which is a small uniform area to which is attached a single number that represents the signal intensity over that area. The image is essentially a numerical (or "digital") description to start with, and only secondarily may get transferred onto film. Computerized image processing is simply the manipulation of these numbers to try and make a scan more informative than having it remain in its original state. One of its great advantages is the capacity for quantifying a large number of measurements in a rapid and uniform manner, of which an example used in this study was to derive a calculated T_1 image from two original ones. It is also possible to remove certain types of artefact, such as signal non-uniformity. With MRI scans such image processing is being performed with increasing frequency and complexity, either replacing or supplementing the use of visual assessments and manual tracing from images on film. Its use is quite straightforward when an area is traced directly on a screen displaying the original images, but it becomes less so as data transformations take place and the identification of various structures becomes automated.

High reliability becomes possible using just one scan, where the computer repeats its operations on the same original numbers, but this will be no guarantee of similar results if the original data is marginally different. Again this reinforces the argument that an adequate test of reliability should include different scans of the same individual before concluding that stable measurements have been obtained.

Segmentation

For many purposes, including structural measurements, it is essential to recognize and group together pixels that are anatomically related. This is called segmentation of an image. It requires not only a similarity in their signal intensity but also some specification of that anatomical relationship. Defining the edge of a structure is one of the most important ways this can be achieved, and is crucial in deriving valid structural measurements.

Drawing around an anatomical structure by hand is, in fact, a simple example of segmentation. It suffers from the disadvantages of needing a clearly visible edge, a steady hand and an abundance of time. The alternatives all involve some numerical decision about the level of signal intensity that will separate one tissue from another (a "cutoff" value), combined with some anatomical guidance about where this cutoff value should be applied on an image.

Automation is clearly desirable if a large number of measurements have to be made, although the time saved should not be at the cost of reduced accuracy and if possible should improve it. A sharp border between two tissues can be readily identified by an appropriate computer program, and measurement then made of the enclosed area. Several methods of automated edge detection are possible but their differences are small compared to other intrinsic aspects of the image that determine the eventual result (Zhu et al 1986). If the border cannot be seen clearly by the naked eye it is unlikely that one program will perform substantially better than another, and if it can be seen clearly then most programs will function with similar competence.

Blurred edges

Poorly defined "fuzzy" edges are a frequent problem during segmentation. This may be an intrinsic part of the anatomy or result from partial volume artefact, and can occur despite high signal contrast between two tissues. In such situations neither automatic edge detection or manual tracing is feasible.

One approach to this problem is to make use of a "filter", which is a program that selects out part of an image and enhances it. Enhancement of the edges between structures can be made in this way by focussing on areas of rapid signal change. However this carries the price of losing information about the original signal intensity values, and is frequently rendered ineffectual by enhancing only patchy segments of an edge rather than its entire length.

A commoner solution, which is dealt with further in the methodology of this study, is to simply set a signal value that will act as a cut-off between the two tissues. Information intrinsic to each scan needs to be used, since a constant value set across all individuals could not accommodate the wide variation in signal intensity values between them. The frequency distribution of signal intensity across each scan is a useful starting point, since ideally one can find the point(s) in a bimodal or trimodal distribution of intensity values which maximally separates the relevant tissues. This approach is often hampered, though, by partial volume artefact obliterating the trough between two modal values to yield only a unimodal distribution. In this situation an appropriate cut-off value may not be easy to identify.

With these various technical considerations in mind, it is now possible to describe the method developed for this present study. As mentioned earlier, the study was

intended to identify any focal lesions, to look at tissue relaxation times, and make volumetric measurements. The latter included temporal lobe volume, and also the cortical and Sylvian fissure volumes, that had not previously been quantified on MRI. Possible differences according to genetic liability were to be emphasised, as argued by Lewis et al (1987). Only cases with typical schizophrenia were to be examined so that results could be generalized to the wider population, but to appreciate whether any structural changes varied with illness duration the sample was to include patients with acute as well as chronic illness. The control group was to be formed of healthy subjects.

THE STUDY

CHAPTER 4 METHODOLOGY

1. SUBJECTS

a) Patients

Patients were selected using operational diagnostic criteria. The Research Diagnostic Criteria (RDC) for schizophrenia (Spitzer et al 1978) were chosen, as opposed to narrower criteria such as the DSM-III-R (American Psychiatric Association 1987), in order to include some patients without chronic illness (see Appendix A). It was envisaged that patients with affective disorder would provide a future psychiatric comparison group, so patients with both affective and schizophrenic symptomatology (RDC schizo-affective disorder) were excluded in order to retain maximum contrast between the two groups.

There were 202 patients, drawn from all admissions to the Maudsley and Bethlem Royal hospitals over the previous 13 years, that had a diagnosis of RDC schizophrenia and met the following inclusion criteria:

a) present age no greater than 50 years. This age limit was imposed to exclude cerebral changes attributable to ageing (Davis & Wright 1977; Gyldensted 1977; Dekaban & Sadowsky 1978; Khang-Cheng et al 1980; Zatz et al 1982; Stafford et al 1988; Jernigan et al 1990).

b) a previous CT scan without evidence of unrelated cerebral pathology, (epilepsy, head injury with post-traumatic amnesia, previous neurosurgery for any reason,

vasculitis, encephalitis cerebral sarcoidosis etc.) or developmental abnormalities, such as partial agenesis of the corpus callosum or cystic septum pellucidum, which although known to occur in schizophrenia would usually be regarded as atypical. The likelihood of co-operation with the MRI procedure would be greater if the patients had already accepted a brain scan and were familiar with such technology. Patient recruitment extended back over 13 years as this was the length of time that these hospitals had operated a CT scanner.

c) no alcohol abuse. Gurling et al (1984) had identified, using MZ twins discordant for alcohol abuse, that a weekly alcohol intake of 55 units was approximately the level at which pathological changes start to appear on CT scans (Ron et al 1982); this level was also supported by data from Harper et al (1988). Therefore any regular alcohol use in excess of 55 units weekly, whether currently or in the past, was taken to exclude a subject. If excessive drinking was likely, but doubt existed about the exact intake, then it was decided to err on the side of caution.

d) no recorded IQ of under 70. Various genetic and other organic abnormalities, not typically seen in schizophrenia, often underly major cognitive impairment.

e) no diagnosis of anorexia nervosa. This disorder can involve demonstrable cerebral abnormalities on CT that can persist beyond the period of obvious starvation and can resemble the changes seen in schizophrenia (Dolan et al 1988; Krieg et al 1989; Palazidou et al 1990), so it was considered inappropriate to include patients with this condition as well as schizophrenia.

d) no history of treated hypertension. Cerebral pathology in hypertension has become more widely appreciated since the use of MRI has identified focal abnormalities that are presumed to be due to vascular events, although it is more prominent in people over the age of 50 years than under (Awad et al 1986; Kertesz et al 1988).

e) suitable family history. In view of the hypothesis about familial and non-familial schizophrenics having different scan findings it was clearly desirable to maximize the number of informative cases which could be clearly allocated to one or other of these two sub-groups. Cases were therefore excluded where there was no adequate family history available and no suitable family members who might provide one. Similarly, patients with either a first degree relative diagnosed as having an affective disorder, or a second degree relative specifically with bipolar disorder, could not be simply categorized as either familial or non-familial schizophrenics, and they were omitted as well.

Attempts were then made to trace these patients through general practice records, family practitioner committees, social services, hospital records, writing to relatives, and using the National Health Service Central Register. Ethical approval to involve them in this study had previously been obtained. If a patient was living with relatives or in a hospital/hostel then the relevant carer was contacted first to ensure that there were no objections to the study; if the patient was living more independently then this first contact was made to their general practitioner. It emerged that eight patients had since died, and a further 54 were either untraceable or were regarded as unsuitable either by virtue of their clinical state or geographical distance. A letter was then sent to 140 patients inviting them to participate, and explaining both the purpose of the study and exactly what it would involve. Sixty-seven accepted, 57 refused and the

remaining 16 gave no reply despite a further attempt to contact them. Of these 67 patients who accepted 17 had a known family history of schizophrenia. Everyone was warned about the risk of metallic implants entering a strong magnetic field but only one patient, with a delusional belief about a transmitter in his head, declined for this reason.

After interview, a further seven patients were excluded due to a history of anorexia nervosa (n=3), treatment for hypertension (n=2), and serious overdose with possible cerebral damage (n=2).

b) Controls

1. A socio-demographic control group. The purpose of the above selection process was to obtain a patient group whose brain scans would be as representative as possible of schizophrenia, but it was quite possible that its stringency had introduced other unforeseen biases. To see if this might be the case the sociodemographic characteristics of the 67 patients in the patient group were compared to those of 43 consecutive schizophrenic patients recently admitted to the same teaching hospitals, part of a larger research sample that interviewed all admissions with a functional psychosis. A comparison between the two groups is given in Table 5.

2. Imaging controls. Healthy controls (n=36) were obtained mainly from local ancillary hospital staff (secretaries, porters, nurses and engineers), and from the local population through an employment agency and a Salvation Army training college. Group matching for age, sex, race and parental social class was made as close as possible, although matching on an individual basis was not carried out. These

variables were considered important since sex and race influence head size and shape, whilst reductions in cerebral volume have been correlated with age (Davis & Wright 1977; Khang-Cheng et al 1980; Jernigan et al 1990). As mentioned in the review the necessity of social class, matching because of its possible influence on head size, is contentious but the use of parental rather than patient social class seems to provide a satisfactory match without distortion from low occupational status consequent to a schizophrenic illness. The results of the group matching can be seen in Table 5.

Identical exclusion criteria applied to the controls as to the patients, except for stipulating the absence of both a past psychiatric history and a family history of schizophrenia. Controls were recruited over the same period as the patients in order that the two groups could be scanned concurrently.

2. CLINICAL ASSESSMENT

Clinical and socio-demographic data were collected through personal interview of the patient and an informant, who was the mother in 34 cases. In most instances these two interviews were conducted on separate occasions, and the majority were carried out at the interviewee's home address. The patient interview was made on a separate day before the scan took place, and the mean interval between these two dates was 19 days.

Semi-structured interviews, drawn up specifically for this study, were used. Socio-demographic data included sex, age, ethnic group, marital state, educational achievement, and a grading of occupation (Goldthorpe & Hope 1974) both for present and highest previous levels. Paternal occupation during the patient's childhood was also recorded. An assessment of their mental and physical state included details of early development, head injuries, alcohol and drug use, illness onset and course, levels of medication and subsequent clinical response. The dosages of current antipsychotic medication were converted into chlorpromazine equivalents using published data (Davis 1976; Hargreaves et al 1987). A detailed family history was taken from the informant as well as the patient.

The other measures included were designed to cover a range of aetiological information, clinical symptoms and measures of disability and poor outcome:

a) the Present State Examination (PSE) of Wing et al (1974), to assess the presence of any psychiatric symptoms over the past month, particularly psychotic symptoms.

b) the Pre-morbid Adjustment Scale (Gittelman & Klein 1969; Kokes et al 1977; Cannon-Spoor et al 1982), which provides an indication of premorbid personality and social adjustment.

c) the Negative Symptom Rating Scale (NSRS) of Iager et al (1985), to record the severity of symptoms such as reduced communication and self-care, poor motivation, lack of emotion and spontaneity, and withdrawal from outside interests and social life. It draws upon the informant's assessment as well as observing and talking to the patient.

d) the Disability Assessment Schedule or DAS (de Jong et al 1985; Jablensky et al 1985; de Jong & Molenaar 1987), an instrument devised by the World Health Organization that measures current social function in people with psychiatric disorders.

e) the Assessment of Involuntary Movements Scale or AIMS (Guy 1976) for recording the presence and severity of tardive dyskinesia in different parts of the body.

f) the Annett scale (Annett 1970) for estimating the degree of left or right handedness shown across a variety of activities. This scale was included because handedness relates to structural asymmetry of the brain, and also non-familial left handedness might provide accessory evidence of some previous brain insult.

g) the New Adult Reading Test or NART (Nelson 1978) for estimating pre-morbid IQ.

h) obstetric details concerning the patient, rated on the scale of Lewis et al (1988) for obstetric complications. Again, this was to elicit evidence that might point to an early

brain insult, relevant both to the aetiology of schizophrenia and the interpretation of their MRI scan. This scale was constructed from previous scales that identified events associated with an increased neonatal morbidity or mortality. A questionnaire (see Appendix B) was compiled to systematically collect these details.

Each interview took approximately 1.5 - 2.0 hours. Measured height was recorded at the time of scanning, along with any recent changes in medication or mental state since the interview took place, and written consent obtained. For women, the point in their menstrual cycle, if it was present, was noted in view of possible MRI changes as fluid balance alters (Rosenthal et al 1985; Grant et al 1988).

Case notes were obtained from other hospitals, both for the patient and for any relative that had been admitted to a psychiatric hospital, and a family history of psychiatric disorder assessed using the Family History-RDC criteria (Andreasen et al 1977). The family history data was also rated for the presence of schizotypal personality disorder, which may be genetically related to schizophrenia, using criteria devised by Kendler et al (1984).

The details from the two interviews with the patient and informant, along with information from the various hospital case-notes, were collated onto a rating sheet that allowed direct data entry into a computer (see Appendix C). This included a measurement of the ventricular-brain ratio from their CT scan, made by manual planimetry on either an X-ray film or at the computer console (Synek & Reuben 1976). Diagnoses were made according to the ICD-9 (World Health Organization 1978) and DSM-III-R classifications, in addition to the RDC.

Information collected from the controls included their age, sex, race, personal and parental occupation, history of head injury or other relevant medical condition, personal and family psychiatric history, current medication and alcohol intake, their NART score and academic achievement, and the Annett scale. Height, menstrual phase, and written consent were obtained at the time of the scan as for the patient group.

3. THE IMAGING PROCEDURE

The scanner was situated at the National Hospital for Neurology and Neurosurgery, and had a 0.5 Tesla superconducting magnet. There were no major changes in the running of this machine over the course of the study. In choosing the image sequences there were several objectives in mind, the requirements of which had to be balanced to achieve the best possible compromise.

A major objective was to obtain maximum contrast between white matter, grey matter and CSF, to allow accurate structural measurements of various grey matter, white matter and CSF regions; in addition, such an objective meant that visual inspection would be sensitive to the presence of any focal lesions. A second objective was to scan the entire brain, but to focus particularly on satisfactory definition of the temporal lobes, the hippocampi and temporal horns. It was also clear that the volume rather than just an area of any relevant anatomical structure had to be obtained if at all possible. A final objective was to include relaxation times in addition to volumetric measurements. The following three sequences were eventually selected to meet these aims, and were kept unchanged throughout the study:

a) The coronal IR_{4420/150/40} sequence

This sequence, forming the main set of images, was chosen for its excellent tissue contrast not only between grey matter, white matter and cerebrospinal fluid but also between chronic lesions and surrounding white matter. This high level of anatomical definition made it very suitable for both structural measurements and the visual assessment of focal lesions. It was based on a modification of the standard inversion-

recovery sequence that was developed for suppressing lipid signal (Bydder & Young 1985; Johnson et al 1987a; Petrie 1987), and is described by the acronym "STIR" since it is a Short inversion Time Inversion Recovery sequence. Its contrast efficiency compared very favourably with other IR and SE sequences available at that time (Johnson et al 1987a). The final parameters selected for this STIR sequence were $T_e = 40$ msec., $T_i = 150$ msec. and $T_r = 4420$ msec. (notated as $IR_{4420/150/40}$), with 20 contiguous 5mm coronal slices. Matrix size was 256 x 256 pixels, the field of view was 30cm, and one excitation was used.

The very long repetition time (T_r), in excess of 4000 msec., maximized both the contrast between grey matter and sulcal fluid and the number of slices obtainable in one multislice STIR image. With this long T_r approximately 20 slices could be collected simultaneously. Since the inversion time (T_i) was short, the echo time (T_e) was also kept relatively short in order to maintain contrast between grey and white matter.

The preferred plane for imaging the limbic system and temporal lobes was coronal, since this showed the temporal lobe anatomy almost perpendicular to its long axis and minimized partial volume artefact; oblique planes, ideal for this purpose, were not then available on this scanner. The temporal lobes normally span about 7 cm. in the coronal plane, and contiguous slices were required to cover this volume without leaving gaps of tissue between them. Twenty slices of 5 mm. thickness, the smallest width that allowed good anatomical definition without compromising image quality, also permitted much of the frontal lobe to be included as well as the temporal lobe.

To ensure that all of the temporal lobe was imaged, the first slice was positioned at its posterior limit, and the final slice reached a variable position in relation to the frontal pole. In some cases, the anterior portion of the frontal lobe was not included, but a greater number of slices would have greatly extended the scan duration. To achieve accurate positioning three initial pilot scans were performed, one in each plane (McManus et al 1989). Unlike a single pilot scan this could not only situate the first slice at the posterior aspect of the splenium but also allowed the images to be placed exactly along the midline, thereby avoiding any asymmetry from misalignment. The splenium was chosen since it was readily visible on the mid-sagittal pilot and lay immediately posterior to the caudal ends of the fornices, dentate gyrus and temporal horns, which were to be used in defining the posterior border of the temporal lobe. Examples of this positioning from the mid-sagittal pilot, and the coronal STIR image itself, are given in Figures 1 and 2.

b) The coronal SE_{1980/40} sequence

This sequence was specifically chosen to allow the calculation of T_1 times from the above STIR images, and for this purpose it had to be a SE sequence with the same T_e and the same number of 5mm. slices in exactly the same position (Figure 3).

The STIR sequence, including the initial pilots, took ~ 23 minutes and there had to be at least one other sequence if any relaxation times were to be calculated from it. This had to be performed consecutively with the STIR, during a single session in the scanner, since these calculations assume that corresponding pixels from each scan represent identical anatomical positions, yet it was regarded unlikely that patient co-operation in keeping still would extend much beyond half an hour. To remain within

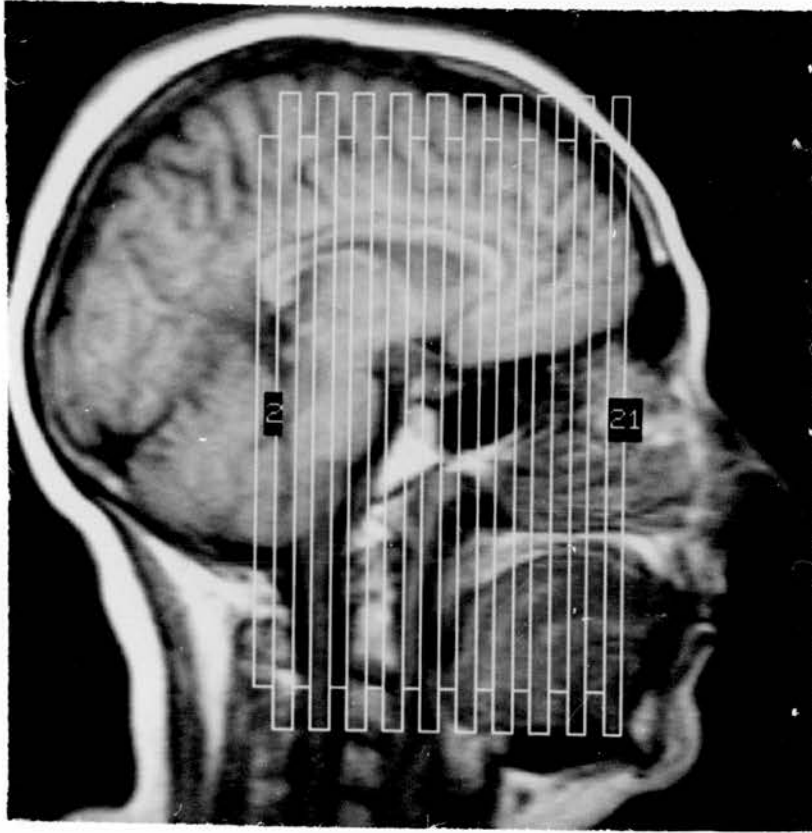


FIGURE 1

THE MIDSAGITTAL PILOT WITH INITIAL
POSITIONING OF THE 20 CORONAL SLICES.

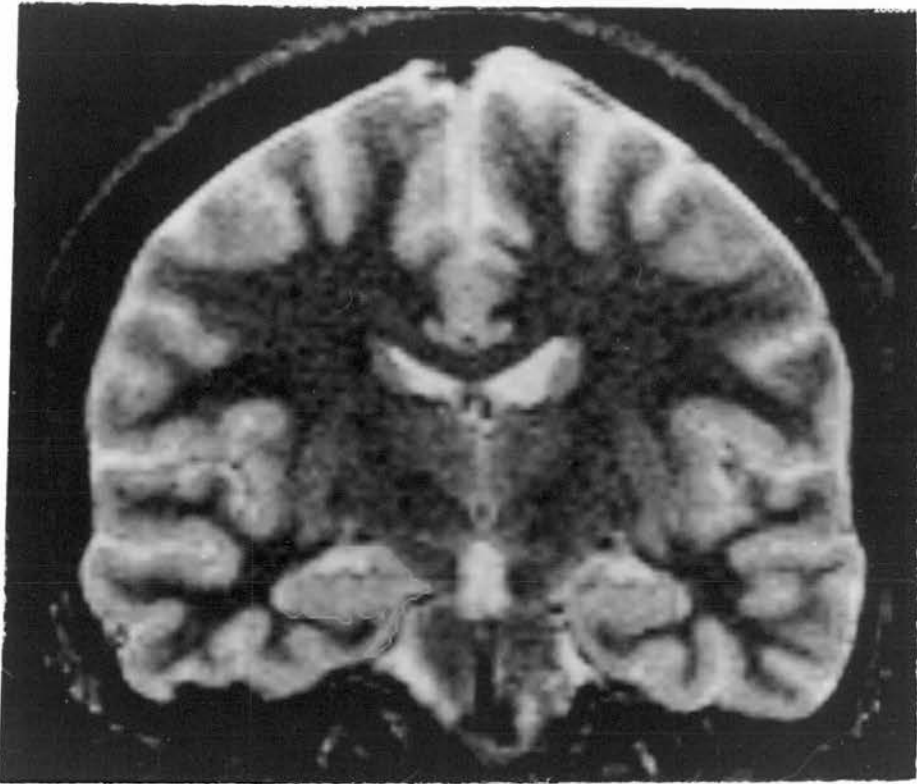


FIGURE 2 THE CORONAL STIR SEQUENCE (IR_{4420/150/40})

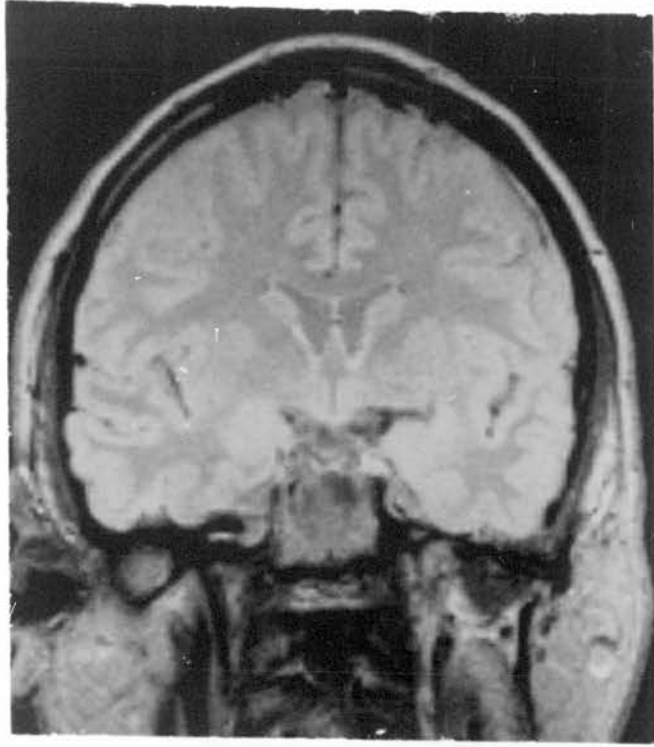


FIGURE 3 A CORONAL IMAGE (SE_{1980/40})



FIGURE 4 A TRANSVERSE IMAGE (SE_{2400/70})

this time limit only one sequence was employed, permitting T_1 times to be obtained in preference to T_2 times, since the latter are probably the less sensitive of the two in detecting chronic gliosis (Barnes et al 1988a).

c) The transverse $SE_{2400/70}$ sequence

A second shorter session covered the entire head, in a single $SE_{2400/70}$ sequence, using 24 contiguous transverse slices that started at the vertex and extended down into the posterior fossa. This allowed measurement of intracranial volume, and the detection of lesions in both infratentorial structures and the parieto-occipital region. This more T_2 -weighted sequence also supplemented the T_1 -weighted appearances of the STIR sequence (Figure 4). Transverse slices meant that areas already covered by the coronal sequences could be viewed differently if changes were of doubtful significance.

Matrix size, field of view, number of excitations and slice thickness were kept the same as above. Whilst white and grey matter had good contrast, cerebrospinal fluid was poorly shown against both these tissues, so that the ventricular system was poorly seen and sulcal fluid volume could not be measured separately. The T_e did not exceed 70 msec. since it would have sharply increased scanning time beyond 10 minutes.

Sixty patients were scanned, along with 36 controls, but afterwards it was clear that the quality of some of the patients' images were too poor to allow any useful data analysis. This low quality arose from either movement artefact or scanner artefact; in addition one scan was accidentally erased from the magnetic tape. In the patient group 49 scans were suitable for white matter relaxation time measurements, 48 for

volumetric measurements, and 42 for basal ganglia relaxation time measurements. In the controls 36 were suitable for the relaxation time measurements, and 34 for the volumetric measurements.

All images were transferred on magnetic tape from the scanner to a graphics display system (Sun Microsystems Inc., California), as well as being kept on hard copy. They were identified by number alone in order to retain blindness throughout the measurement procedures.

4. VISUAL ASSESSMENT OF THE IMAGES

The first step in analysing the scans was to inspect them in detail for the presence of any lesions or other obvious structural abnormality. This was carried out with the help of an experienced neuro-radiologist, who made this assessment on all the hard copy scans. In this way, all three multislice images were simultaneously examined for each subject, and comparison made between them. Each scan was viewed on three separate occasions, without access to any previously recorded comments, to ensure that any changes were consistently reported.

Examination was made in all areas for both focal lesions and for more diffuse changes in signal intensity. If present, lesions were described by their number, appearance and situation, excluding the normal variant of increased periventricular intensity around the anterior horns (Zimmerman et al 1986). Each component of the lateral ventricles was specifically assessed for both enlargement and asymmetry, and the size and position of any pools of cerebro-spinal fluid in the sulci were recorded. Assessment included any asymmetry of the cerebral lobes and heterotopic grey matter, but not cortical malformations such as macrogyria and polymicrogyria (Piven et al 1990).

5. VOLUMETRIC MEASUREMENTS AND THEIR VALIDITY

The following structural measurements were all obtained from slices obtained using the STIR sequence. The first three of these measurements were truncated volumes of the relevant region, since this sequence did not cover the entire brain, and were taken as a single reading from both hemispheres; the others were complete volumes taken from each hemisphere separately:

- cortical volume (including temporal lobe cortex).
- sulcal fluid volume.
- subcortical tissue (including temporal lobe white matter).
- temporal lobe grey matter volume.
- temporal lobe white matter volume.
- hippocampal volume.
- volume of the temporal horn.
- volume of the body and frontal horn of the lateral ventricle.
- Sylvian fissure volume.

These measurements were all acquired from a single set of readings off each slice, so that other measurements could subsequently be calculated from them:

- total temporal lobe volume: the temporal lobe white and grey matter volumes.
- cerebral volume: the cortex plus subcortical tissue and hippocampal volumes.
- intracranial volume: the volume of the cerebrum, lateral ventricles and sulcal fluid.

Volumes of structures on each slice were taken as their area multiplied by 5 mm. (slice thickness), and relevant slices then added together to obtain overall volumes.

These area measurements were obtained using a combination of three different techniques - manual traces, an automated edge-detector program, and a cutoff value to distinguish grey matter from sulcal fluid. The automated edge detector was used on the border between white and grey matter, which was sufficiently sharp for this purpose, and the manual traces were applied at those points where additional anatomical knowledge was required, for example in tracing around the hippocampi or Sylvian fissures. Grey matter and CSF were outlined as a single area by one or both of these two traces and then separated using the cutoff value. As described earlier (see "segmentation", p. 80) this combination of traces and cutoff values is a common strategy when trying to divide an image into its anatomical constituents.

In the case of intracranial volume a second estimate, for the whole supratentorial volume, was also derived from the transverse SE image.

a) Initial correction of images for artefact

The use of automated traces and a cutoff value operate on an image's digital data and, when applied over different parts of an image, it is assumed that the normal anatomical variations in signal intensity are not distorted by other influences. One such artefact in these images involved signal non-uniformity caused by the shape of the receiver head coil (see p. 76). The signal was brighter in peripheral areas, close to the physical structure of the head coil, compared to the central area that was more distant from it. Although this is not immediately obvious during human scanning, it can be demonstrated if a water-filled phantom that occupies the entire diameter of the head coil is scanned using the same STIR sequence (Figure 5).

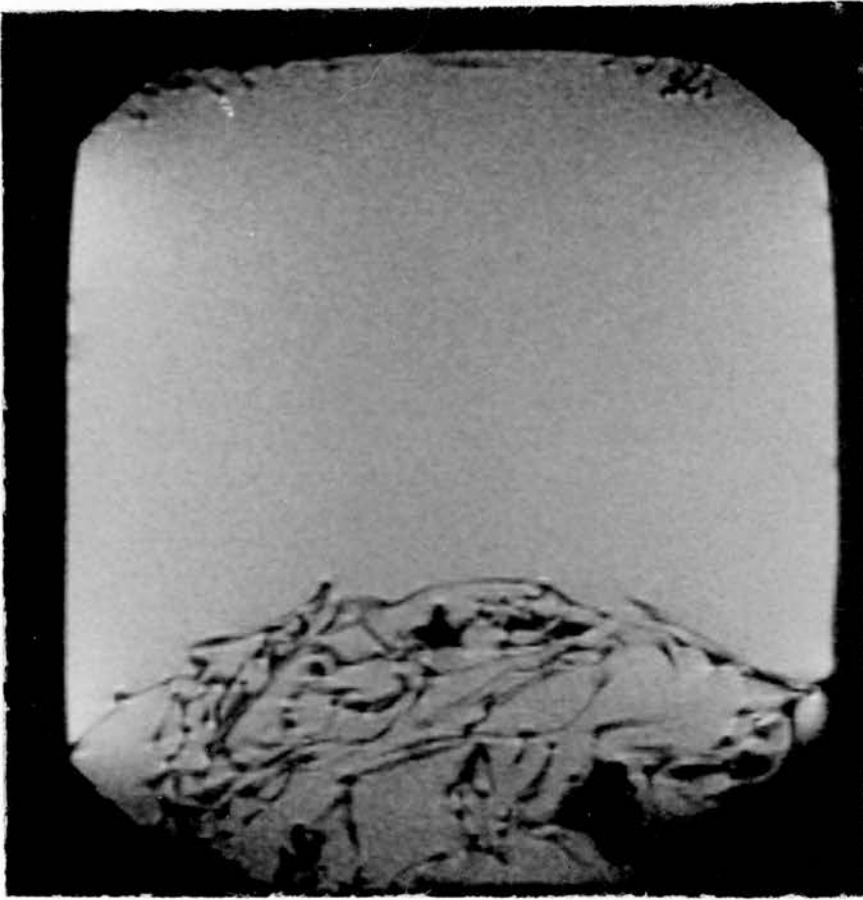


FIGURE 5

PHANTOM SCAN SHOWING NON-UNIFORMITY
OF THE SIGNAL PERIPHERALLY

(lines at the bottom are to be ignored)

This artefact was removed by matching the three dimensional position of each subject's scan, relative to the head coil, to that of the water-filled phantom, and then dividing each pixel of the former by the corresponding pixel of the latter.

Another important artefact, where pixels do not represent the correct area (geometric distortion), could be excluded since regular scanning of phantoms had shown any such distortion to have been less than 1% in each dimension.

Subsequent structural measurements were all made within an image analysis software package called "ANALYZE" (Robb & Barillot 1989).

b) Determining the edge between cortex and subcortical white matter

The distinct border between cortical grey matter and subcortical white matter can be seen, not only visually (Figure 2), but also numerically from the overall frequency distribution of the pixel values in an image. In nearly all subjects the modal values of white and grey matter, and the point between the two distributions that optimally separated them, could be clearly seen (Figure 6).

It was this excellent contrast between grey and white matter that allowed them to be rapidly and reliably separated using an automatic edge-tracking program. The program available simply required the user to identify one pixel on the relevant edge and it then connected up adjacent pixels of similar intensity to form a line; if the result was not entirely satisfactory then the original pixel value could be subsequently adjusted. This approach was not only faster than tracing around each structure by hand but also avoided the problem of manual inaccuracy.

It is important to note that, in Figure 6, there is insufficient sulcal fluid to form any demonstrably separate fluid peak. This was true of nearly all subjects, apart from two patients that had conspicuous sulcal enlargement where a distinct fluid distribution could be seen (Figure 7).

c) Manual traces

Where the automated trace encountered the hippocampal-amygdala complex it was necessary to superimpose a second trace manually in order to outline this structure and the temporal horn accurately, and to define the medial border of the cortical grey matter. It also served to exclude all infratentorial structures, thereby completing the effective separation of cortical grey matter and sulcal fluid from the remainder of the cerebrum (Figure 8).

Other manual traces, whose placement is described below, were required to define the lateral ventricles, the Sylvian fissures, and the temporal lobe cortex.

For many of the subcortical nuclei, their unclear edges meant that neither a manual trace nor an automatic edge-tracking program could be reliably used. White matter and these subcortical nuclei (excluding the hippocampal-amygdala complex) were therefore regarded as a single tissue compartment.

d) Grey matter/cerebrospinal fluid separation

The complex folding of the gyri gave rise to sufficient partial volume artefact with sulcal fluid that, despite good contrast in their signal intensities, this border was too

obscure to allow any reliable trace to be made. This is reflected in the absence of a fluid peak in the frequency distribution of pixel values (Figure 6).

In this situation it became necessary to choose a signal intensity cutoff value that would approximate as closely as possible the boundary between them. This decision had to be made individually for each scan, since there was too much variation in absolute signal intensity between subjects to apply a single value across different scans. Two practical alternatives existed for obtaining this cutoff value:

i) a visual interactive method

Along the top half of the screen four slices were simultaneously displayed in their original form, termed "grey scale" images since a full range of contrast from black to white was included (Figure 9). Along the bottom half were the same slices, except the only contrast was either pure black or pure white, decided according to whether values in the grey scale image were above or below a certain threshold. This black/white threshold was then moved up or down by the user until the white area matched exactly the sulcal area seen on the grey scale image. The black/white threshold value at this point was taken as the cutoff between the two compartments. This interactive method was performed on three separate occasions for each scan, and the mean value taken.

ii) isolating cerebrospinal fluid from each image

The frequency distribution of cerebrospinal fluid, not obscured by the grey matter (Figure 6), could be made visible by creating a new image for each person. On each

slice of the original image a trace was drawn around the fluid in the lateral ventricles, keeping clear of the ventricular edge. The remainder of the image outside this trace was discarded, so that twenty slices with small areas of fluid on some of them were retained separate to the original ones. A frequency distribution of this new image then revealed the fluid compartment in isolation (Figure 10). This approach is discussed further in Appendix D, but essentially a cutoff value was derived from the mean and standard deviation of this distribution.

The first of these methods was preferred since it had the advantage of greater face validity, insofar as the rater saw where the boundary was being situated for any given cutoff value, whereas the second was calculated without any such display. In view of the uncertainty about this boundary, it was decided to retain both methods, to see if some further validation of the former could be gained from the latter by obtaining congruent results. In actual fact, the two methods agreed to within 5% in 67 (82%) of cases (see Appendix D).

Simply applied to the whole image such a cutoff value paid no regard to anatomical differences between pixels of the same intensity value, so at best it yielded a global volume for the image's entire fluid compartment and at worst included misleading signal from unwanted structures such as the sinuses. Anatomical specificity was achieved by applying it only to pixels within a traced region of interest. The automatic trace used above had already separated off a region of interest that contained the cortical grey matter and sulcal fluid, so concomitant use of the cutoff immediately allowed these two to be distinguished and their areas measured. In similar fashion, the previous manual trace around the hippocampus and temporal horn, combined with this same cutoff value, yielded their individual areas.

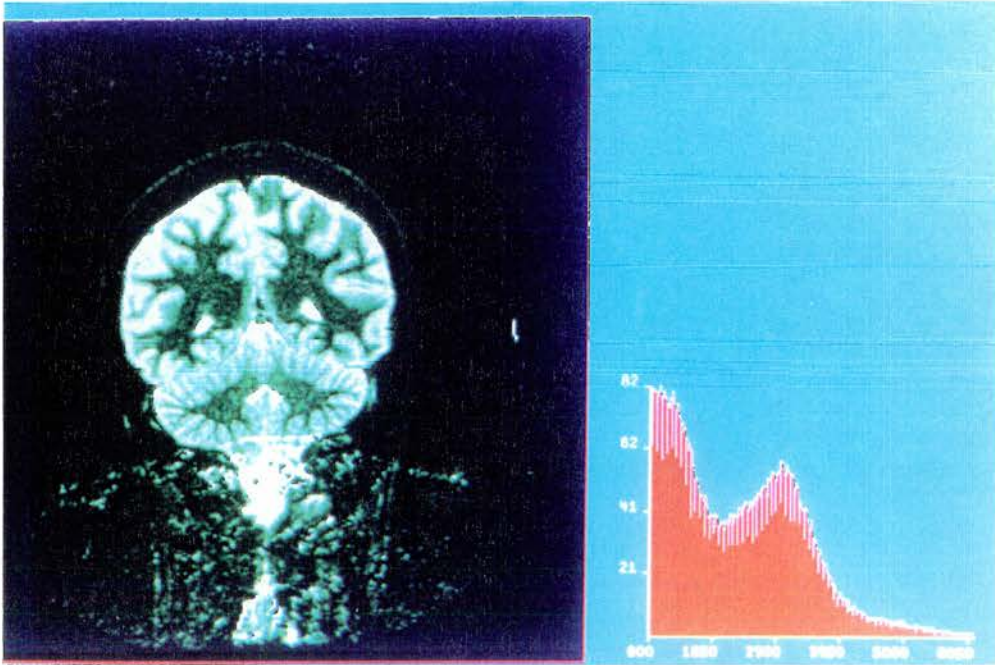


FIG. 6 The overall frequency distribution of signal intensity: common appearance.

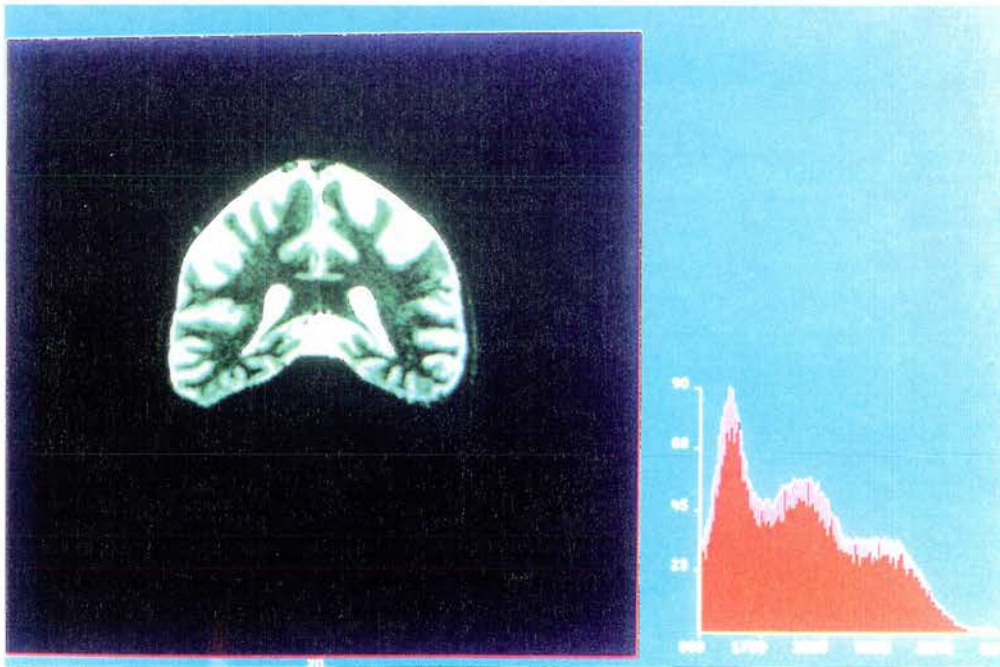


FIG. 7 The overall frequency distribution of signal intensity: sulcal enlargement.

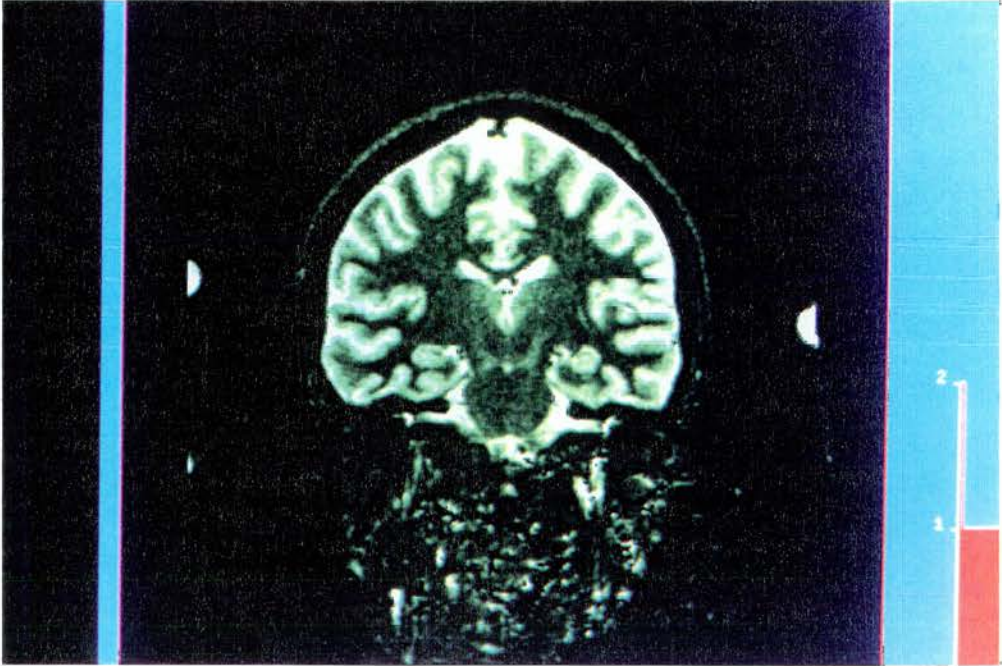


FIG. 8a Original STIR sequence used in Fig. 8b.

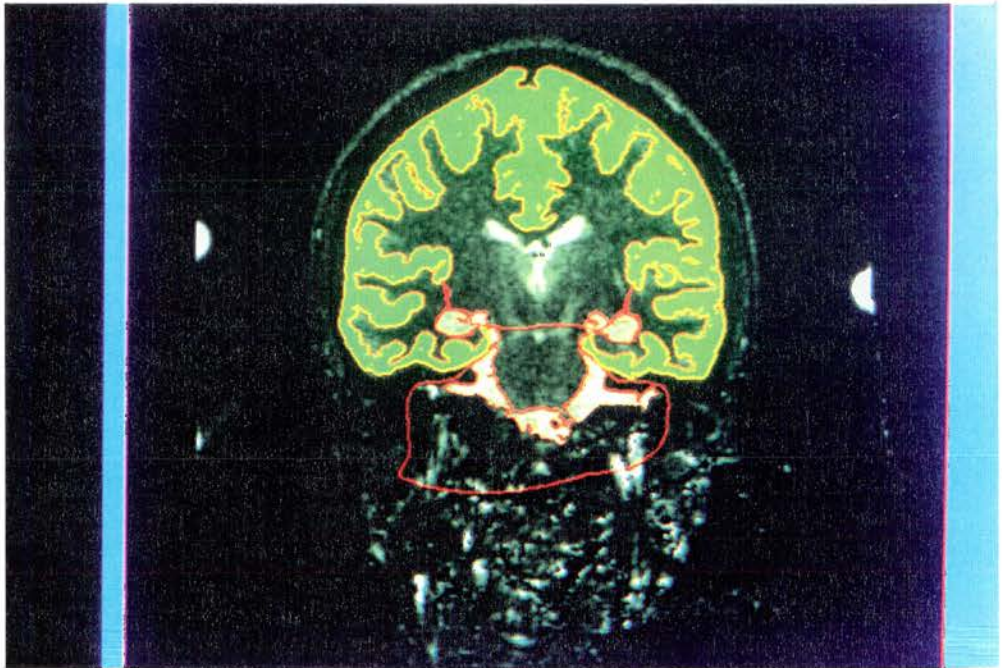


FIG. 8b Cortex and sulcal fluid separated from white matter by automated edge detection.

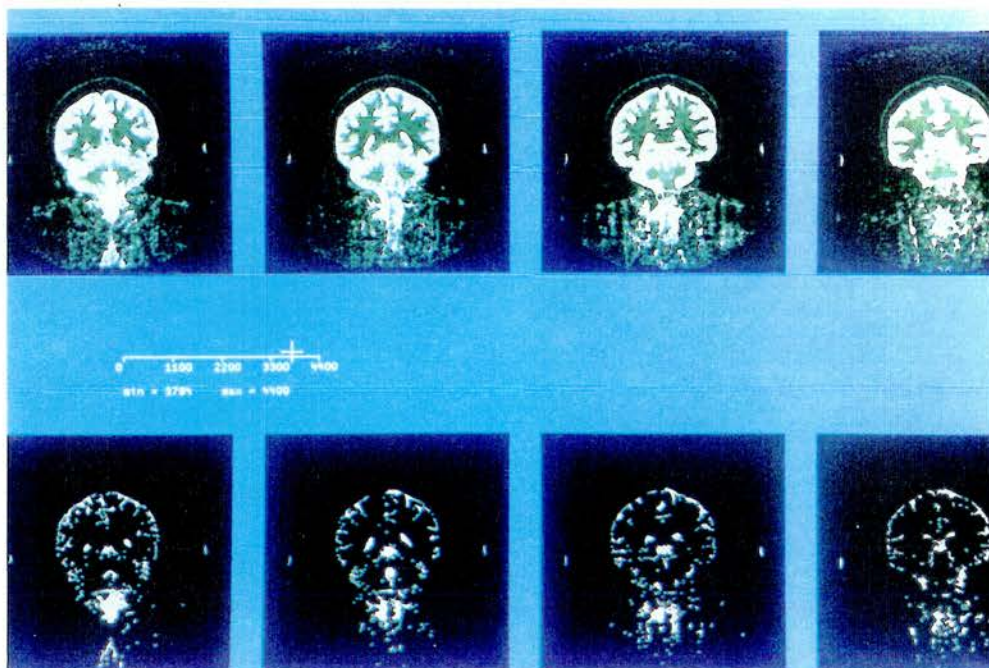


FIG. 9 Deciding a fluid cutoff value by adjusting the lower images to best match the upper ones.

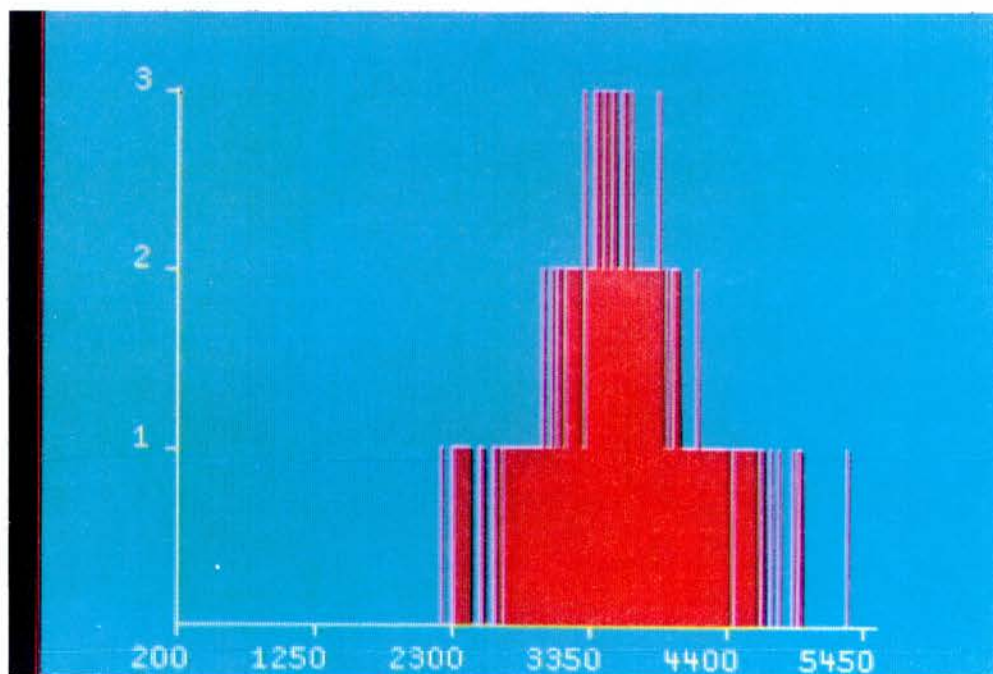


FIG. 10 The distribution of signal intensity values from images edited to contain fluid alone.

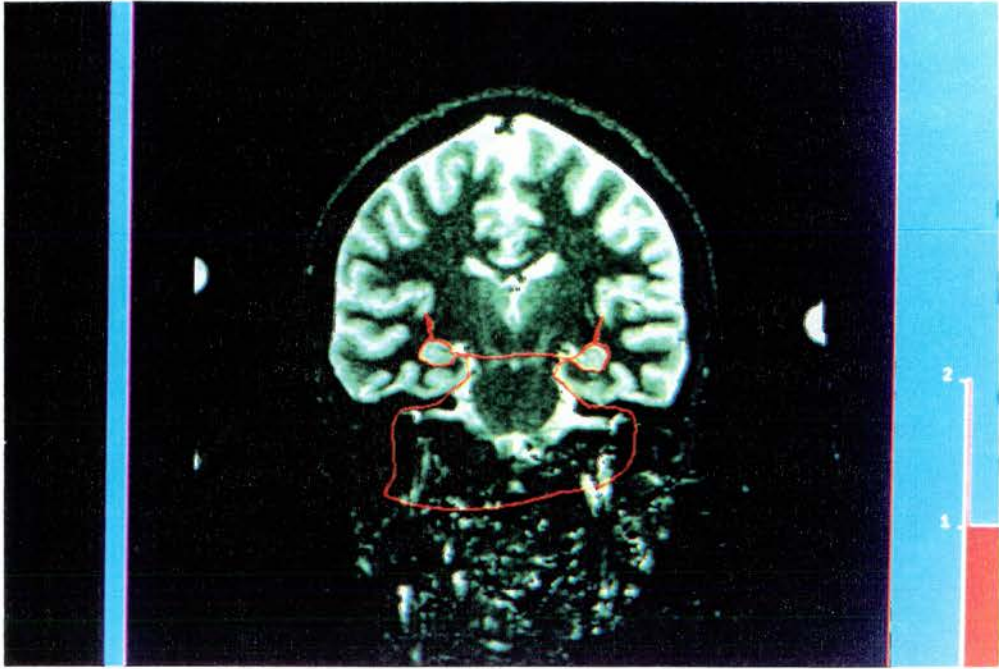


FIG. 11 A trace around the hippocampi and temporal horns, excluding the infratentorial area.



FIG. 12 Measuring left temporal lobe white matter.

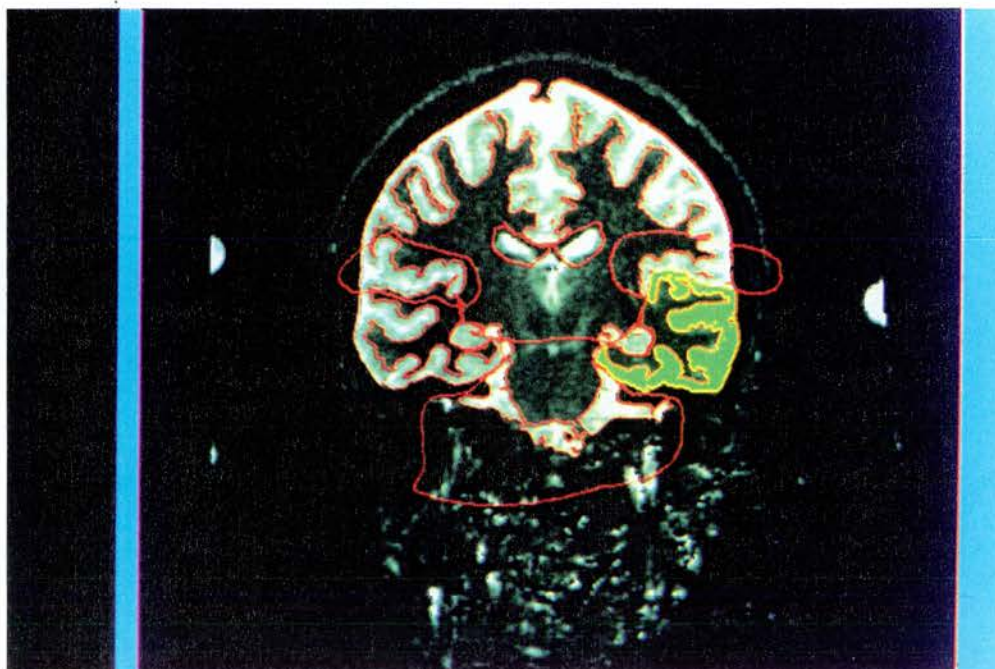


FIG. 13 Measuring the left temporal lobe cortex and its adjacent sulcal fluid.

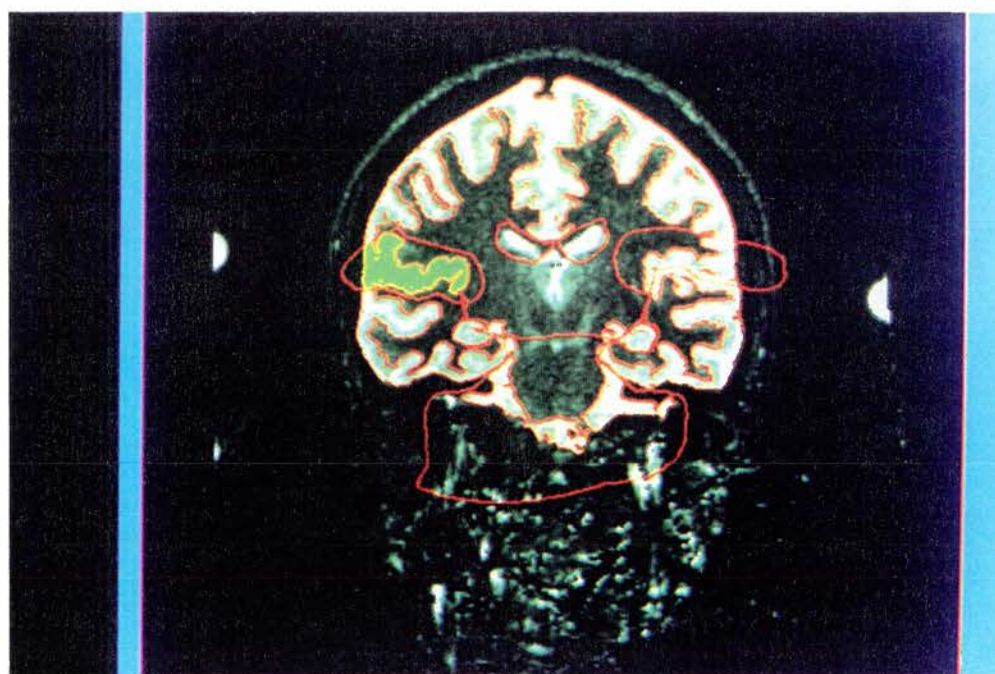


FIG. 14 Measuring the right Sylvian fissure and its adjacent cortex.

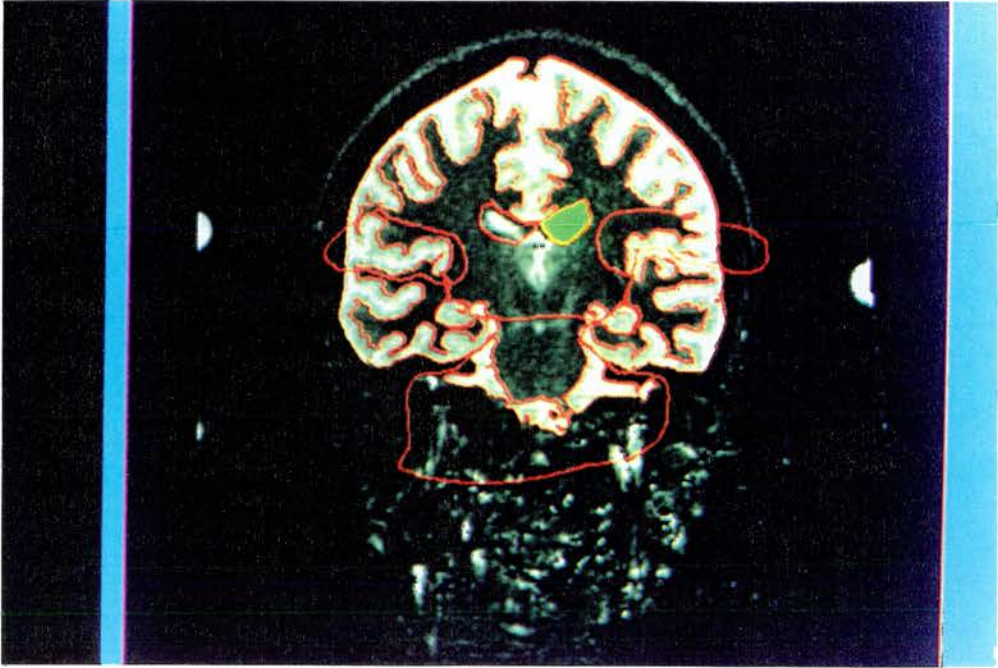


FIG. 15 Measuring the left lateral ventricle and its surrounding white matter.

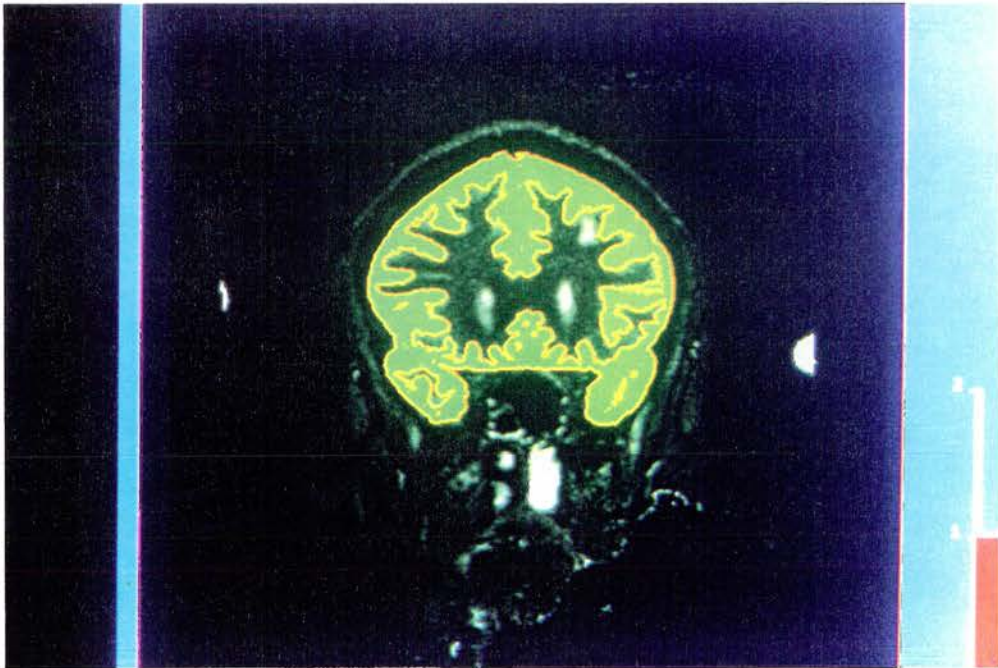


FIG. 16 A more anterior slice - separating cortex and sulcal fluid by automated edge detection alone.

e) Acquiring the volumetric measurements

The posterior limit of the temporal lobe was identified. In this coronal slice the temporal horn was clearly separate from the body of the ventricles and not connected to it through the trigone. It corresponded to the fornix and dentate gyrus curving down into the temporal lobe. Anteriorly from this slice it was possible to measure the hippocampus and temporal horn.

Measurements on each slice followed the same logical order, using a neuro-anatomical atlas for reference (Nauta & Feirtag 1986). A single line was drawn manually around both hippocampi, excluding all infra-tentorial structures (Figure 11). Within this region of interest, the fluid cutoff value separated the areas of the hippocampus and temporal horn. A spur was included in the trace, going across the stem of the temporal lobe white matter.

The automatic trace was next applied, which in combination with the first trace defined the cortex and sulcal fluid (see Figure 8b), again calculated as separate areas using the fluid cutoff value. The temporal lobe white matter and remaining subcortical area were then measured, using the fluid cutoff in the latter to exclude the third and lateral ventricles and cisterns.

The temporal lobe grey matter was measured on each side by adding a further trace along the Sylvian fissures. Removing this and drawing around the adjacent cortex, using the cutoff to select just the fluid component, allowed each Sylvian fissure itself to be measured. The Sylvian fissure was measured anteriorly until it either merged

into the medial cisterns or became obliterated by the sphenoid wing. These traces and the areas measured are demonstrated in Figures 12, 13 and 14.

Each lateral ventricle with a surrounding rim of white matter was then defined, and the area of cerebrospinal fluid similarly separated off (Figure 15).

On more anterior slices the amygdala and diencephalic structures disappear and, as the ventral cortex abuts onto the midline, the first trace becomes redundant (Figure 16). The frontal and temporal lobes separate, necessitating more than one automatic trace to cover the total cortex, but the principle underlying the measurement remains unaltered. Eventually the temporal lobe, Sylvian fissure and ventricular traces can all be omitted, leaving just the frontal grey and white matter plus sulcal fluid to be measured by one automatic trace in combination with the fluid cutoff value.

f) Validity and reliability

The validity of this method can be seen by comparing the volumetric data in the controls to that of healthy controls from other studies (Table 6). The results showed good agreement, except perhaps for the hippocampal-amygdala complex where volumes were slightly lower. This reflected a degree of uncertainty when tracing the amygdala, which often had a poorly defined boundary, that led to both this rather conservative estimate and its low inter-rater reliability. The proportion of the cerebrum, cortex and sulcal fluid to the intracranial volume as a whole was also consistent with previous data (Table 6C).

Inter-rater reliability was examined, using the intra-class correlation coefficient (Bartko & Carpenter 1976), by two raters analysing all these volume measurements from the same eight scans. Test-retest reliability was similarly assessed by re-measuring off the same scan, after an interval of several weeks, the volume of each structure in 10 different subjects. Whether repeated scans on the same individual produced identical volumes was also examined, using six scans collected on one subject over two months; for this purpose the standard deviation over the six scans, expressed as a percentage of the mean value for each volume (the coefficient of variation) was used. These reliability results are given in Table 7. The temporal horn had poor inter-rater reliability, because of its unclear boundary, and extremely poor reliability on repeated scans of the same person, due to the partial volume artefact of such a small volume. Reliability in measuring the Sylvian fissure volumes was also slightly lower than with other structures because of partial volume artefact.

Given the importance of the fluid cutoff value in these measurements, it was essential to establish that the two groups were being similarly measured in this respect. Expressing the fluid cutoff value, determined by the visually interactive first method, as a percentage of the mean CSF value showed that this was indeed the case, being 79.3% in controls and 80.1% in patients.

The size of volumetric change caused by a slight variation in this cutoff value was also ascertained. Eight scans were re-measured, using two different cutoff values for each one, and the largest percentage change occurred in the sulcal fluid, Sylvian fissure and temporal horn volumes. The magnitude of this change was twice as great if it expanded rather than contracted the fluid compartment. This reinforced the importance of being conservative in estimating how low to set the cutoff value.

g) Intracranial volume estimated from the transverse slices

A subsequent measurement of intracranial volume used the transverse slices which, unlike the coronal ones, covered the entire supratentorial volume. After correction of the non-uniformity artefact all extracerebral tissues were removed off each slice, to leave a new image comprised of brain and sulcal fluid alone. This was readily automated since the inner table of the skull has an absence of signal that clearly demarcates the brain from more peripheral tissue. Each image was viewed to correct anatomical errors, and slices below the temporal lobes discounted to arrive at the requisite supratentorial volume, which was possible in 47 of the patients and 32 of the controls.

6. T₁ MEASUREMENTS AND THEIR RELIABILITY

As described earlier, in 3(a) and (b) of this chapter, the IR_{4420/150/40} and SE_{1980/40} sequences yielded two sets of coronal images covering an identical anatomical area. For each equivalent pixel, the signal intensities on these two sets of images were used to calculate its corresponding T₁ value by standard two-point algorithms based on the Bloch equations (see p. 68). In this manner, multislice images were constructed displaying only the tissue T₁ times (Figure 17). The accuracy and precision of T₁ time measurements on this scanner had already been investigated in detail (Johnson et al 1987b), and during this study attention continued to be paid to those factors that influence scanner precision (Miller et al 1989).

By displaying these T₁ images within "ANALYZE", a region of interest (ROI) could be defined in a specific tissue in order to measure its mean T₁ value. The centrum semiovale, comprising a large volume of white matter where readings could safely be made without other tissues intruding into a ROI, was chosen first in order to develop a measurement technique of adequate reliability. Measurements were then extended to the grey matter and basal ganglia.

a) Measurement of white matter T₁ values

On each slice the largest circular ROI that could be positioned solely in the centrum semiovale was selected, and its diameter then reduced to yield an area of 0.74 cm² (54 pixels, equivalent to 0.37 cm³ in volume). Adjacent slices to this one were then examined to ensure that no grey matter or cerebro-spinal fluid could intrude into the ROI and cause partial volume artifact. If this did occur then the ROI was adjusted

with minimum change to its position and size until any such partial volume artifact was avoided. Only one ROI was measured for each side of a particular slice, and the mean value of the pixels in each ROI constituted a single T_1 measurement (Figure 18).

The mean T_1 value of a single ROI was recorded from each hemisphere on each of 18 slices (the end slices were omitted as partial volume artifact could not be excluded there), to give a 2 x 18 matrix of results for each subject. Slice position was measured with reference to the anterior commissure rather than the splenium, as the former is a more developmentally stable landmark (Talairach & Szikla 1967). Position was recorded in centimetres anterior (+) or posterior (-) to this structure. Since the commissure itself was often not visible, the bifurcation of the frontal horns, which lies just superior to it and was clearly visible in all cases, was the actual landmark used.

Test-retest reliability was assessed by one person re-measuring, from T_1 images of 13 different subjects, a ROI from each side of two separate slices (i.e. four different ROI per subject). The intra-class correlation coefficient was 0.89-0.98 ($p < 0.001$); the mean difference on re-measuring any of these four ROI was between 0.2 and 2.8 msec., according to which ROI was chosen. This technique is also highly reliable between raters using the same scan; the intra-class correlation coefficient in this case, using scans from 11 different subjects, was 0.97 - 0.99 and the mean difference between two raters of each ROI was 0.3 - 2.8 msec. In both cases the 95% confidence limits for these mean differences were within 0 ± 5 msec. Measurements in the smaller volume of temporal lobe white matter had lower reliability (intra-class coefficients of >0.6), and they were not considered further as this figure could not be readily improved

upon. For subsequent grey matter readings the reliability was equally low, again due to partial volume artefact, and they were not pursued either.

After developing such a technique it became useful to know the theoretical limit imposed on its reliability, to gauge whether or not further improvements were possible. Such a limit would be imposed by this scanner's level of random electronic noise, which would determine a minimum standard deviation in T_1 values occurring across individual pixels regardless of all other factors. This standard deviation can be calculated for such a T_1 image by deriving its level of noise from the mean and standard deviation of the air background signal in the original SE and STIR data (Tofts 1986). Two slices each from four subjects were examined in this manner to yield an overall predicted value that was then compared to the T_1 standard deviation actually measured in the white matter of these eight slices. The observed standard deviation for T_1 values from the 54 pixels in a single ROI averaged 28.5 msec. and that attributable to electronic noise alone was 25.5 msec. Noise therefore accounted for a mean of 90% (SD \pm 10%) of the observed standard deviation, and the standard error of the mean value from such a ROI could not fall much below 3.5 msec. These figures suggested that, using this scanner, this method's reliability could not be substantially improved any further.

Patients and controls were compared using those 14 slices that were anatomically comparable for all subjects, and analyses refer to these measurements alone. To simplify presentation of the results an overall mean T_1 value for each individual, taken from all relevant slices, is used where possible.



FIGURE 17

A CALCULATED CORONAL T_1 IMAGE

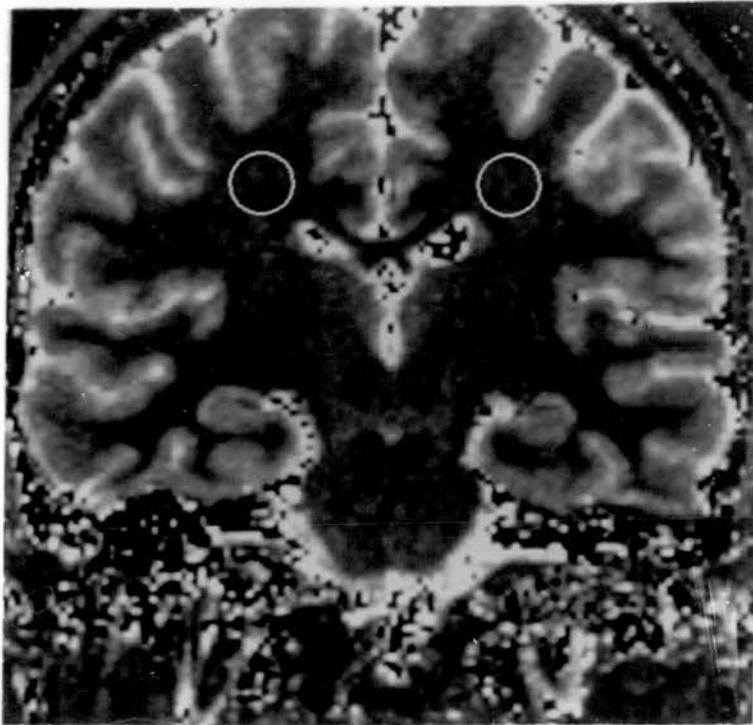


FIGURE 18

A T_1 IMAGE WITH A REGION OF INTEREST PLACED
IN THE WHITE MATTER OF EACH HEMISPHERE

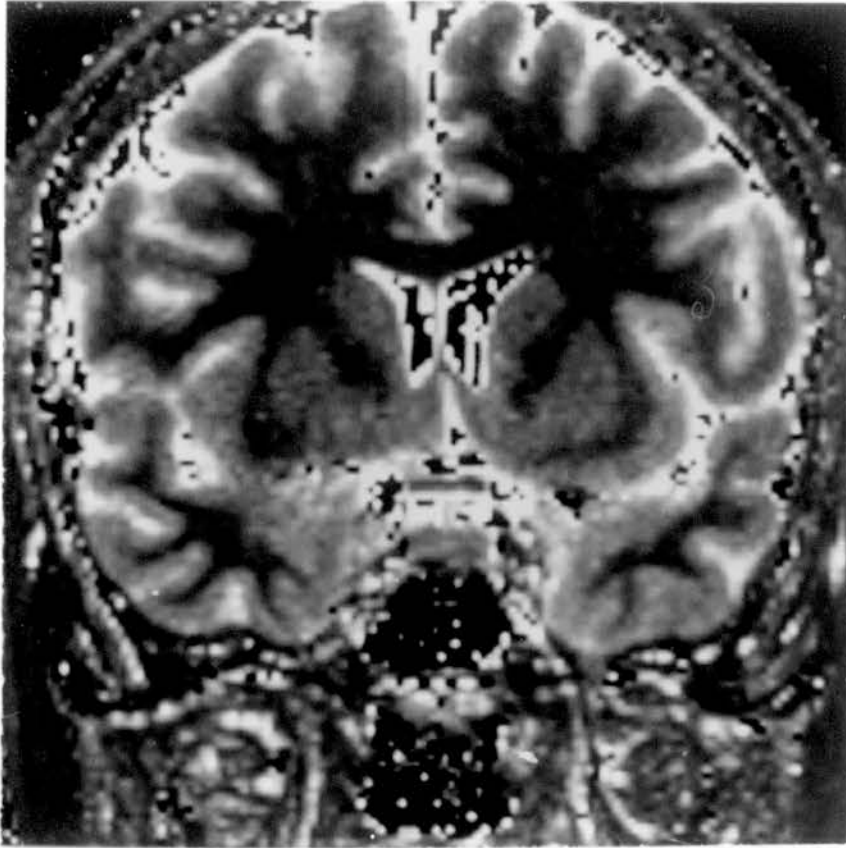


FIGURE 19 THE HEAD OF THE CAUDATE NUCLEUS AND THE PUTAMEN, AS SHOWN ON A T_1 IMAGE.

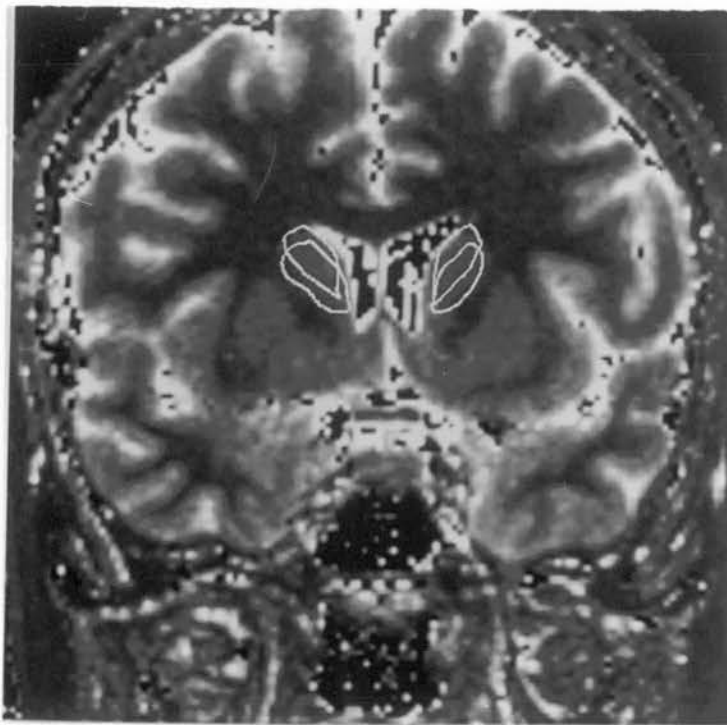


FIGURE 20 A TRACES SUPERIMPOSED ON FIGURE 19 TO SHOW CAUDATE POSITION ON ADJACENT SLICES

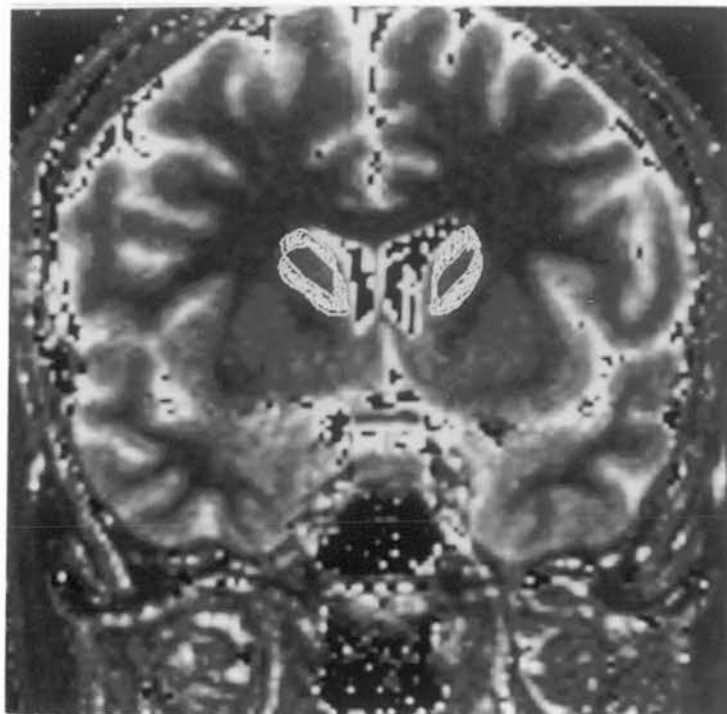


FIGURE 20 B THE CENTRAL AREA IS THEN MEASURED AS IT IS GUARANTEED FREE OF PARTIAL VOLUME ARTEFACT

b) Measurement of basal ganglia T₁ values

The slice where the caudate head and putamen joined was identified to obtain an internal reference point close to the anterior commissure. The putamen, globus pallidus and caudate were readily visible against surrounding white matter or ventricular fluid (Figure 19). The block of slices containing these structures was then identified and, since the globus pallidus could also be distinguished from the putamen (Figure 17), a ROI was traced around each structure on each slice.

A T₁ measurement was only made after excluding partial volume artefact through an examination of the two adjacent slices. This involved outlining the same structure on each of these three slices and, since the trace from one slice remained on the screen after calling up its neighbour, it was possible to identify the tissue that was common to all three (Figure 20). A measurement off the middle slice was consequently ensured free of unwanted tissue.

Readings could be obtained from the putamen on three slices (designated as 1.0, 0.5 and 0 cm posterior to the caudate/putamen junction), from the caudate on one slice (0.5 cm), and the globus pallidus on one slice (1.0 cm) in at least 60% of subjects. The three putamen slices were analysed separately in order to detect possible differences within this structure, and to allow comparison at equivalent positions between the putamen and either the caudate or globus pallidus.

The test-retest reliability for one person re-measuring values of the caudate, putamen and globus pallidus from eleven separate scans gave an intra-class correlation coefficient of 0.97 or greater in each area ($p < 0.001$). Inter-rater reliability using the

same scan was also high; the intra-class correlation coefficient was 0.88 or greater, except for the right globus pallidus where it was 0.76 ($p < 0.01$).

The reliability over time of basal ganglia T_1 values was assessed by re-scanning the same individual eleven times over several months in exactly the same position. This provided a more stringent test of reliability since it included possible variance from changes over time in the scanner and the subject, plus the effects of re-positioning in the scanner, in addition to measurement technique. In each ROI the standard deviation over these 11 readings was approximately 30 msec., equivalent to 6% of the mean.

7. NORMAL T₁ VARIATION

In measuring white matter relaxation times from controls and schizophrenics there was a wide scatter of values, and it was unclear how much of this was actually attributable to real differences between individuals, and if so what their source might be, and how much arose from scanner variance. It was therefore important to explore different facets of normal variance first, to reduce the risk of missing a genuine pathological difference or misinterpreting a group difference as pathological when in actual fact it arose from some other variable inadequately matched across the two groups.

Different sources of variance were examined through the use of three separate sets of data. The first simply provided a baseline to gauge the relative size of other effects.

a) Short term scanner variation

This first set started with a measurement of the minimum possible variance for this particular scanner in its present operating condition (re-scanning reproducibility), assessed by scanning one healthy person twice without removal from the scanner. Measurements from the 18 x 2 ROI, described above, were taken from identical positions on each scan, so that an adequate assessment of reproducibility was possible even though only two scans were performed. Next, the variance due to simply coming out of the scanner and then being re-positioned as closely as before (subject re-positioning), could be calculated as any variance additional to re-scanning reproducibility that such a procedure involved. The same person as above had three consecutive scans, only coming out of the magnet between each one and then being re-positioned using the customary three pilot scans.

b) Medium term variance of subjects and scanner combined

In this second set, variation was considered which arose from subjects as well as the scanner. This involved the scanning of two healthy male volunteers five times over two months, at 1-2 week intervals. In this manner it was possible, using an analysis of variance, to separate out the effects of three different factors:

- i) Anatomical position Measurements were taken from white matter in both the parietal and frontal of each hemisphere.
- ii) Medium term machine drift, measured over eight weeks as variance that was common to both subjects.
- iii) Medium term variation within one individual, measured as fluctuation specific to each individual as distinct from the scanner drift common to both. It was assumed this arose from physiological changes in the white matter.

c) Variance between subjects

The final set examined the 36 healthy controls to highlight normal demographic differences between subjects, due to gender or age for example.

Sources of normal variation in the basal ganglia T_1 measurements could not be explored in this manner, since the small number of measurements available in each person did not allow multivariate analysis between only two subjects. It was feasible, however, to look at the demographic and anatomical differences existing within the 36 healthy controls.

8. ANTIPSYCHOTIC DRUGS AND T₁ VALUES - AN ANIMAL MODEL

On comparing T₁ relaxation times between schizophrenics and controls, it was necessary to exclude an effect of antipsychotic drugs that might obscure or mimic genuine pathological differences. An animal model was used to investigate whether or not this could be the case.

Three healthy adult cats were used in this additional study. Each animal was initially scanned free of drugs to obtain baseline data. Chlorpromazine was then administered for one month in a daily dosage of 4 mg kg⁻¹ intra-peritoneally, which is equivalent in terms of behavioural effects to that used in humans (Karkischenko 1968; Hoffmeister & Wuttke 1969; Ellinwood & Kilbey 1977). The intraperitoneal route was chosen to achieve more consistent tissue levels, since if given orally there is substantial first pass hepatic metabolism (Cassano & Placidi 1969). The animals were then scanned at weekly intervals over the four weeks of the study.

Anaesthesia was induced with pentobarbitone, which has no effect on brain relaxation times (Karlik et al 1986), and imaging performed on the same machine used in the human study according to the method of Barnes et al (1988b). The field of view was 15 cm, and the pixel dimensions were 0.6 x 0.6 x 5 mm. After a sagittal pilot scan three single slice images, each of 5 mm. width, were acquired in the coronal plane at the level of the thalamic nuclei. These images were based on three different sequences in order to calculate both T₁ and T₂ values, using similar two-point algorithms to those applied in the main study. The T₁ images were derived from IR_{2000/40/500} and SE_{2000/40} sequences, and the T₂ images from the SE_{2000/40} and a further

SE_{2000/120} sequence. A bottle of manganese chloride placed directly above the head of each cat was used as a stable phantom.

On each calculated image easily identifiable white matter was measured, in both hemispheres, at the base of the supra-sylvian gyrus (centrum semiovale) and in the internal capsule. In order to obtain more precise readings from grey matter the thalamic nuclei were selected, instead of the basal ganglia, because of their greater size and clearer definition. A region of interest covering eight pixels was placed in each of these six areas, as shown in Fig. 21. Each scan was rated blindly and readings taken from the phantom used to standardize all these brain measurements.

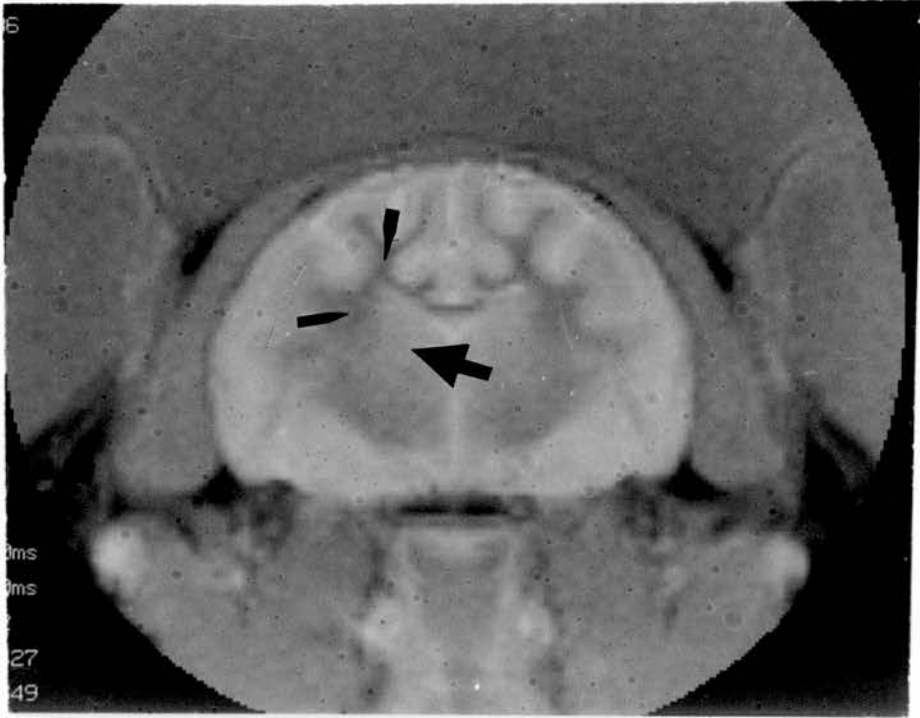


FIGURE 21 CORONAL T_1 -WEIGHTED IMAGE OF THE CAT BRAIN,
WITH THE SITES OF MEASUREMENT INDICATED.

(thalamus=broad arrow, white matter=thin arrow)

9. STATISTICAL ANALYSIS

a) Socio-demographic characteristics of the control and schizophrenic groups

Comparison was made for each variable according to whether the data was parametric (t-test) or non-parametric (Mann-Whitney U test or a chi-square test).

b) Clinical data in the schizophrenic group

Clinical data was examined in relation to scan measurements. For assessing clinical outcome a single broad sub-grouping was employed in place of the several narrower items originally collected. Three different items that related to outcome (total duration of inpatient treatment, total NSRS score, and total DAS score) were taken and patients sub-grouped through a cluster analysis. Running SPSS/PC+ software (Norusis 1988) two different clustering methods were used, that of Ward and the "average linkage between groups", to ensure that cluster formation was stable.

c) Visual assessment of the images

The two groups were compared by chi-square tests for each category rated.

d) Structural measurements

A log or square root transformation was applied to those volumetric data that showed a skewed rather than a Gaussian distribution. Initial comparisons between the patient and control groups were then carried out using an unpaired t-test.

Subsequent comparisons relied on the use of multiple regression. In most cases one dependent variable was regressed upon two or three independent variables, using the transformed data as appropriate. Residual values were examined for evidence of either non-linearity or inequality of variance that might invalidate the results.

e) Measurements of T_1 time

In both white matter and the basal ganglia the T_1 values from each slice were normally distributed without obvious outliers, so analysis used parametric tests. For the small number of statistical analyses concerning the basal ganglia, either t-tests or a one way analysis of variance (ANOVA) were used.

For group differences in white matter T_1 values a multivariate analysis of variance (MANOVA) was used, to avoid inflating the risk of a type 1 error through multiple significance testing of many separate ROI. This involved a design of slice and hemisphere side as "within subject" factors to allow for within subject correlation, and sex and subject group as "between subject" factors (Norusis 1988). T_1 values from the block of 14 slices comparable in all subjects were used as the dependent variables. The between-subject factors were examined first, followed by their interaction with the within-subjects factors as shown by the Hotelling's T statistic.

To examine the variance in normal appearing white matter T_1 times another statistical program (SAS 1985) was used which, along with MANOVA, included a procedure for estimation of the components of variance (the "VARCOMP" procedure in a general linear model). In all these analyses third order and higher interactions were excluded because they were assumed to have negligible effects.

RESULTS AND DISCUSSION

CHAPTER 5

1. CLINICAL AND SOCIODEMOGRAPHIC CHARACTERISTICS OF THE TWO GROUPS

There was adequate matching for age, height, handedness and race between controls and schizophrenics, but obvious differences in IQ and educational achievement (Table 5). However parental occupational level was similar, and this would be expected to control for some aspects of pre-morbid social and family environment. All but four of the patients satisfied DSM-III-R as well as RDC criteria for schizophrenia.

Patients were predominantly male, but the healthy control group was deliberately maintained at an equal sex ratio to allow an adequate number of women for testing whether normal sexual differences existed in various measurements. Patients drank less alcohol than controls but both groups had a low weekly intake. Only three patients were off all prescribed drugs, whilst 10 controls were taking some form of medication, usually a contraceptive pill. Individuals who were not indigenous British were mostly West Indian (17 schizophrenics, 13 controls), with a smaller minority of black African and Asian subjects (3 schizophrenics, 1 control).

Schizophrenia in the patients was of moderately chronic duration, with an average of 4.5 admissions and a total in-patient stay of 3.3 years; 63% were unemployed. Their mean age at psychosis onset was 22.2 years.

Discussion

Controversy still surrounds the ideal choice of a control group for a neuro-imaging study of schizophrenia (Andreasen et al 1990), but it seems unlikely that the findings from this study could be attributable to an error in matching schizophrenics to controls. Our subjects were compared on parental social class, which in respect of neurodevelopment seems a more relevant variable than the patients' own social class, and found to be very similar. Although there were clear group differences in IQ this most probably arises from the illness itself, and IQ per se has yet to be shown to have any substantial influence on cerebral or cortical volumes. The necessity of controlling for racial differences in brain size, which in this study was achieved by taking intracranial volume into account, is emphasized by the large post-mortem series of Khang-cheng et al (1980). Gender differences were allowed for by entering gender as an independent variable in the analysis of T_1 values, and by allowing for differences in intracranial volume in the volumetric measurements.

2. VISUAL MRI ASSESSMENT

Results

Inspection of the images on the full sample of 60 patients and 36 controls revealed no significant differences between the two groups (Table 8). Ratings showed consistency across the three viewings, and were only accepted if reported similarly on at least two of these occasions.

In the control group 61% had definitely normal scans, defined as an absence of sulcal or ventricular enlargement and focal abnormalities. Focal sulcal enlargement and small isolated areas of high signal in the white matter accounted for most of the observed abnormalities. Normal scans were present in only 40% of the schizophrenics, and this difference was attributable to greater sulcal and lateral ventricular enlargement. Sulcal enlargement was extensive in two patients (Figure 7), with a slight preference for the left Sylvian fissure seen in five patients but only one control. The lateral ventricular enlargement seen in seven patients affected the frontal horn, body and trigone equally, but only involved the temporal horn in one case. Ventricular asymmetry of any degree was equally common in both groups.

Sulcal enlargement in combination with either ventricular enlargement or white matter lesions appeared to discriminate best the patients from the controls, occurring in nine patients but only one control.

The small areas of high signal were exclusively seen in the white matter, apart from one in the globus pallidus of a control. In both groups they predominated in the

frontal lobes, being usually one or two in number, but neither hemisphere was affected preferentially. Only one control and four patients showed more than five of these punctate abnormalities. One patient had a lesion involving the grey matter (left occipital cortex).

Ventricular enlargement occurred in one familial and six non-familial schizophrenics, but the sulcal prominence and white matter abnormalities appeared equally frequent in the familial as the non-familial.

Discussion

The only other comparable assessment in schizophrenia has been the study of Waddington et al (1990), which included 47 patients and 25 healthy controls and found a similar excess of sulcal enlargement and ventricular dilatation. Enlarged cortical sulci were seen in 23% of their patients, comparable to our figure of 27%, with diffuse and focal sulcal enlargement being equally common and the latter commonest over the parietal lobes. It is likely the difference in controls (only 4% of their controls had sulcal enlargement compared to 19% in our study) arose because the sulcal fluid signal is particularly prominent on the STIR sequence so that, in effect, a low threshold was adopted for recording sulcal enlargement. Furthermore, Waddington et al (1990) noted that the ventricular system was dilated in 17% of patients and 4% of controls, the degree of which did not correlate with any sulcal enlargement, which again shows agreement with our findings. They commented on asymmetrical dilatation of the left ventricular body in two patients, and the present study also contained one patient with gross asymmetry of the same kind.

Small foci of abnormal white matter signal were unambiguously identified in 19% of controls and 22% of patients. These findings are in agreement with those of Awad et al (1986) who reviewed 106 MRI scans of neurological referrals under the age of 40 and, counting these foci only where they appeared incidental to any neurological illness, found they were present in 22%. They were equally common in those under 20 years as in those over that age. Waddington et al (1990) also found such foci in 16% of their healthy controls. However our figures are higher than those of Fazekas et al (1988) and Kertesz et al (1988) where, out of 38 healthy subjects under fifty contained in these two studies, only one such abnormality was reported. The reason for this discrepancy is not clear, but it may be that our images gave greater contrast of such foci against the white matter, and more scrupulous searching over a larger volume of the brain was involved. It is known that these abnormalities show a clear increase in number over the age of fifty but their pathological significance in the elderly appears to be minor (Awad et al 1986; Hunt et al 1989). Their aetiology is uncertain but they are probably ischaemic in nature. What they mean in a younger age group is still obscure, but we concur with Waddington et al (1990) that in schizophrenics they are no commoner than in healthy controls. Similar foci are also detectable in other psychiatric patients, since Dupont et al (1990) have noted their presence, persistent on follow-up, in nine out of 19 young bipolar patients.

CHAPTER 6 NORMAL VARIANCE IN T₁ VALUES

A. RESULTS

1. WHITE MATTER (CENTRUM SEMIOVALE)

The following results were obtained from investigating the T₁ variance in white matter, using the three separate data sets described in section 7 of the Method.

a) Variance due to scanner

These results derived from the repeat scanning of one healthy subject, whose mean T₁ value over all 18 slices and both scans was 366 msec. Results for scanner reproducibility showed that, over the 18 ROI in each hemisphere, the difference between two equivalent ROI on the two scans had a mean value of 3.4 msec (95% C.L. of 0.8 to 5.9 msec).

With the additional effect of re-positioning between consecutive scans the mean difference between equivalent ROI was slightly lower at 1.6 msec (95% C.L. of -1.0 to 4.2 msec).

The mean differences seen above for scanner reproducibility and re-positioning are very close to those seen in the reliability study, involving two separate measurements of identical data. All these values might be explicable by random electronic noise.

b) Variance from both subjects and scanner

Data collected over two months from five scans on each of two male subjects were examined by a single analysis of variance for medium term changes in both subjects and scanner, and for differences according to anatomical position (Table 9).

In this table a "main effect" identifies the variability in a total set of measurements that arises from one specific source, such as slice position. An "interaction effect" identifies the variability that arises from two sources after removing their individual contribution. Thus "side by slice" is the variability in measurements from all slices on both sides after allowing for variability of the two sides and different slices separately. The "mean square" value relates to variability arising from each main effect or interaction, allowing for degrees of freedom (DF). The "F ratio" relates the mean square value for each term to the residual mean square, which is variability of no identifiable source. The "p value" of each F ratio indicates whether or not a term is significantly greater than this residual term. The final column of this table provides an estimate of the variance expected in the general population for that source, and its relative size is given as a percentage of the total; this assumes that the sample is representative of the general population. An estimate of the standard deviation for each factor (in milliseconds) is available as the square root of these figures.

Differences between subjects constitute the largest source of variability, as shown by the "person" main effect; the mean T_1 value, taken over all 18 slices for each individual, had a difference in these two subjects of 29 msec (95% C.L. of 13 to 44 msec). This is shown in Figure 22, which gives the mean T_1 value over all the slices of one hemisphere as it varies with time and between the two subjects.

FIG. 22 TWO SUBJECTS: T1 DIFFERENCES BY SIDE AND TIME

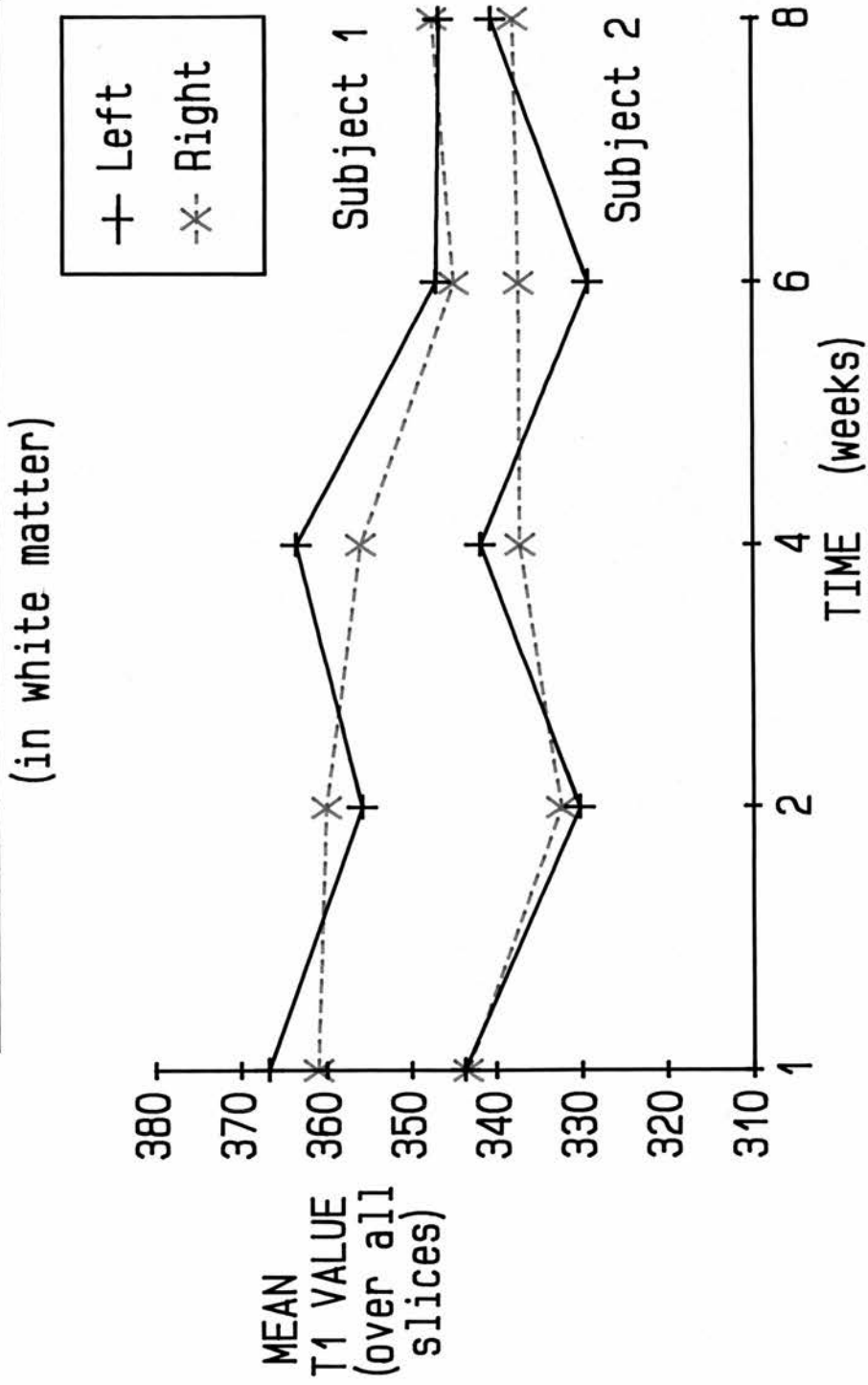
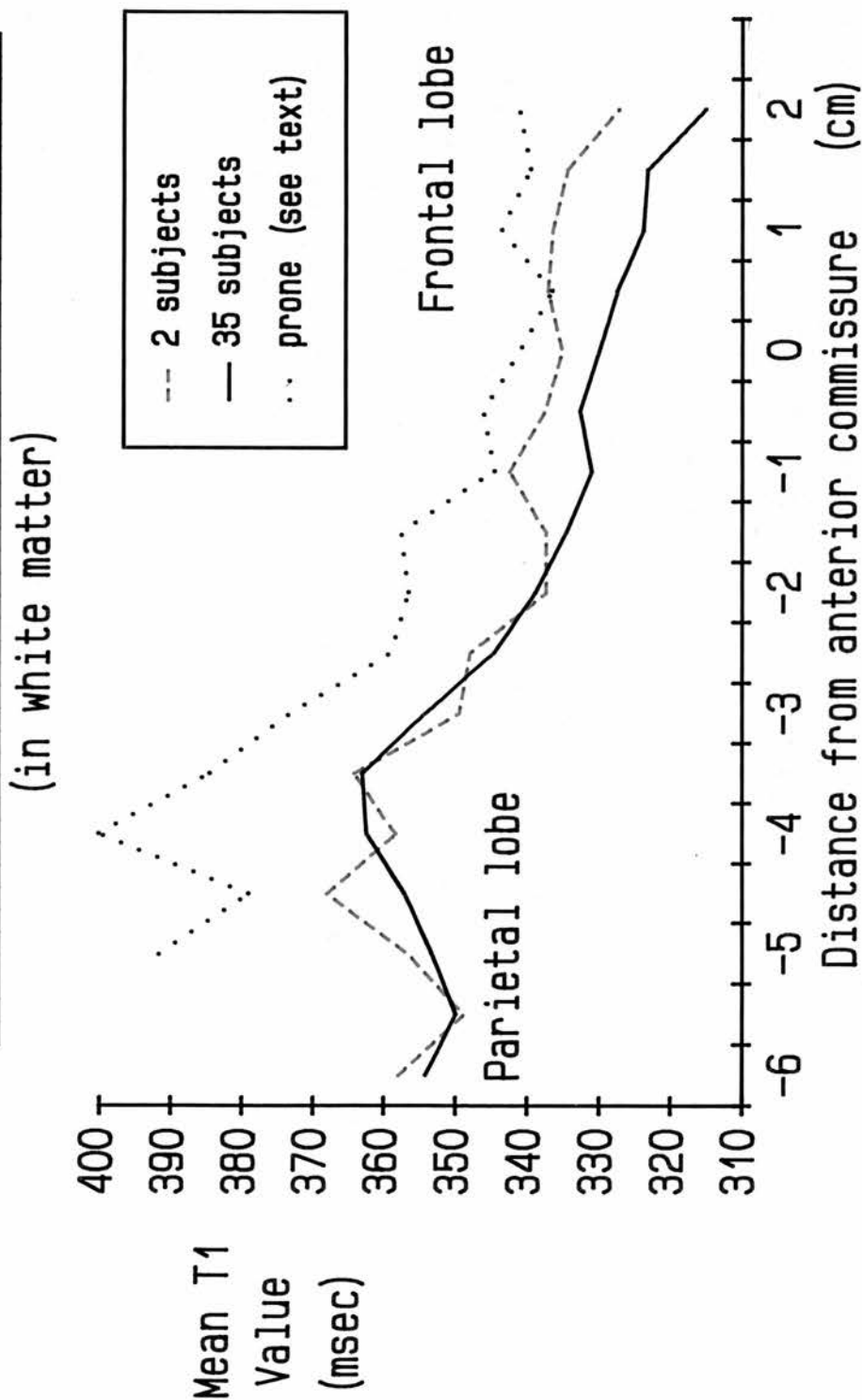


FIG. 23 INFLUENCE OF ANATOMICAL POSITION ON T1 VALUES



Secondly, within one individual the most critical factor was not variation over time but anatomical position, namely the slice position from which the measurement was taken, indicated by the "slice" main effect. The large change in T_1 values that occurred with an alteration of slice position in these two subjects is demonstrated in Figure 23 (note that the mean T_1 value here is different to that defined above and comes from the T_1 values at the same anatomical position in different people).

The "side" main effect shows that there is no discernible difference in measuring the right hemisphere rather than the left, for any slice in either subject; the effect of the "side by time" component is significant but essentially reflects asymmetrical fluctuations over time rather than a consistent laterality effect (Figure 22).

Thirdly, highly significant statistical effects are observed over time, although they are comparatively trivial when viewed against the effects of slice position and inter-individual differences. The "time" main effect can be regarded as short term machine drift that is common to both subjects over the 2 months. It is demonstrated, for example, in Figure 22 where left hemisphere values in each subject change in tandem.

Of interest is the interaction effect "person by time", referring to short term variation within each individual, which constitutes a greater proportion of the total variance than short term machine drift. This result can be seen in Figure 22 where differences between the two subjects are clearly shown, not only in their mean values, but in the changes occurring over the 2 month period. One subject shows a marked drop in T_1 values over the last two scans, whilst for the other there is no such change.

This latter effect was examined in further detail using a multivariate analysis of variance (MANOVA) that included a polynomial term to allow for the different time intervals between scans. This was done to see whether a linear change over time remained significant. Such a change in T_1 of -14.4 msec over the 2 months was observed in the first subject (95% C.L. of -4.0 to -24.7 msec), but in the second the equivalent change was clearly non-significant at only -1.9 msec (95% C.L. of +3.5 to -7.3 msec.).

c) Differences between subjects

The results from the 36 healthy controls confirm that no difference exists between right and left hemispheres (mean difference = 1.02 msec with 95% C.L. of -0.69 to +2.7), and that the effect of slice position on T_1 could also be seen in this wider group (Figure 23). No relationship of T_1 to age, time of day when scanned, social class, IQ, educational level or race existed. The overall mean T_1 value in this group of 36 subjects was 338 msec. (95% confidence limits 334-343, SEM 2.4, SD 14.6), pooling all the measurements from 18 slices and both hemispheres for the entire group.

This larger sample also provides a way of testing the estimates of variance given in the final column of Table 9, by adding the relevant sources of variance together. The estimated variance across subjects for one ROI in the same side and slice position would involve the effects of time, person, their interaction and the error term (ie $13+141+23+53 = 230 \text{ msec}^2$), and the estimated standard deviation would therefore be its square root i.e. 15.2 msec. The variance observed in reality was 199 - 428

msec². (SD of 14.1-20.7 msec), according to which slice was chosen, so the relative size of different effects shown by their percentage in Table 9 appears to be validated.

A multivariate analysis of variance in this group also showed a main effect of sex (MANOVA, $F=4.35$, $p=0.04$), where women ($n=17$) had lower values than men by 10 msec. on average. This effect occurred just in frontal lobe slices anterior to the anterior commissure. The influence of the menstrual cycle was therefore considered, since it entails a fluid balance alteration. Each woman with a regular cycle ($n=14$) was allocated, for their current one, to one of four time-blocks: the week immediately preceding menstruation, the time of its occurrence, one week after or two weeks after its cessation. There was no discernible change in T_1 values over these four time-blocks (MANOVA, $F=0.97$, $p=0.44$), although the sample was small.

No long term drift was apparent during the eighteen months in which these 36 volunteers were scanned, although it was not possible to quantify this accurately since these individuals were scanned only once.

It was initially uncertain whether the change in T_1 with anatomical position was due to either scanner artefact or the multislice sequence, or in fact arose from a genuine anatomical effect. Three approaches were used to answer this question:

a) To separate these effects one person had a scan in the prone, rather than the customary supine, position while reversing the multislice profile so that its relation to the scanner was unchanged. In this way the anatomical position was changed by 180° but the scanner and the sequence were unaltered. The same anatomical effect was seen in both scans (Figure 23).

b) Two phantoms of uniform T_1 value were scanned in the same plane using these same sequences, and multislice T_1 images constructed to allow T_1 measurements across twelve slices for each one. The range of values in the two phantoms were 302-307 msec. (SD 1.54 msec.) and 341-346 msec. (SD of 1.48 msec.) with no evidence of consistent drift according to slice number.

c) The original SE and STIR image intensities were measured in six randomly selected subjects, using the same ROI technique, and were plotted against anatomical position. A similar change to that shown in Figure 23 occurred in all six T_1 -weighted STIR images (moving anteriorly there was a mean decrease of 15%) but in none of the T_2 -weighted SE images (moving anteriorly there was a mean increase of 3%), which again suggested this T_1 change was not simply a scanner artefact otherwise it would have appeared in the T_2 -weighted images as well.

Each of these three approaches suggested, therefore, that there was a genuine T_1 change with anatomical position.

2. BASAL GANGLIA

Figure 24 demonstrates that there is substantial T_1 variation within the same nuclei. There was a significant increase in T_1 values from the posterior to the anterior putamen (ANOVA, $F=5.15$, $p=0.03$). It was not possible to collect data across sufficient slices to examine the smaller globus pallidus and caudate head for such an effect.

The difference in T_1 values between the caudate, putamen and globus pallidus appears in Figure 25. On comparing the putamen and globus pallidus at the same slice level (they coincide most often at 1.0 cm posterior to the reference point) a significantly higher mean value is apparent in the putamen (unpaired t-test, $t=6.09$, $p<0.001$; mean difference of 46.9 msec., 95% CL = 39.8 to 54.0). The putamen and caudate also differ, but to a less marked degree, on the slice 0.5 cm. posterior to the reference point, with a higher mean value in the caudate (unpaired t-test, $t=2.64$, $p=0.01$, mean difference of 23.8 msec., 95% CL = 13.6 to 33.9).

Allowing for these effects there was no significant difference between the sexes, and no significant correlation with age or IQ. No significant differences existed between the two hemispheres for any of these structures.

FIG. 24 SLICE POSITION AND PUTAMEN T1
VALUES IN HEALTHY CONTROLS
 (mean T1 shown by horizontal bar)

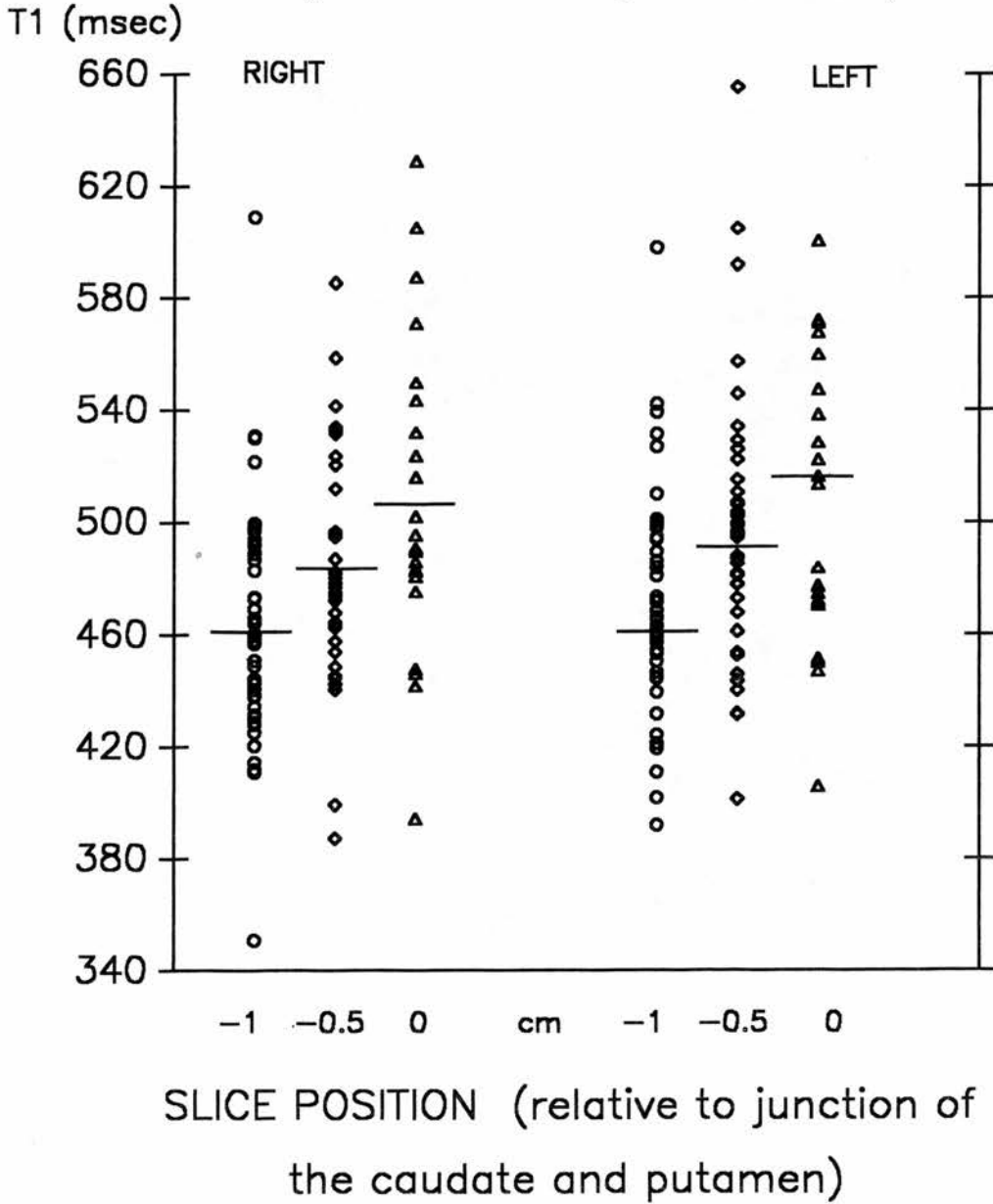
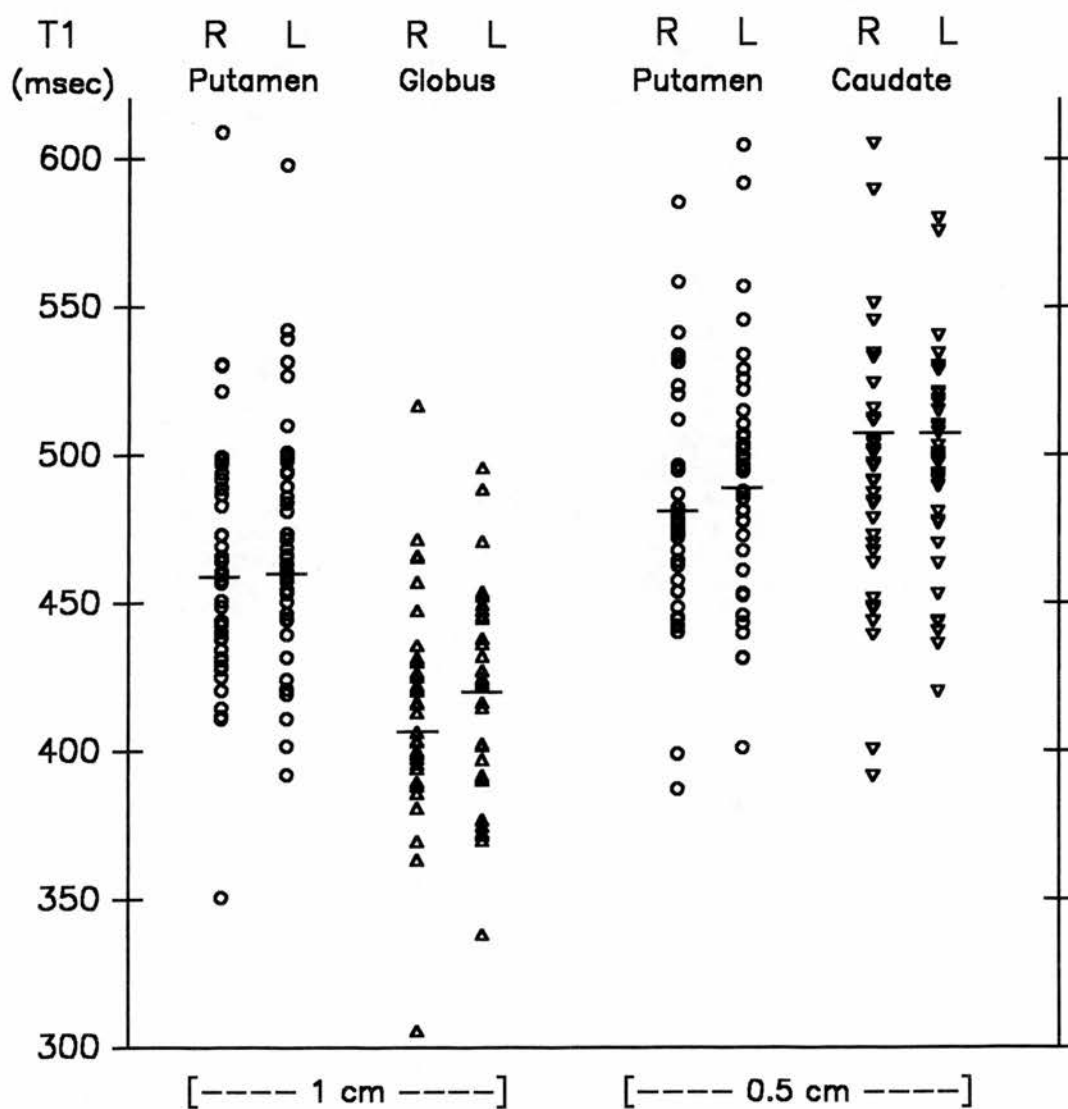


FIG. 25

BASAL GANGLIA T1 DIFFERENCES
(mean value shown by horizontal bar)



SIDE AND SLICE POSITION

(distance posterior to caudate/putamen junction)

B. DISCUSSION

1. MEASUREMENT TECHNIQUE AND SCANNER EFFECTS

The T_1 measurement technique appeared satisfactory, and in white matter at least its reliability was as high as could be achieved, given the level of random noise on this machine. The multislice T_1 images used in this study had the advantage of allowing partial volume artifact to be confidently excluded from a region of interest, which is not possible with a single slice technique simply because adjacent voxels cannot be seen. The disadvantage of multislice images is that they may give less accurate values than a single slice image (Johnstone et al 1987b), but inaccurate T_1 times did not appear to be a problem in these analyses.

Concerning the scanner it is clear that careful re-positioning need not add any variability to a scanning procedure and can be made with great accuracy. In these results the mean difference between three re-positioned scans was in fact a little lower than for two scans not involving removal from the scanner, and in both cases the variability is no greater than that expected from unavoidable electronic noise. Similar estimates of T_1 precision by other groups (Kjos et al 1985; Breger et al 1986; Johnson et al 1987b; McFall et al 1987) suggest that the level of noise in this scanner is not atypical.

2. ANATOMICAL AND PHYSIOLOGICAL T₁ DIFFERENCES

The change in T₁ that occurred over different anatomical positions within the centrum semiovale was of interest. Similar reports of lower values in frontal white matter have been reported with axial slices (Besson et al 1987b; Johnstone et al 1987b; Ormerod et al 1987) but it is the magnitude of this effect that is most striking in this study. Although Kjos et al (1985) did not observe it in 43 patients without diffuse brain pathology the three negative attempts to identify artefactual explanations for this observation lead one to believe that it is genuine. In particular obtaining the same result from scanning one subject prone, which effectively isolates the anatomical effect, seems difficult to explain on the basis of either scanner or sequence artefact.

The fact that healthy controls also show considerable T₁ variation within the basal ganglia does not appear to have been shown so clearly before, although two previous studies have reported higher values in the caudate nuclei than the putamen (Kjos et al 1985; Breger et al 1986). The T₁ relaxation time was highest in the caudate head and lowest in the globus pallidus, and within the putamen an increase occurred on moving rostrally. This difference was particularly apparent between the putamen and globus pallidus, but it remains uncertain whether this arises from their differences in iron content or is due to some other factor. The gradient within the putamen seems difficult to explain on the basis of scanner artefact since white matter T₁ values showed the opposite effect on moving anteriorly.

The possible existence of gender differences in T₁ times of white matter, which in this study amounted to 10 msec., has not been previously reported either. Garber et al

(1989b) saw no such effect in their controls, but only nine men and five women were included. Whether the explanation lies in real tissue heterogeneity or is an artefact from other gender differences such as body or head size is not clear. The number of women studied at various points over the menstrual cycle was small, so the absence of any T_1 change is only a tentative conclusion, and it would have been preferable to re-scan several women over the course of their cycle. A T_1 change over the cycle has been reported in red blood cells (Rosenthal et al 1985), and in the head there is an 11% fluctuation in the volume of cerebro-spinal fluid (Grant et al 1988).

A further point of interest was the fluctuation in T_1 values over two months seen in one healthy subject, since an apparently physiological change was as large as 14 msec. This remains a tentative finding, but needs to be investigated further before regarding changes of this magnitude in patients as pathologically important.

There seems to be agreement with other studies that there is no difference in T_1 values between the right and left hemispheres (Kjos et al 1985; Breger et al 1986) nor does it change with age (Besson et al 1987b; Christie et al 1988; Garber et al 1989b).

No specific examination for diurnal variation was made, but no evidence was seen of such an effect in the controls. Sostman et al (1986) looked at mice for diurnal changes in T_1 and failed to find any for liver, heart or kidney although the brain was not included. Although temperature has an effect on T_1 of 2-4% per degree (Nelson & Tung 1987), it is normally under close homeostasis in human subjects and therefore unlikely to be a major influence.

CHAPTER 7

T₁ VALUES IN SCHIZOPHRENICS AND CONTROLS

A. RESULTS

1. GROUP DIFFERENCES IN THE WHITE MATTER

The overall mean T₁ value for the patients was 340 msec (95% confidence limits 335-345, SEM 2.5, SD 17.6), and the corresponding control value was 338 msec (95% confidence limits 334-343, SEM 2.4, SD 14.6). Comparing the two groups, either in total or for each sex separately, showed no significant group differences (Table 10).

The overall mean difference between the two hemispheres in the patients was 0.5 msec (95% confidence limits -1.2 to 2.1), and none of the slices taken in isolation suggested a localised laterality effect.

Table 11 shows the result of a MANOVA to compare the T₁ values in the patients and controls over the 14 slices anatomically comparable between all subjects, allowing for sex differences. No overall group difference is seen; nor is there any suggestion from the interaction terms of any group difference localized to one side or certain slices.

2. GROUP DIFFERENCES IN THE BASAL GANGLIA

No significant group differences were seen in any of the ten ROI measured (Table 12). Again no difference between the two hemispheres for equivalent structures was seen in the patient group.

3. WITHIN PATIENT COMPARISONS

Analysis within the patient group did not reveal any association between either white matter or basal ganglia T_1 values and the following variables - age at psychosis onset, illness duration, social function, best level of function in the past five years, presence of specific psychotic symptoms on the PSE, negative symptoms, current neuroleptic dose (chlorpromazine equivalent over the preceding month), obstetric complications, developmental delay, handedness or family history of schizophrenia.

In the basal ganglia there was no association between T_1 values and the lifetime amount of depot neuroleptic, the use of anticholinergics, tricyclic antidepressants or benzodiazepines, or the response to neuroleptic drugs.

Eight patients had an AIMS score of two or more, indicating the presence of tardive dyskinesia; basal ganglia T_1 values in this group were similar in all ROI compared to those who had a score of less than two (Mann-Whitney, $p>0.14$).

B. DISCUSSION

1. POSSIBLE LIMITATIONS OF THE STUDY

The advantages of this study over previous ones, in terms of its sample size, high reliability and allowance for normal T_1 variation, lend weight to its negative findings, but two possible limitations do need to be considered:

i) The patients may be atypical because they were highly selected, due to both the practical and theoretical requirements of this study. However, when compared to unselected schizophrenic patients admitted to the same hospitals, the experimental group was very similar in age, sex, race, IQ and age of onset. The experimental group was in fact more chronic than this control series, as might be expected since the investigated patients were drawn from admissions over the previous 13 years. Their chronicity of illness demonstrates that the negative findings are not explicable by the exclusion of patients with a poor outcome. Another factor to consider was the clear difference that existed between the patients and controls in terms of IQ, educational achievement and sex ratio. However, the first two of these variables were shown not to be significantly related to T_1 times, and gender differences were allowed for in the statistical analysis.

ii) It might be argued that a normal T_1 time does not exclude a T_2 alteration, which would also be indicative of white matter pathology, and which the design of this study would have overlooked. Yet this is unlikely, since it is rare to observe a substantial T_2 alteration without any corresponding T_1 change. The converse situation of an elevated T_1 but normal T_2 is more common, and can occur in the presence of gliosis

(Barnes et al 1988a). The normal T_1 in these schizophrenics was consistent with the lack of evidence for gliosis in recent neuropathological studies (Roberts et al 1987; Stevens et al 1988). Nonetheless, Bruton et al (1990) showed at post-mortem that in schizophrenia gliosis could occur in the white matter and in such cases tended to associate with focal pathology; it is therefore possible that patients with such gliosis were largely screened out of this study when focal lesions were identified on CT. Had they been included then a T_1 alteration may have been seen.

2. COMPARISON WITH OTHER STUDIES

Comparison of these present findings with previously reported work is difficult as results of either relaxation times or signal intensity have shown little consistency. This is probably due to a variety of problems such as receiver coil non-uniformity, short term scanner variation, partial volume artifact and software changes (Smith et al 1987b; Rossi et al 1988b; Kelsoe et al 1988). In addition, there has been virtual silence on whether there is any association between these measurements and the clinical characteristics of schizophrenia. It is the basal ganglia that have shown the strongest evidence for possibly abnormal relaxation times in schizophrenia.

a) Basal ganglia

Contrary to previous reports (Fujimoto et al 1985; Besson et al 1987a; Andreasen et al 1989), we found no difference between schizophrenic patients and healthy controls in T_1 relaxation times of the basal ganglia. The reasons for this discrepancy are not immediately apparent. The patient sample used by Besson et al (1987a) was similar to that of the present study but that of Fujimoto et al (1985) consisted entirely of chronic male patients. Both these groups had used 10mm transverse, as opposed to 5mm coronal, slices and the normal anatomical variation described above was not taken into consideration. Andreasen et al (1989) differed in finding only a left striatal increase in T_1 , rather than a bilateral one, and had a sample size of only six subjects in each of the schizophrenic and control groups. However, although the 95% confidence limits presented here for the basal ganglia remain large enough to contain a significant group difference, their consistency in being centred around zero suggest that it does not exist. Neuro-pathological findings suggest that if there is any

abnormality in the basal ganglia it is likely to be restricted to the internal portion of the globus pallidus, where reduced volume has been described (Brown et al 1986; Bogerts et al 1990a), but this volume is too small to have been examined specifically on MRI. We could not confirm any relationship between T_1 values in the basal ganglia and tardive dyskinesia, measured on the AIMS scale, as described by Besson et al (1984,1987a).

b) White matter

There are few available results from other groups for comparison. Despite the small sample size, the most satisfactory study to date has been that of Andreasen et al (1989), who also found no alteration in white matter T_1 values. We could not replicate the finding of Besson et al (1987a) that T_1 in the left frontal white matter increased with the severity of positive symptoms. A frontal T_1 increase has been described in affective disorders (Rangel Guerra et al 1983; Dolan et al 1990) but it remains unknown whether this has any relevance to schizophrenia.

There are other disorders, such as multiple sclerosis (Miller et al 1989), dementia (Christie et al 1988), and obsessive compulsive disorder (Garber et al 1989b), where a diffuse T_1 abnormality in normal appearing white matter has been identified, and the difference between patients and controls ranged from 13-17 msec. Knowing the normal variance between subjects it was possible to estimate that the sample size in our study had over 80% power to detect a pathological difference of 10 msec. or more in T_1 values if it existed, so the chance of a type 2 error was small.

c) Inter-hemispheric differences

The absence of any inter-hemispheric difference in the patients also deserves comment. Breger et al (1986) found, as in this study, that no inter-hemispheric difference in white matter T_1 exists in healthy subjects. Therefore, while Rossi et al (1988b) described an inter-hemispheric difference of 3-6% in the white matter of schizophrenics doubt must be raised about their findings since a similar difference was also seen in controls. Fujimoto et al (1985) provide another report of higher left sided values in the white matter, but from the present study the confidence limits of -1.2 to 2.1 msec suggest that no such difference exists. Previous reports of significant differences derive from the use of paired t-tests, which are powerful in detecting any difference but need to be viewed with caution since small differences can result from non-uniformities within each slice.

In view of the reduced cortical volume observed it remains possible that any T_1 changes in schizophrenia are limited to the cortical grey matter. An increased T_2 in the dorsolateral cortex of the left frontal lobe has been reported (Andreasen et al 1989), but without any corresponding T_1 change. In the present study such measurements were omitted as preliminary work failed to yield good T_1 reliability, due to partial volume artefact from adjacent white matter and sulcal cerebrospinal fluid, but improved methodology should allow this question to be settled in future.

CHAPTER 8

T₁ AND T₂ VALUES IN THE ANIMAL MODEL

Results

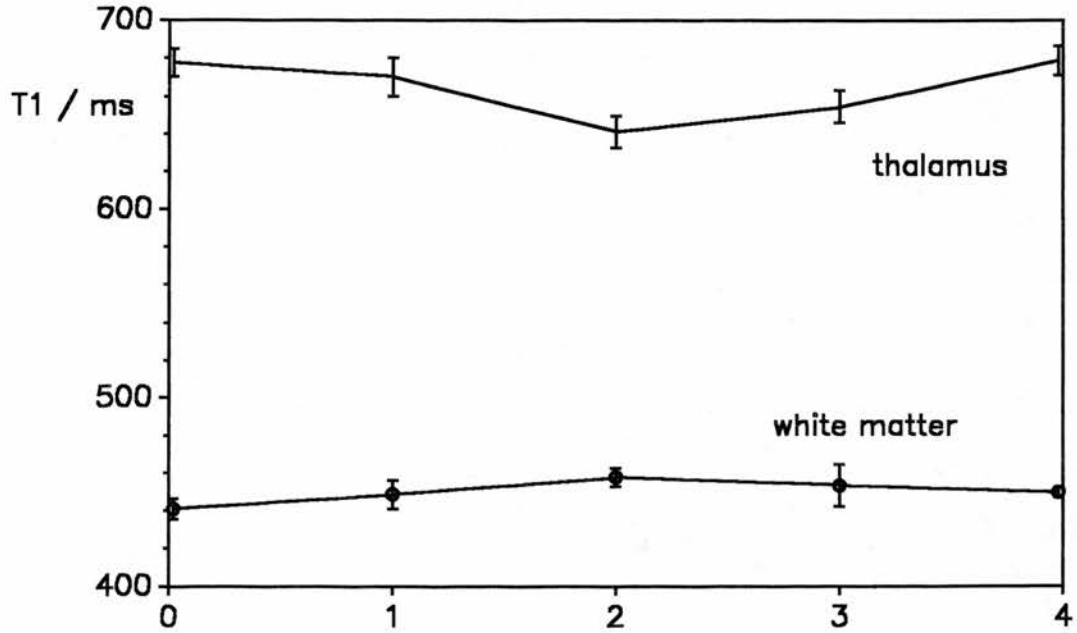
There was no difference in either T₁ or T₂ from equivalent ROI in each of the two hemispheres, so the values from left and right sides were pooled. Non-parametric tests were used due to the small number of data points. Readings from the white matter regions were averaged into a single measurement since they exhibited no significant differences at any time.

Figure 26 shows the pattern of change in T₁ and T₂ for white matter and thalamus during the four week course of chlorpromazine, at a dosage of 4 mg kg⁻¹ daily. In the thalamus there was a T₁ decrease over the first fortnight, from 677 to 641 ms, followed by a return to the baseline value (679 ms) by the end of the month. This transient decrease was significantly different to both the baseline and final values (Mann-Whitney test, p<0.01). While a similar trend was seen in thalamic T₂, the changes were not statistically significant.

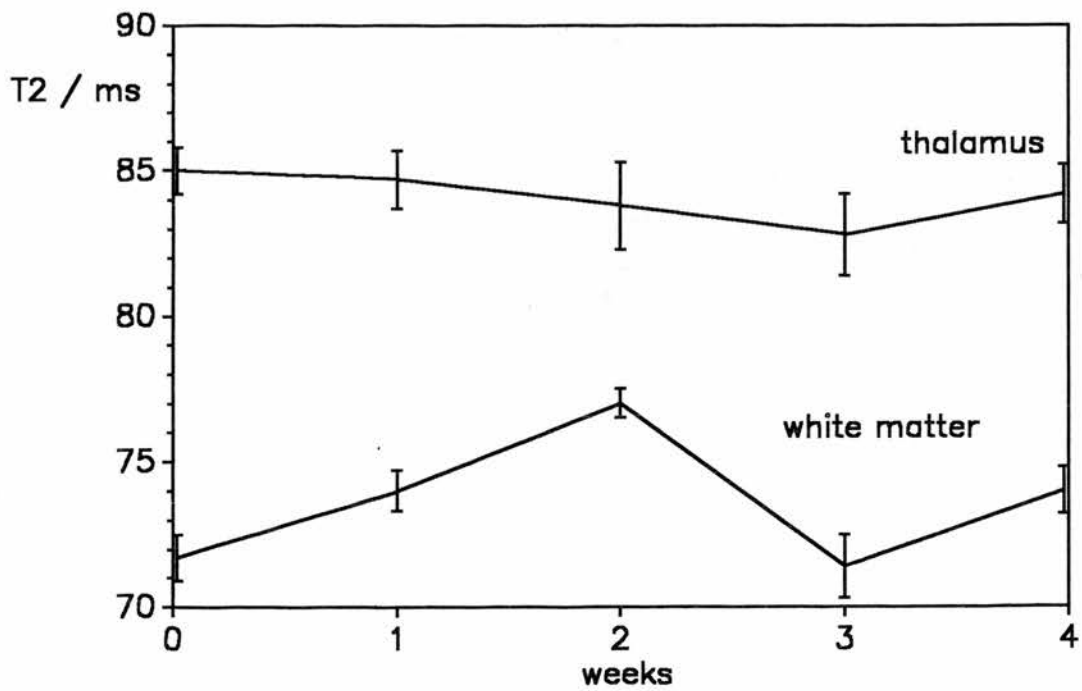
In white matter there was a T₂ increase over the first two weeks from 72 to 77 ms which then quickly returned to normal by the third week. The differences between each of these three values and that of the succeeding week is significant in each case (Mann-Whitney test, p<0.02). There was no change in the T₁ of white matter.

FIG. 26 CHLORPROMAZINE EFFECTS ON T1 AND T2 VALUES
OVER 4 WEEKS FROM COMMENCEMENT

(a) (the mean and its standard error)



(b)



Discussion

In this animal model, no sustained change of T_1 or T_2 times was detected in either the thalamus or white matter after administering chlorpromazine for a month. There was only a transient change in T_1 and T_2 , maximal after two weeks and involving a decrease of 36 ms in thalamic T_1 and an increase of 5 ms in white matter T_2 . An increase in white matter T_2 has been previously observed following injections of "DPT", which contains chlorpromazine, promethazine and pethidine (Huber et al 1987), but a decrease in grey matter T_1 has not previously been reported, and there is no immediate explanation for this pattern of results. Longer term studies as well as the use of other antipsychotic drugs are required before concluding that drugs do not influence basal ganglia T_1 times, since new effects may occur with more prolonged administration. It is also possible that the basal ganglia show an effect where the thalamus does not. The absence of any major drug change is supported by the more general lack of T_1 effects from various pharmaceutical agents tested in animals (Karlik 1986), although Fujimoto et al (1987) has reported that, after a single intravenous dose of haloperidol, a T_1 rise occurred in the striatum of dogs.

The influence of neuroleptics therefore seems unlikely to be a confounding factor in interpreting T_1 measurements from the schizophrenic group. If neuroleptics were elevating T_1 values in these patients, which could be argued from the results of Fujimoto et al (1987), it would imply that in the drug free state they were lower than in the controls, which is improbable given that pathological change usually involves a T_1 increase.

CHAPTER 9

VOLUMETRIC MEASUREMENTS

A. RESULTS

Those volumetric measures showing a positively skewed distribution underwent a log or square root transformation to achieve normality, and unless specified otherwise all analyses used results from the coronal STIR images. The raw data for each volumetric measurement are given in Table 13, which also includes a comparison between the two groups for each variable. Adjusting the significance level for the number of comparisons, the only significant difference between the two groups was the greater volume of both Sylvian fissures in the schizophrenic group.

1. INTRACRANIAL VOLUME

Although no significant difference in intracranial volume was initially seen between the two groups (Table 13) this comparison did not take the effects of gender, race and height on this measurement into account.

Multiple regression of intracranial volume on gender, race and height showed that the strongest influence was gender, that height had little effect additional to gender, and race had an independent significant influence (Table 14). When the effects of all three variables, or just gender and race, were accounted for no underlying group differences in intracranial volume emerged. The intracranial volume was unrelated to age or IQ.

2. CEREBRAL, SULCAL AND CORTICAL VOLUMES

From Table 13 it can be seen that, of these three variables, only sulcal volume exhibited any noteworthy group difference using a t-test. However, a far more powerful statistical approach was tried by adjusting each variable for intracranial volume, which has an over-riding influence on the volumes of nearly all structures contained within the head, before attempting to compare the two groups. To exemplify this, in the controls the correlation between cerebral and intracranial volume had a Pearson's coefficient of 0.97. Such an adjustment would permit more subtle pathological differences that might exist to emerge. Multiple regression was used for this purpose, which allowed the variance due to one or more variables like intracranial volume to be identified before testing if any additional group effect reached significance.

The analysis therefore examined the volumes of the cerebrum, sulcal fluid, cortex and subcortical tissue, using an initial regression on intracranial volume in each case to adjust for intracranial volume. Subcortical tissue was defined to mean all white matter and central grey matter.

In case other independent variables created a spurious group effect, the influence of age, gender, height, race and IQ on these volumes were all first ascertained. After allowing for intracranial volume there was still a significant influence of height on the cerebral, sulcal fluid and subcortical tissue volumes, but the remaining variables were of no consequence. The one exception to this was the cortex where an effect of age as well as height existed, with cortical volume decreasing with age. The analyses were therefore carried out with height as a further independent variable before testing

for any group difference, and in the case of the cortical volume age was also entered (Table 15). In subsequent analyses of other volumetric measures these same factors were considered, but only in the temporal lobe grey matter volume was the additional entry of height required.

It can be seen from Table 15 that the patient group had a significant increase in sulcal fluid and a corresponding decrease in cerebral volume. A selective decrease in cortical volume, without change in subcortical volume, accounted for the lesser cerebral volume in the schizophrenic group.

Although these analyses contained two highly correlated variables (height and intracranial volume), rendering it difficult to ascertain their relative contributions, the final group difference between patients and controls only considered their joint contribution and was therefore unaffected by this fact. Essentially the same pattern is observed if height is omitted from the regression, only the group differences are slightly smaller. The main finding was therefore a selective decrease in cortical volume; however in pursuing this result at least three possible sources of error needed to be excluded.

i) Poorer quality images might have spuriously elevated fluid volumes

In images where the quality was poorer than average, the fluid cutoff value might have been chosen in a way that overestimated sulcal fluid and underestimated the cortical volume. This could have introduced a systematic bias between the two groups since poorer quality images were, not unexpectedly, commoner in the patients than in

the controls. Eleven such images (eight from patients) were identified and removed before repeating the volumetric analyses (Table 16).

To exclude the possibility of having used an erroneous cutoff value, the 67 cases where the two methods used for its determination differed by less than 5% were also re-examined. The results are contained in Table 16. Not everyone with a poorer quality image fell into the group excluded for this second analysis, so these two analyses looked for the same effect from two slightly different angles, but in both cases the results continued to show the same group differences.

ii) Inconstant anatomical position of the frontal slices

The slices were anchored to the splenium posteriorly which, with a fixed number of slices, necessarily involved the anterior slices being placed differently from one person to another. Conceivably slices at the frontal pole included different tissue proportions to those more posteriorly, which may have possibly introduced a systematic bias. In order to answer this question it was necessary to compare an anatomically similar block of slices, which excluded the more anterior ones. Such a block was created with its posterior limit as the posterior boundary of the temporal lobe, and its anterior limit the previously identified anterior commissure. A repetition of the four regression analyses, using these more restricted and "uniform" volumes, was carried out (Table 17) and the same pattern of differences between patients and controls remained, although the reduction in cortical volume showed a trend rather than a significant effect.

iii) Incomplete intracranial volume

The possibility also remained that intracranial volume did, in fact, differ between the two groups but was not detected due to its incomplete coverage by the coronal slices used in these measurements. This would not provide an obvious explanation for the reduction in cerebral volume relative to intracranial volume but, given the central role of intracranial volume in these analyses, it was still important to know whether this could be the case. Such a possibility was examined using data from the transverse slices, which covered all of the intracranial volume above the tentorium. The previous analysis (Table 14) was repeated, only using this more complete measurement of intracranial volume (Table 18), with again no apparent group difference.

This pattern of group differences therefore appeared robust, insofar as it survived with very little change these attempts to uncover artefactual explanations. This is noteworthy given the small volumes involved. The magnitude of the cerebral decrease, for example, lay in the range 2 - 13 cm³ depending on the calculation used, and this was mirrored by a increase of similar size in the sulcal volume.

3. REGIONAL VOLUMES - TEMPORAL AND FRONTAL LOBES

a) Temporal lobe structures

Regional measurements were then examined to see if localized pathological effects might underlie these changes in the overall cortical volume (Table 19). A regression of each volumetric measure was made on intracranial volume, and this revealed a striking increase among the patients in the volume of both Sylvian fissures, without associated ventricular enlargement. A decrease in the right temporal lobe volume was also seen in the patient group, in contrast to the left temporal lobe structures where not even a trend in this direction was seen. For the smaller volumes of the temporal horns and hippocampi the influence of intracranial volume was no longer obvious, so direct comparisons were made (Table 13); they revealed no significant group difference.

It remained possible that the overall increase in sulcal fluid volume was solely due to Sylvian fissure enlargement, and that similarly the general decrease in cerebral and cortical volume arose just from changes within the temporal lobes. This possibility was refuted by examining three new variables that removed these specific regional volumes:

- i) the volume of the Sylvian fissures was subtracted from the sulcal volume.
- ii) the volume of the temporal lobes was subtracted from the cerebral volume.
- iii) temporal lobe cortical volume was subtracted from the overall cortical volume.

Analysed in the same manner as the original ones it was clear that the same pattern of significant group differences still remained apparent in these three new variables ($0.01 < p < 0.03$ in each case).

The question was also pursued whether or not a selective decrease occurred in the volume of the temporal cortex, over and above any generalized cortical decrease. To control for any generalized cortical decrease the volume of the temporal cortex was first regressed on this newly created cortical volume variable, which only reflected cortical changes outside the temporal lobe. A subsequent group difference would have indicated a selective decrease in the temporal cortex, but no such specificity was observed ($p > 0.2$ for both right and left temporal cortex).

b) Frontal lobe volumes

The removal of slices constituting the anatomically uniform posterior block from the total set, left volumes derived from the frontal slices alone. These were analysed to see if frontal changes were also observable, and again the results were significant ($0.01 < p \leq 0.05$) for cerebral, cortical and sulcal volumes.

c) Inter-hemispheric differences

The examination of inter-hemispheric differences was a further attempt to detect regional changes, in this case lateralized changes, by looking at deviations from the normal pattern of asymmetry. To analyse the sulcal, cerebral, cortical and subcortical volumes in this way they were re-measured for each hemisphere separately, using an additional midline trace, on a random subsample of 36 cases (20 patients and 16

controls) blind to diagnosis. These inter-hemispheric differences are shown in Tables 20(A) and 20(C). A significant difference from normal was seen with cortical volume, and this was further analysed by comparing the two groups separately on their cortical volume from each hemisphere. As shown in Table 20 (B), however, this failed to identify clearly which side was most abnormal, although a trend favoured the right hemisphere. The difference between the Sylvian fissures reflected a greater enlargement on the left side (Table 19). In the temporal lobes there was an alteration in the normal inter-hemispheric difference of its grey matter but not white matter, and again this is explained by a greater decrease in the right temporal grey matter than left. In schizophrenics the hippocampi showed a significant difference to the usual pattern, namely of being larger on the right side, but the measurement of each side individually was unable to demonstrate any abnormality (Table 13).

Making use of all these cerebral, cortical, sulcal, temporal lobe and Sylvian fissure volumetric differences between patients and controls, a discriminant function analysis could allocate three-quarters of each group correctly. No distinct sub-groups could be identified within the patient sample based on the presence or absence of these various scan abnormalities.

4. CLINICAL ASSOCIATIONS OF VOLUMETRIC CHANGES

The scan variables examined for clinical associations were the deviations of the volumetric measurement in each patient from its normal value as predicted by the control group. These predicted normal values were obtained from a regression, in the control group alone, of each volumetric measurement on intracranial volume. The size of these deviations in the patient group were taken to reflect the extent of any pathology more closely than the original measurements unadjusted for head size. There was no significant association between these deviation scores and sex, race, age at onset of schizophrenia or DSM-III-R diagnostic subtype. There were too few patients to examine each PSE syndrome individually, but taking all patients who had shown either hallucinations, delusions or thought disorder in the past month there was no difference to those who had remained asymptomatic.

There were many ratings that related to outcome so an attempt was made to condense this information into a single variable, thereby avoiding the problem of initially testing many individual items for significance. Using the standardized total scores of the Disability Assessment Schedule, the Negative Symptom Rating Scale and the total duration of inpatient treatment, a cluster analysis was performed to separate patients into three outcome groups. Membership of these three groups was relatively stable on comparing two different methods of cluster analysis. The validity of these groups was supported by the fact that the poorest outcome category was very significantly related to younger age of illness onset, poorer drug response, male sex, greater duration of schizophrenic symptoms, current presence of schizophrenic symptoms, longer duration of unemployment and lower level of best possible function in the previous five years. There were 14 cases in the favourable category, 20 in the

intermediate one, and 14 in the poor outcome category. A comparison of their mean deviation scores for cerebral, sulcal, cortical and Sylvian fissure volumes revealed only a weak relationship between outcome and scan abnormality (Table 21), which failed to even approach significance. Subsequent scrutiny of individual items related to outcome revealed unemployment as the only one associated with scan appearances; having more than two years unemployment out of the previous five was related to reduced cerebral volume (Mann-Whitney, $p=0.04$), reduced cortical volume (Mann-Whitney, $p=0.01$), and increased sulcal fluid (Mann-Whitney, $p=0.04$).

In regard to possible aetiological factors neither the presence of a family history of schizophrenia nor obstetric complications showed any relationship to scan measurements, but a moderate correlation was observed for the total score on the premorbid personality scale. In the 23 patients in whom sufficient information was available to rate this scale, poorer premorbid personality appeared to be associated with both increased sulcal fluid ($r=-0.44$, $p=0.03$) and decreased cerebral volumes ($r=0.40$, $p=0.06$). No significant relationship was observed between these latter variables and premorbid IQ or parental social class.

Tardive dyskinesia was commoner in patients with a larger left Sylvian fissure (Mann-Whitney, $p=0.04$). There was no relationship between deviation scores and the presence of akathisia, neurological soft signs, left handedness, the amount or duration of antipsychotic medication, or previous use of electroconvulsive therapy.

These clinical analyses are to be regarded as only preliminary; more comprehensive exploration will occur once a sample of psychiatric controls with affective disorder has been scanned with the same protocol as these schizophrenic patients.

B. DISCUSSION

The main findings in this section were, in the schizophrenic group, a generalized reduction in cerebral and cortical volume, and a reduction of temporal lobe volume on the right but not the left. No reduction in hippocampal volume was seen, and no association was evident between poorer outcome or increased genetic risk and the severity of these scan abnormalities.

1. DECREASED CORTICAL VOLUME

The most striking result was the generalised decrease in cortical volume in the schizophrenic group; this seemed to account for the decreased cerebral volume as there was no accompanying subcortical change. There was also no firm evidence that the temporal cortex was selectively decreased over other cortical areas. These findings throws into question recent assumptions about the localization of the underlying pathology, which has become focussed on the medial limbic structures to the relative exclusion of more diffuse changes. Contrary to expectation, we observed no reduction in hippocampal volume. Despite the potential importance of any hippocampal or parahippocampal pathology it is unlikely that it can explain all the functional deficits observed in schizophrenia, such as the excess of neurological soft signs (Seidman 1983), the frontal reduction in cerebral blood flow, or the dysfunction in smooth pursuit eye movements (Holzman et al 1984). The connection between cortical atrophy and psychotic illness in fact extends as far back as Meynert (1884).

The little available direct evidence seems to support this finding of a generalised cortical decrease. There has been one preliminary report of an MRI study that

examined cortical and subcortical volumes separately in schizophrenia and also found a selective cortical reduction (Zipursky et al 1990). In a post-mortem study, Pakkenberg (1987) was able to calculate a separate volume for the cortex and subcortical white matter, and again there was a specific cortical reduction. Pakkenberg also described a reduction of the subcortical grey matter, but in this study the subcortical tissue volume was not subdivided into central grey matter nuclei and white matter, so unfortunately it was not possible to explore this finding further.

The neuropathological study by Conlon (1972) suggested that cortical thickness was reduced and that this was due to a decreased number of neurones, especially in the deeper layers (IV and V), but only three patients were examined and it was not done blindly. More recently, Benes et al (1986) found that neuronal density showed a diffuse decrease in most layers of the prefrontal and motor cortex, although significant only in layers VI and III respectively. The fact that the glial density and neuronal-glia ratio were not increased was taken to indicate a non-degenerative disorder. Our finding of selective reduction in cortical volume without apparent white matter involvement is an unusual pattern, but one that also fits well into current thinking that many cases of schizophrenia have an underlying neurodevelopmental failure.

2. DECREASED CEREBRAL AND INCREASED SULCAL VOLUMES

The present results of a decreased cerebral volume and increased sulcal volume can be compared to post-mortem, CT and other MRI studies in schizophrenia.

The post-mortem evidence comes from three studies (Brown et al 1986; Pakkenberg 1987; Bruton et al 1990) each with a sample of 29-56 schizophrenics, where in each case fixed brain weight was reduced by 4-8%, although Bruton et al (1990) comment that fresh brain weight showed only a 2.8% difference. Total brain weight is usually about 1300 gm. (Davis & Wright 1977; Kang-cheng et al 1980; Bruton et al 1990) so a 5% reduction means a 65 gm. loss of cerebral tissue. Davis & Wright (1977) give brain density as 1.04, so measuring its weight and volume give comparable figures.

Sulcal enlargement has been a recurrent observation in CT studies (Weinberger et al 1979; Takahashi et al 1981; Nasrallah et al 1982; Rieder et al 1983; Pfefferbaum et al 1988; Rossi et al 1988a; Shelton et al 1988; Stahl et al 1988; Vita et al 1988b; Scottish Schizophrenia Research Group 1989; Serban et al 1990), but its quantification has proved difficult due to artefact from adjacent bone and partial volume effects (Jacobsen et al 1985). Historically it is of interest that, even before CT scanning, pneumo-encephalographic studies had produced this same finding (Lempke 1935; Haug 1962). The idea that reduced cerebral volume may underlie this phenomenon was left implicit, rather than actively explored, until relatively recently (DeLisi et al 1987; Johnstone et al 1989b; Pearlson et al 1989). The finding from the present study that the Sylvian fissures are peculiarly prone to enlargement in schizophrenia has been noted before on CT (Takahashi et al 1981; Dewan et al 1986; Stahl et al 1988; McCarley et al 1989). Sulcal enlargement can also be seen in affective disorders

(Nasrallah et al 1982; Rieder et al 1983); in this respect it tallies with the non-specific nature of ventricular enlargement in these same disorders.

In conspicuous contrast other MRI studies have largely failed to find any decrease in cerebral size (Tables 1 & 2). Although free from some of the artefacts inherent to CT they do, however, present problems of their own. One major weakness is that most derive cerebral area from a single slice, instead of making a volumetric measurement. Brown et al (1986) illustrate this point when they found no difference in cerebral area on a single coronal slice from the same schizophrenic brains that were 6% lighter in weight than controls with affective disorder. Measurements of cerebral area should therefore be viewed with some reservation if it is a small reduction in cerebral volume that is being considered. Of the two volumetric MRI studies reported one has yielded a preliminary report of reduced cerebral volume (Nasrallah et al 1990) while the earlier one of Kelsoe et al (1988) found no difference. It seems quite plausible that, as with lateral ventricular enlargement, the range of cerebral change is sufficiently wide that some studies will not detect a significant reduction simply due to random sampling. Certainly the number of studies that point in the direction of reduced cerebral volume seem too numerous to ignore, and can be taken as broadly supportive of the present results.

These studies also provide further, indirect, evidence relating to the existence of a decrease in cortical volume. The present results, and also those of Pakkenberg (1987), suggest that a decrease in cortical volume will also cause a decrease in cerebral volume, so that observations of decreased cerebral volume may well be due to an underlying reduction in cortical volume. The same argument could be applied to sulcal enlargement, which also implies some reduction in cerebral volume.

3. REGIONAL VOLUMETRIC ABNORMALITIES

The question of whether the cerebral or cortical changes can be located to one hemisphere alone or to just one lobe does not receive a clear answer in this study. The most prominent result in this respect was the significant diminution of right temporal grey matter in schizophrenics compared to controls. However, even after excluding the temporal lobes, decreases in cerebral and cortical volumes were observed so the temporal lobes cannot be the sole culprit, nor was the decrease in volume of the temporal cortex significantly greater than in other areas of cortex. This does not support the notion of an isolated temporal lobe abnormality, even though it is clearly involved.

On looking for laterality effects, the usual pattern of inter-hemispheric difference in cortical volume, was reversed in schizophrenics (Table 20A). Normally, the right frontal cortex, which constituted the majority of the cortical volume included in these images, is larger than the left. There was a trend to suggest the patients had a right sided volume decrease (Table 20B). This can be partly explained by the smaller right temporal cortex mentioned above. The right temporal white matter was also significantly smaller in volume than the left, but these readings are less robust than those from the cortex because of their lower reliability. This induces doubt as to whether any genuine white matter abnormality was detected. Sylvian fissure enlargement in the schizophrenics was, on the other hand, more pronounced on the left (Table 19), a finding that echoes Bogerts et al (1990c). These variable findings would be compatible with a diffuse process affecting the cortex. The notion that this pathology is perhaps uneven as well as diffuse receives support from the striking

Sylvian fissure enlargement that occurred against a background of less impressive sulcal increase elsewhere.

Previous MRI results have clearly favoured the brunt of any temporal lobe reduction falling on the left (Coffman et al 1989; Johnstone et al 1989a; DeLisi et al 1990; Rossi et al 1990; Suddath et al 1990), with only Bogerts et al (1990b) clearly suggesting otherwise. A possible explanation for our finding of right temporal lobe reduction is that our patients may have been less chronic than those previously reported, as a relationship between chronicity and left temporal lobe reduction has been described (DeLisi et al 1990). This does not seem to apply, however, given that the mean duration of total inpatient treatment exceeded three years and their age at onset was very similar to that of other studies. Definitions of the temporal lobe's posterior boundary vary slightly from one study to another, but this should not influence inter-hemispheric differences appreciably. The boundary chosen here was, in fact, identical to that of Bogerts et al (1990b) and very similar to that of Suddath et al (1989). Our failure to correlate temporal lobe volume to indices of chronicity, as described by DeLisi et al (1990) when comparing first episode to more chronic cases, may stem from insufficient numbers of individuals with recent onset illness to provide the necessary range of variation. The inter-hemispheric difference in hippocampal volume was compatible with a left-sided decrease but a comparison between the two groups did not confirm this suspicion.

4. ABSENCE OF VENTRICULAR ENLARGEMENT

The visual impression of greater lateral ventricular size in patients was not confirmed volumetrically, unlike that of sulcal and left Sylvian fissure enlargement. Volumetric enlargement of the lateral ventricles has been well demonstrated on MRI (Kelsoe et al 1988; Suddath et al 1989; DeLisi et al 1990) and the likeliest explanation is that ventricular enlargement existed in this sample but was simply not detected as significant, since the 95% confidence limits for the difference between patients and controls ranged from -0.94 to +3.68 cm³. Such negative results have not been uncommon on CT (Jernigan et al 1982; Shelton & Weinberger 1986; Iacono et al 1988; Serban et al 1989). Ventricular enlargement may be more posterior than anterior (Kelsoe et al 1988; Crow et al 1989) which, given our omission of the posterior horn and part of the trigone, provides an alternative explanation for this negative finding. Also, since ventricular enlargement relates to cognitive impairment and negative symptoms, the greater cooperation required for this study compared to a CT scan investigation may have excluded some patients with larger ventricles. The fact that there was enlargement of the sulci but not the ventricles bears out previous work that found relatively little correlation between these two measures (Weinberger et al 1979; Nasrallah et al 1983b; Waddington et al 1990).

The other negative finding in respect of the ventricles was the lack of any significant temporal horn difference, contrary to the left sided enlargement reported by others (Crow et al 1989; Bogerts et al 1990b). The poor reliability of these measurements makes it necessary to interpret them with caution.

5. METHODOLOGICAL CONSIDERATIONS

At first glance the finding of reduced cortical volume is vulnerable to criticism because, despite statistical significance, a small difference of less than 5% may well fall within the bounds of some systematic measurement bias. However, the neuropathological evidence leads one to expect that any genuine decrease would be in this order of magnitude so it cannot be dismissed too lightly on these grounds. Consideration also needs to be given to the fact that, on visual assessment alone, two of these patients showed unsuspected and severe sulcal enlargement with a corresponding reduction in both their cerebral and cortical volumes. Cortical volume reduction clearly does occur, therefore, so the question is more whether such patients are isolated examples or whether they form the extreme tail of a broader and much commoner range of abnormality.

a) Validity of the measurements

If, however, one did wish to argue that this result arose from an artefact, the likeliest explanation would seem to lie in the choice of the fluid cutoff value for the volumetric analyses. A systematic error at this stage could have accounted for the increased sulcal volume as well as the reduced cortical volume. However this possibility seems unlikely since close attention was paid to validating this aspect of the method. The chosen cutoff value was marginally higher in the patient group which would mitigate against obtaining reduced cortical volume in the schizophrenic group. Also, the findings remained significant when cases where there was most doubt about the cutoff value were excluded (Table 16). Cross-checks were also made on the intracranial

volume estimate and the effect of anatomical variability in slice position, but the pattern of results remained stable.

b) The multiple regression technique

The multiple regression analyses used in this study allowed for the association between intracranial volume and the volumes of the cerebrum and cortex, which is something that other studies appear to have omitted. Intracranial volume has been infrequently examined in relation to other cerebral structures, other than through the use of ratios such as VBR which are relatively crude tools for this purpose (Zatz & Jernigan 1983; Harvey et al 1990). This regression technique, similar to previous analyses on CT (Zatz & Jernigan (1983) and, outside schizophrenia research, on MRI (Condon et al 1988; Jack et al 1989), was therefore able to highlight the small difference in cortical volume that existed between the groups. Much of the debate around the results of Andreasen et al (1986, 1990) centred on alterations of either intracranial or cerebral volume, but maybe it was their relationship rather than each individually that was the key issue - if so, it was completely overlooked.

c) The effect of age on volumetric measurements

Davis & Wright (1977) measured both intracranial and cerebral volume in normal subjects under 55 years and showed a tight linear correlation (gradient=0.93), which was very similar to the controls in this study (gradient=0.91, $r=0.97$). They were able to show a clear decline in brain volume relative to intracranial volume after this age, which has also been detected by others on CT scans (Zatz et al 1982; Stafford et al 1988). Between adolescence and age 50-60 the decline is perceptible but of smaller

magnitude (Condon et al 1988; Pfefferbaum et al 1988; Stafford et al 1988; Jernigan et al 1990). In this study only a minor decrease of cortical volume in relation to age was seen, as could be expected from the age of the sample, and no relationship was seen between sulcal volume and age. Other groups have also failed to notice any substantial effect of age on sulcal size in relatively young samples (Iacono et al 1988; Shelton et al 1988; Vita et al 1988b).

d) The image processing method

The image processing method also showed close similarities to other studies, each of which had achieved good reliability and validity in their measurements (Suddath et al 1989; Jack et al 1989; Lim & Pfefferbaum 1990), which in turn supports the validity of the present findings. The latter used a non-uniformity correction, through applying a frequency filter, followed by a similar visually interactive method of deciding tissue cutoff points. They also extracted the cerebral outline from surrounding skull and soft tissue, as in our study, but employed a slightly different technique to achieve this end. Suddath et al (1989) relied on an automatic edge-detection program to identify structures, with signal intensity values standardized in a manner analogous to our own, except they included a useful colour banding to display the tissue boundaries visually. Jack et al (1989) assessed temporal lobe volumes through a similar combination of traces and cutoff values, again relying on more interactive techniques where tissue contrast was low.

6. CLINICAL ASSOCIATIONS OF SCAN ABNORMALITIES

The most likely clinical associations of reduced cerebral or cortical volumes would be those clinical features related to the severity of sulcal enlargement on CT. These include poor pre-morbid personality (Weinberger et al 1980; Pearlson et al 1985; Williams et al 1985), cognitive impairment (Reider et al 1979; Nasrallah et al 1983b; Serban et al 1990) and social deterioration (Pandurangi et al 1988). Neither chronicity of illness nor the prominence of negative symptoms appear to relate to sulcal enlargement on CT (Pfefferbaum et al 1988; Shelton et al 1988; Vita et al 1988b; Serban et al 1990).

In the present study, the poorer premorbid personality in those patients with most abnormal scans repeats these earlier CT findings, and again it points to the likelihood of these structural changes preceding the clinical onset of schizophrenia. At this point of our analysis only 23 patients had a suitable informant to complete the scale, but the correlation was significant for sulcal enlargement, and showed a trend for reduced cerebral volume. The lack of any correlation on CT between scan abnormality and either negative symptom severity or illness chronicity is also confirmed here on MRI. However, the present findings do not support any association of scan abnormality with cognitive impairment or social deterioration. Selecting only patients with an early onset to their schizophrenia, using the definition of Johnstone et al (1989b) did not reveal the same correlation they found between lower pre-morbid IQ and reduced cerebral volume.

The potentially important association between tardive dyskinesia and left Sylvian fissure enlargement remains tentative, and requires replication before any weight can be placed upon it.

Our failure to find differences in sulcal enlargement between familial and non-familial patients adds to a similar result from Vita et al (1988b), nor was such a distinction seen with any of the other volumes recorded.

Chronic unemployment was the patient characteristic associated most strongly with scan abnormality, and only one other study into schizophrenia has highlighted this variable (Pearlson et al 1984), where it was related to ventricular enlargement on CT. It is possible that, in a competitive market, seeking out and holding down a job is particularly revealing of certain functional deficits that are related to these structural brain abnormalities in schizophrenia.

7. A NEURODEVELOPMENTAL PERSPECTIVE ON SCHIZOPHRENIA

It seems implausible that, on its own, such a small reduction in cortical volume can be held to account for the severe functional deficits observed in schizophrenia. This reduction is far more likely to be a consequence of some diffuse pathological process, primarily involving a neuronal abnormality, the severity of which is poorly reflected in macroscopic appearances. It is therefore at the cellular level, rather than the macroscopic one, that functional correlations are likely to be found. This pathological process might involve a small but critical area such as the hippocampus or, as the present findings suggest, some diffuse defect in the function and synaptic connections of the cortical neurones. Thus any overt cortical and ventricular abnormalities may be simply epiphenomena of the underlying pathology, important in telling us something about its extent and natural history, but too distant from key pathophysiological mechanisms to yield much solid clinical understanding.

Taken in conjunction with what is known of the natural history of lateral ventricular enlargement, and the early antecedents of the illness, it is tempting to speculate that the diffuse cortical volume reduction may indicate the presence of some neurodevelopmental disorder. Normally, in foetal life, there is a proliferation of the neuroepithelium around the ventricles and subsequent projection of these immature neurones out to the cortex in a radial fashion, with glial fibres acting as guiding cables (Nowakowski 1987; Volpe 1987). In humans this radial migration is maximal at 11-16 weeks, after which neuronal proliferation slackens off. There is then a secondary phase of movement within the layers of the cortex, tangential to the first, with relatively more glial proliferation. These processes, in the rat at least, occur simultaneously with hippocampal development (Bayer & Altman 1987; Sidman &

Rakic 1982), and in humans the temporal and frontal cortex normally have rich connections with the hippocampus. From about 24 weeks of gestational age, there ensues a phase of dendritic growth, synapse formation and eventual pruning back of the neuronal population. This latter elimination can involve a substantial proportion of the total pool of neurones, and serves to streamline a dense but disorganized network into one far more suited to normal cerebral function.

There are several steps along this complex path of cortical development that, if interrupted, could disturb the function of the cortex with only slight alteration to its volume and without affecting the white matter. A disturbance of the sub- and periventricular neuro-epithelium might explain the subtle and diffuse ventricular enlargement, varying in severity according to the nature and timing of the pathological process (Nishimura et al 1986). This developmental link between the ventricular neuro-epithelium and the cortex might also provide an explanation for the relationship observed between such ventricular enlargement and the degree of hypofrontality on functional imaging (Berman et al 1987; Smeraldi et al 1987; Vita et al 1990). Benes et al (1986) and Colon (1972) found it was the deeper cortical layers that were most affected in schizophrenia, and the fact that in monkey cortex the few D_2 receptors present are laminated in a deeper layer, namely layer V (Goldman-Rakic et al 1990), could provide another possible link, this time to the D_2 antagonism of antipsychotic drugs. The degree of early cell death in specific parts of hamster cortex has been related to adult numbers of neurones in those same areas (Finlay & Slattery 1983).

Vascular events may also influence these neuronal processes, since the foetal and neonatal brain has an immature vasculature which readily permits cerebral infarction or haemorrhage under conditions of hypoxia or hypercapnia. A diffuse neuro-

developmental abnormality with more focal vascular events superimposed on it might be one explanation for its variable severity in different anatomical areas, although aberrant cortical development itself need not be entirely uniform. This pathological picture is termed hypoxic-ischaemic encephalopathy and the distribution of lesions varies according to maturational age (Volpe 1987). In the foetus or premature neonate, there tends to be haemorrhage into the lateral ventricles from the choroid plexus, while ischaemic damage is largely periventricular due to the relative underperfusion of this area. Periventricular necrosis can lead to compensatory enlargement of the lateral and third ventricles. In the full term neonate infarction predominantly occurs in the hippocampus and diencephalon, along with watershed infarcts at the boundaries of the anterior, middle and posterior cerebral arteries in areas that become association cortex in the adult (Lewis 1989). The depths of the sulci are also relatively avascular so infarction could cause later sulcal widening. Transient hypoxia, comparable to that seen perinatally, causes selective loss of pyramidal cells (Johansen 1983) and dopaminergic neurones (Weinberger & Cohen 1982), mediated via the excitotoxic action of glutamic acid, and perinatal injury can also interfere with normal axonal elimination (Janowsky & Finlay 1986).

In primates the medial temporal lobe develops mainly in the last trimester of pregnancy, although the hippocampus continues growth up to 2 years postnatally (Rakic & Nowakowski 1981) and this is partly dependent on environmental stimuli (Walsh 1981). The right temporal lobe develops 1-2 weeks ahead of the left, which may help to explain how an insult at one point in time could cause a lateralized abnormality. The enlarged Sylvian fissures and smaller right cortical volume observed in this study may not be such an unusual pattern if viewed neuro-developmentally, since dyslexic children show a reduced width of the right frontal lobe in combination

with a bilaterally reduced volume of cortex around the insula (Hynd et al 1990). Since the hippocampus expands to fill the temporal horn its developmental failure could well result in temporal horn enlargement. Normal growth of the hippocampus proceeds along its longitudinal axis, so the observation of a decrease in its length rather than cross-sectional area (Bogerts 1990c) would also be consistent with such a failure.

Neurodevelopmental changes in myelination (Yakovlev & Lecours 1967; Sidman & Rakic 1982) and synaptic density (Huttenlocher 1979; Feinberg 1983) continue throughout childhood and adolescence, especially in the association areas, and are paralleled by functional changes in cortical metabolic and EEG activity (Kety 1956; Feinberg 1983). This provides a possible explanation of how the functional consequences of an earlier structural abnormality may be delayed for many years before eventually manifesting themselves in a recognizable fashion (Goldman & Galkin 1978). The myelination during adolescence of cortical-hippocampal fibres that pass in close proximity to the parahippocampal gyrus may be particularly important in schizophrenia (Benes et al 1989).

This neurodevelopmental approach, first advanced in the early decades of this century (McKenzie 1912; Turner 1912; Southard 1914; Rosanoff et al 1934) has, in the light of more recent knowledge, become a source of considerable speculation (Weinberger 1987; Murray et al 1988). One of its major attractions is in providing a framework within which a multiplicity of genetic and environmental aetiological factors could operate to give a broadly similar end result (Barth 1987), manifested as the clinical syndrome called schizophrenia but containing a diversity of deficits.

CONCLUSIONS

Methods for measuring the volume of cerebral structures, and the relaxation times in both white matter and the basal ganglia, have been presented and their validity and reliability established. The volumetric measurements satisfactorily separated grey matter, white matter and cerebrospinal fluid in areas of anatomical interest.

Results from applying this method to the scans of 49 schizophrenics compared to 36 healthy controls have revealed a small decrease in the cortical volume of the former, without apparent change in the volume of underlying subcortical tissue. Such changes were observed throughout the temporal, frontal and anterior parietal cortex of both hemispheres, although there was some evidence of more severe involvement in the right temporal lobe. This cortical change was accompanied by an increase in the sulcal fluid volume, and this was particularly obvious in the Sylvian fissures. There was no excess of focal lesions on visual assessment.

Neuropathological research into schizophrenia has, so far, provided good evidence of grey matter abnormality in the parahippocampal gyrus and hippocampus, and gross post-mortem examination has suggested a more general loss of cerebral tissue. The present findings would accord well in postulating a more global alteration of cortical grey matter. The lack of any reduction in hippocampal volume in this study may reflect a technical difficulty in measuring such a small structure from the images used.

The T₁ results showed that there were substantial differences both within and between healthy subjects, particularly in regard to anatomical position. This was true for both the white matter and the basal ganglia. After taking such variation into account no T₁ abnormality in either the centrum semiovale or basal ganglia was seen in schizophrenia. There was no evidence that antipsychotic drugs had distorted this comparison. A reduction in volume of the globus pallidum has been shown neuropathologically, but a convincing imaging abnormality in this structure has yet to be shown. Neuro-imaging and neuropathology studies appear to agree that white matter is unaffected in schizophrenia.

Correlations of clinical outcome with these MRI structural abnormalities were sparse. There was no evidence to support the original hypothesis that a family history of schizophrenia would be associated with distinctive structural changes. The present results, along with those from a substantial number of other studies, seem most readily understood if placed firmly within the perspective that a neurodevelopmental disorder underlies many, if not all, cases of schizophrenia.

On reaching this point one cannot but be struck by reflecting on what Southard (1914) concluded from his own careful post-mortem work. He was in no doubt that there were changes in the cortical appearance, and that "the coarse atrophy...often does not appreciably alter the brain weight, at least outside the limits of expected variation." More striking than the cortical surface, however, was "the high proportion of cases with internal hydrocephalus" but with "no evidence that this internal hydrocephalus is due to generalized brain atrophy...it is possible it begins more posteriorly....It is associated with cases of long duration, although not with all cases of long duration." He suspected that the majority of these structural abnormalities arose from "a normal

stock of brain cells, although their arrangement and development are at times early interfered with". These lesions required "care and deliberation in their description and explanation...(they) do not effect global lacunae in the cortical neuron systems, but they are of a more finely selective character. Under the microscope it may be difficult to say, without elaborate micrometry, that one area is worse off than another; but convincing evidence of the gross convolitional extent of the process is got by the naked eye and by the finger."

One might understandably see the results of recent neuro-imaging studies as barely more than a footnote to this, but in fact progress has been made in substantiating and elaborating the general position set out so clearly by Southard. More importantly, by linking functional and structural imaging with neuropathology and neurochemistry there is the promise of considerably greater understanding ahead.

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TABLES

TABLE 1
VOLUME OF THE CEREBRUM AND CEREBRAL LOBES
IN SCHIZOPHRENICS AND CONTROLS ON MRI

| <u>Author</u> | <u>Sample Size</u> [§] | <u>Image plane</u> | <u>Frontal Lobe Volume</u> | <u>Temporal Lobe Volume</u> | <u>Cerebral Volume</u> |
|------------------------|---------------------------------|---------------------|----------------------------|--|------------------------|
| Kelsoe et al (1988) | 24 S 14 C | Multiple Coronal | NS | NS | NS |
| Suddath et al (1989) | 22 S 17 C | Multiple Coronal | NS | Grey matter reduced bilaterally by ~20% | - |
| DeLisi et al (1990) | 45 S 20 C | Multiple Coronal | - | Reduced bilaterally, left more than right. | - |
| Bogerts et al (1990b) | 34 S 25 C | Multiple Coronal | - | Reduced on the right by 9% (men only). | - |
| Suddath et al (1990) | 15 discordant MZ twin pairs | Multiple Coronal | - | Grey matter reduced on the left by 6%. | - |
| Nasrallah et al (1990) | 20 S 20 C | ? | - | NS | Reduced |

§ S = schizophrenics C = controls

N.S. = non-significant

TABLE 2
AREA OF THE CEREBRUM AND CEREBRAL LOBES
IN SCHIZOPHRENICS AND HEALTHY CONTROLS ON MRI

| <u>Author</u> | <u>Sample Size^s</u> | <u>Image plane</u> | <u>Frontal Lobe Area</u> | <u>Temporal Lobe Area</u> | <u>Cerebral Area</u> |
|-------------------------|--------------------------------|--------------------|--------------------------------|---------------------------|----------------------|
| Andreasen et al (1986) | 38 S 49 C | Midsagittal | Reduced | - | Reduced |
| Smith et al (1987a) | 33 S 23 C | 3 planes | NS | - | NS |
| DeMeyer et al (1987) | 25 S 12 C | Transverse x 2 | Reduced & asymmetrical (L<R) | - | NS |
| DeLisi et al (1988b) | 28 S 19 C | Coronal x 2 | - | Reduced bilaterally | - |
| Johnstone et al (1989a) | 21 S 21 C | Coronal x 2 | - | Reduced on the left | NS |
| Stratta et al (1989) | 20 S 20 C | Transverse x 1 | Reduced length & width on left | - | NS |
| Hauser et al (1989) | 24 S 24 C | Midsagittal | - | - | NS |
| Uematsu et al (1989) | 40 S 17 C | Midsagittal | NS | - | - |

TABLE 2 (continued)

| <u>Author</u> | <u>Sample Size</u> [§] | <u>Image plane</u> | <u>Frontal Lobe Area</u> | <u>Temporal Lobe Area</u> | <u>Cerebral Area</u> |
|-------------------------|---------------------------------|----------------------------|--------------------------|--|----------------------|
| Coffman et al (1989) | 36 S 14 C | Coronal x 2 | NS | Reduced on the left | NS |
| Rossi et al (1990) | 17 S 13 C | Coronal x 1 Midsagittal | - NS | Reduced bilaterally, left more than right | - NS |
| Andreassen et al (1990) | 52 S 48 C | 3 planes | NS | - | NS |

§ S = schizophrenics, C = controls N.S. = non-significant

TABLE 3 MID-SAGITTAL MEASURES IN SCHIZOPHRENICS COMPARED TO CONTROLS

| Author | Sample Size [§] | Length | Corpus Callosum Width | Corpus Callosum Area | CCBR* | Septum Pellucidum Area | 4 th Ventricle Area |
|-------------------------|--------------------------|--------|--------------------------|-------------------------|-----------------------|---------------------------|-----------------------------------|
| Smith et al (1987b) | 29 S 21 C | - | NS | NS | NS | - | - |
| Matthew et al (1985) | 18 S 18 C | Longer | - | NS | NS | Increased area | NS |
| Nasrallah et al (1986b) | 38 S 49 C | NS | ↑ dextral women | NS | NS | - | - |
| Stratta et al (1989) | 20 S 20 C | NS | NS | NS | Decrease | - | NS |
| Kelsoe et al (1988) | 24 S 14 C | - | NS | NS | - | - | - |
| DeLisi et al (1988b) | 28 S 19 C | - | - | NS | - | - | - |
| Uematsu et al (1989) | 40 S 17 C | NS | NS | NS | ↑ anterior CC only | Increased area | - |
| Hauser et al (1989) | 24 S 24 C | NS | ↓ dextral women | NS | NS | - | - |

§ S = schizophrenics, C = controls

* CCBR = corpus callosum to brain ratio

N.S. = non-significant

TABLE 4 RELAXATION TIMES AND SIGNAL INTENSITY MEASUREMENTS IN SCHIZOPHRENICS COMPARED TO HEALTHY CONTROLS

| <u>Authors</u> | <u>Sample Size</u> [§] | <u>Image Planes</u> | <u>Sequence</u> * | <u>Results in Schizophrenics</u> |
|------------------------|---------------------------------|---------------------|---|---|
| Smith et al (1987b) | 16 S 13 C | Coronal | SE _{250-500/50} IR _{1500/450/50} | Generally increased signal in all areas (frontal and anterior temporal lobes), but only on IR sequence. |
| Johnstone et al (1986) | 27 S 12 C | ? | SE _γ | No change in peri-ventricular signal in acute illness. |
| Besson et al (1987a) | 23 S 15 C | 3 planes | ? | Bilaterally increased T ₁ in corpus striatum. Increased T ₁ in temporal lobe white matter ? related to positive symptoms. |
| Fujimoto et al (1985) | 46 S 20 C | Transverse | ? | Bilaterally increased T ₁ in corpus striatum and caudate nuclei. Possible T ₁ decrease in frontal white matter. |
| Rossi et al (1988b) | 12 S 12 C | Transverse | SE _{1800/50-120} | Greater L > R signal asymmetry than controls, seen in the frontal white matter and temporal grey matter. |
| Kelsoe et al (1988) | 24 S 14 C | Coronal | IR _{3583/600/7} | General increased signal in all areas by approximately 5%. |

§ S = schizophrenics, C = controls.

* IR = inversion recovery sequence, SE = spin echo sequence.

TABLE 5 SOCIO-DEMOGRAPHIC AND CLINICAL DETAILS

| <u>Variable</u> | <u>Normal Controls</u> (n=36) | <u>Schizophrenic Patients</u> (n=49) | <u>P Value</u> | <u>§Schizophrenic Controls</u> |
|--|--------------------------------------|---|---------------------|------------------------------------|
| Age (years) | 31.6 | 31.1 | NS ¹ | 27.7 |
| Sex (male : female) | 19:17 | 38:11 | 0.03 ² | 33:10 |
| Race (indigenous British : other) | 22:14 | 29:20 | NS ² | 21:22 |
| Premorbid IQ | 118 | 103 | 0.0001 ¹ | 106 |
| Age at psychosis onset (years) | - | 22.2 | - | 22.7 |
| Total in-patient stay (years) | - | 3.3 | - | 1.0 |
| Handedness : % left | 16 | 11 | NS ² | - |
| Height (cm.) | 172.3 | 174.7 | NS ¹ | - |
| Units of alcohol per week | 7.6 | 3.1 | 0.02 ³ | - |
| Years of education | 13.1 | 12.0 | 0.07 ³ | - |
| Father's level of occupation (0-36) | 16.6 | 16.3 | NS ³ | - |
| No. of admissions | - | 4.5 | - | - |

§ Data from 43 consecutive admissions to the same hospitals with schizophrenia, collected to assess the effects of selection bias in the study group (see text). Significance tests shown do not involve this group.

¹ Two tailed t-test, ² Chi-square test, ³ Mann-Whitney U test, NS = non-significant.

TABLE 6 VALIDITY OF THE VOLUMETRIC MEASUREMENTS

A) ANATOMICAL STRUCTURES

| <u>Volume</u> (in cm ³) | <u>DeLisi</u> (1990) | <u>Kelsoe</u> (1988) | <u>Suddath</u> (1990) | <u>Bogerts</u> ¹ (1990b) | <u>Jack</u> (1989) | <u>Davis</u> ² (1977) | <u>Condon</u> (1988) | <u>Present</u> <u>study</u> |
|--|-------------------------|-------------------------|--------------------------|--|-----------------------|-------------------------------------|-------------------------|--------------------------------|
| Intracranial [§] | (1200) | - | - | - | - | (~1400) | (~1500) | 1263 [§] |
| R. temporal lobe | 60 | 53 | 51 | 68 | 61 | - | - | 53 |
| L. temporal lobe* | 57 | 49 | 47 | 59 | 59 | - | - | 47 |
| R. hippocampus | - | - | - | - | 2.8 | - | - | - |
| L. hippocampus | - | - | - | - | 2.5 | - | - | - |
| R. hipp/amygdala | 4.5 | 6.1 | - | 4.8 | - | - | - | 4.0 |
| L. hipp/amygdala | 4.4 | 6.2 | - | 4.7 | - | - | - | 3.8 |

¹ Calculated as the mean of the male and female values published.

² All results are from MRI studies except for this post-mortem result.

[§] Intracranial volume in present study excluded the posterior fossa, unlike Davis & Wright (1977) or Condon et al (1988). DeLisi et al (1990) took brain volume without the brainstem. The brain minus cerebellum weight was 1250 gm. in Harper et al (1988).

* The right minus left difference in temporal lobe volume was 7 cm³ in Jack et al (1988).

TABLE 6 (continued)

| B) CEREBROSPINAL FLUID | | | | | | | | | | |
|---|------------------|------------------|-------------------|---------------------------------|-----------------------------|------------------|------------------|------------------|--|--|
| Volume (in cm ³) | DeLisi (1990) | Kelsoe (1988) | Suddath (1989) | Bogerts ¹ (1990b) | Crow ² (1989) | Condon (1988) | Cramer (1987) | Present study | | |
| R. LV (total) [§] | 5.6 | 7.7 | 5.7 | - | - | - | ~ 8 | - | | |
| L. LV (total) | 5.5 | 7.5 | 6.0 | - | - | - | ~ 8 | - | | |
| R. and L. LV (body and anterior horns only) | - | - | - | - | 6.5 | 14.3 | - | 7.9 | | |
| R. temporal horn | 0.37 | - | - | 0.67 | Quoted as 1.1 | - | - | 0.29 | | |
| L. temporal horn | 0.28 | - | - | 0.58 | for R+L | - | - | 0.29 | | |

¹ as in Table 6a.

² All results are from MRI studies except for this post-mortem result.

[§] Data are shown for the total lateral ventricular volume on each side since they would be roughly comparable to the anterior half of the lateral ventricular system as measured in this study.

There are no comparable data for the anterior sulcal fluid volumes (mean value of 41 cm³ in this study), but total sulcal fluid volume was reported as 80-100 cm³ (Condon et al 1988; Grant et al 1989).

TABLE 6 (continued)

C) VOLUMES PROPORTIONATE TO INTRACRANIAL VOLUME

| <u>Volumes</u> (as a % of intracranial volume) | <u>Hubbard</u> ¹ (1981) | <u>Gado</u> ² (1982) | <u>Pfefferbaum</u> ² (1988) | <u>Davis</u> ¹ (1977) | <u>Jernigan</u> ³ (1990) | <u>Harper</u> (1988) | <u>Present study</u> |
|--|------------------------------------|---------------------------------|--|----------------------------------|-------------------------------------|----------------------|----------------------|
| Cerebrum | 89 | - | - | ~ 92 | ~ 91 | - | 91 |
| Sulcal fluid | - | 6.1 | - | - | ~ 8 | 7.3 | 7.3 |
| Cortical GM | 43 | - | - | - | 46 | - | 45 |
| Sylvian fissures | - | - | ~ 1 | - | - | - | 1.0 |

¹ = Post-mortem study,

² = CT study,

³ = MRI study.

Both Hubbard & Anderson (1981) and Gado et al (1982) included people over the age of 50 years.

The white:grey matter ratio varies from 0.6-1.3 (Miller et al 1980; Pakkenberg 1987; Lim & Pfefferbaum 1989) according to technique. In the present study central grey matter was combined with white matter, and the ratio of this slightly different subcortical:cortical volume ratio was 1.0. A comparable ratio calculated from Pakkenberg's data (1987) was 0.8.

TABLE 7 RELIABILITY OF VOLUMETRIC MEASUREMENTS

| <u>Volume</u> | <u>Test-retest</u> (intra-class correlation coefficient) | <u>Inter-rater</u> | <u>Repeat scans</u> (SD/mean as a %) |
|-----------------------|---|--------------------|---|
| Cerebrum | 0.99 | 0.99 | 1.8 |
| Cortical GM | 0.96 | 0.74 | 2.5 |
| Sulcal fluid | 0.99 | 0.99 | 2.9 |
| Right temporal GM | 0.90 | 0.87 | 3.9 |
| Left temporal GM | 0.94 | 0.96 | 2.4 |
| Right temporal WM | 0.99 | 0.96 | 13.3 |
| Left temporal WM | 0.97 | 0.87 | 13.6 |
| Right hippocampus | 0.81 | 0.45 | 4.8 |
| Left hippocampus | 0.89 | 0.36 | 6.1 |
| Right temporal horn | 0.99 | 0.99 | 47.1 |
| Left temporal horn | 0.98 | 0.93 | 40.0 |
| Right lat. ventricle | 0.99 | 0.99 | 4.3 |
| Left lat. ventricle | 0.99 | 0.99 | 4.8 |
| Right Sylvian fissure | 0.99 | 0.99 | 16.4 |
| Left Sylvian fissure | 0.98 | 0.97 | 19.7 |

GM = grey matter, WM = white matter.

It can be seen that high reliability in re-measuring a structure from the same scan is no guarantee of low variation when measuring it on repeat scanning.

TABLE 8 **VISUAL ASSESSMENT OF THE IMAGES**
 (compiled from three ratings on each)

| <u>Observation</u> | <u>Controls</u> (n = 36) | <u>Patients</u> (n = 60) |
|---|-----------------------------|-----------------------------|
| Sulcal enlargement (focal or general) | 7 (19%) | 16 (27%) |
| Lateral ventricular enlargement | 1 (3%) | 7 (12%) |
| Lateral ventricular asymmetry | 9 (25%) | 16 (27%) |
| Focal high signal white matter abnormality | 7 (19%) | 13 (22%) |
| Definitely normal | 22 (61%) | 24 (40%) |

None of these group differences are significant on a chi-square test.

TABLE 9 **ANALYSIS OF VARIANCE IN WHITE MATTER T₁**
VALUES OF HEALTHY SUBJECTS

Two subjects scanned 5 times each over 2 months.

| <u>Main effect</u> | <u>Mean Square</u> | <u>D.F.</u> | <u>Value of F</u> | <u>Sig. of F value</u> | <u>Variance estimate in msec² (% total)</u> |
|--------------------|--------------------|-------------|-------------------|------------------------|--|
| Person | 33364 | 1 | 621 | 0.0001 | 141 (33) |
| Slice | 2504 | 18 | 47 | 0.0001 | 88 (20) |
| Time | 1977 | 4 | 37 | 0.0001 | 13 (3) |
| Side | 36 | 1 | 1 | 0.41 | - - |
| <u>Interaction</u> | | | | | |
| Person x Slice | 500 | 14 | 9 | 0.0001 | 92 (21) |
| Person x Time | 920 | 4 | 17 | 0.0001 | 23 (5) |
| Time x Slice | 84 | 72 | 2 | 0.008 | 10 (2) |
| Time x Side | 261 | 4 | 5 | 0.001 | 6 (2) |
| Side x Slice | 71 | 18 | 1 | 0.18 | 2 (1) |
| Side x Person | 178 | 1 | 3 | 0.07 | 1 (1) |
| <u>Residual</u> | 54 | - | - | - | 53 (12) |

TABLE 10 **WHITE MATTER T₁ VALUES IN PATIENTS**
AND CONTROLS
(in normal appearing white matter)

| <u>Group</u> | <u>Mean T₁</u> (msec) (95% C.L.)* | <u>S.D.</u> (msec) | <u>Mean Inter-hemispheric</u> <u>Difference (msec)</u> (95% C.L.)* |
|------------------------|--|-----------------------|--|
| Controls (n=36) | 338 (334 - 343) | 14.6 | 1.0 (-0.7 to 2.7) |
| - male only | 343 (336 - 350) | 15.0 | 3.0 (1.0 to 5.0) |
| - female only | 333 (327 - 340) | 12.7 | -1.2 (-3.8 to 1.5) |
| Patients (n=49) | 340 (335 - 345) | 17.6 | 0.5 (-1.2 to 2.1) |
| - male only | 340 (334 - 346) | 17.5 | -0.2 (-2.0 to 1.9) |
| - female only | 341 (328 - 355) | 18.5 | 2.3 (-1.0 to 5.7) |

* 95% C.L. = 95% confidence limits.

None of the above group differences are significant on a t-test.

TABLE 11 **MANOVA OF WHITE MATTER T₁ VALUES IN PATIENTS AND CONTROLS**

(multivariate analysis of variance with slice position and side as within subjects factors)

a) Between-subject factors

| <u>Source of variance</u> | <u>Sum of Squares</u> | <u>DF</u> | <u>F Value</u> | <u>Sig. of F</u> |
|---------------------------|-----------------------|-----------|----------------|------------------|
| Group | 2636 | 1 | 0.4 | 0.55 |
| Sex | 8192 | 1 | 1.1 | 0.30 |
| Group by Sex | 14420 | 1 | 2.0 | 0.17 |

b) Interaction of between- and within-subject factors

| <u>Source of variance</u> | <u>Hotelling's T</u> | <u>DF</u> | <u>Approx F</u> | <u>Sig. of F</u> |
|---------------------------|----------------------|-----------|-----------------|------------------|
| Slice Number | 13.24 | 13 | 69.3 | 0.001 |
| Group by Slice | 0.15 | 13 | 0.8 | 0.67 |
| Sex by Slice | 0.21 | 13 | 1.1 | 0.38 |
| Group by Sex by Slice | 0.13 | 13 | 0.7 | 0.76 |

TABLE 12 BASAL GANGLIA T1 VALUES IN PATIENTS AND CONTROLS

| <u>Region of interest</u> ¹ | <u>Control (mean)</u> | <u>N</u> | <u>Patient (mean)</u> | <u>N</u> | <u>95% C.L. for group difference</u> ² |
|--|-----------------------|----------|-----------------------|----------|---|
| R. putamen (1.0) | 461 | 33 | 461 | 42 | -16.5 to 17.7 |
| L. putamen (1.0) | 463 | 33 | 472 | 42 | - 9.1 to 26.5 |
| R. putamen (0.5) | 480 | 35 | 480 | 42 | -20.4 to 19.6 |
| L. putamen (0.5) | 490 | 35 | 497 | 42 | -12.3 to 27.7 |
| R. putamen (0) | 502 | 24 | 509 | 24 | -21.9 to 36.5 |
| L. putamen (0) | 512 | 23 | 508 | 24 | -32.3 to 25.9 |
| R. globus pall. (1.0) | 407 | 30 | 415 | 37 | -8.0 to 24.6 |
| L. globus pall. (1.0) | 424 | 31 | 422 | 36 | -19.6 to 16.2 |
| R. caudate (0.5) | 508 | 32 | 495 | 38 | -34.0 to 8.8 |
| L. caudate (0.5) | 508 | 31 | 497 | 36 | -29.7 to 9.1 |

Globus pall. = globus pallidus, R = right, L = left.

¹ The distance in cm. of the region of interest from the caudate-putamen junction is given in brackets (see text for further explanation).

² On t-test all group differences yield $p > 0.2$

TABLE 13 **VOLUMETRIC MEASURES: PATIENTS & CONTROLS**
(mean and standard deviation)

| <u>Structure</u> | <u>Controls</u> (cm ³) | <u>Patients</u> (cm ³) | <u>t-test¹</u> <u>p value</u> |
|---------------------|---------------------------------------|---------------------------------------|---|
| Cranium* | 569.9 ± 71.4 | 582.5 ± 58.4 | 0.32 |
| Cerebrum* | 520.2 ± 60.9 | 518.1 ± 47.2 | 0.95 |
| Sulcal fluid* | 41.8 ± 16.4 | 55.2 ± 27.9 | 0.02 |
| Cortex* | 257.3 ± 31.5 | 254.9 ± 28.2 | 0.76 |
| Subcortical tissue* | 262.9 ± 34.2 | 263.2 ± 30.8 | 0.97 |
| R. Temporal GM | 35.4 ± 4.9 | 34.6 ± 5.0 | 0.49 |
| L. Temporal GM | 31.8 ± 5.2 | 32.5 ± 4.5 | 0.51 |
| R. Temporal WM | 12.9 ± 2.9 | 12.2 ± 3.3 | 0.28 |
| L. Temporal WM | 10.7 ± 2.8 | 10.6 ± 2.8 | 0.89 |
| R. Hippocampus | 3.97 ± 0.50 | 4.04 ± 0.52 | 0.53 |
| L. Hippocampus | 3.82 ± 0.54 | 3.70 ± 0.50 | 0.30 |
| R. Temporal horn | 0.29 ± 0.18 | 0.36 ± 0.25 | 0.20 |
| L. Temporal horn | 0.29 ± 0.22 | 0.34 ± 0.24 | 0.11 |
| R. Lat. ventricle* | 3.80 ± 2.83 | 4.15 ± 2.56 | 0.27 |
| L. Lat. ventricle* | 4.05 ± 2.41 | 5.06 ± 3.25 | 0.07 |
| R. Sylvian fissure | 2.29 ± 1.27 | 3.19 ± 1.49 | 0.005 |
| L. Sylvian fissure | 3.15 ± 1.67 | 4.61 ± 2.01 | 0.001 |

¹ Variables transformed as appropriate for a t-test. Untransformed variables show similar 'p values' if the Mann-Whitney test is used instead.

* These coronal volumes do not cover the full extent of this structure.

TABLE 14 INTRACRANIAL VOLUME IN PATIENTS & CONTROLS
(truncated volume from the coronal slices)

MULTIPLE REGRESSION - EFFECTS OF GENDER, RACE AND HEIGHT

| <u>Independent variables</u> (in order of entry) | <u>F change</u> | <u>R² change</u> | <u>Significance of F change</u> |
|---|-----------------|-----------------------------|-------------------------------------|
| Gender | 38.5 | 0.33 | 0.0001 |
| Height [§] | 3.5 | 0.03 | 0.07 |
| Race | 19.8 | 0.13 | 0.0001 |
| Group | 0.02 | 0.00 | 0.89 |

[§] Height and gender are highly correlated - the former has a significant association with intracranial volume if gender is omitted, and partial correlation coefficients suggest that the relative influence of each is approximately equal. However, as shown, height accounts for little variance additional to that attributable to gender.

TABLE 15 GROUP DIFFERENCES IN CEREBRAL, SULCAL, CORTICAL AND SUBCORTICAL VOLUMES

REGRESSION UPON INTRACRANIAL VOLUME, HEIGHT AND GROUP.

| <u>Dependent Variable</u> | <u>Independent variable</u> (in order of entry) | <u>F change</u> ¹ | <u>P value of the</u> <u>F change</u> ¹ |
|------------------------------|--|------------------------------|---|
| Cerebral Volume | Intracranial volume | 410.6 | < 0.0001 |
| | Height | 11.7 | 0.001 |
| | Group | 9.5 (6.6) | 0.003 (0.01) |
| Sulcal Fluid | Intracranial volume | 33.5 | < 0.0001 |
| | Height | 22.7 | < 0.0001 |
| | Group | 8.3 (4.8) | 0.005 (0.03) |
| Cortical volume [§] | Intracranial volume | 126.4 | < 0.0001 |
| | Height | 13.0 | 0.0006 |
| | Group | 5.1 (3.3) | 0.03 (0.07) |
| Subcortical tissue | Intracranial volume | 130.0 | < 0.0001 |
| | Height | 0.1 | 0.71 |
| | Group | 1.6 (1.5) | 0.20 (0.23) |

¹ The group change seen if the analyses do not include height, only intracranial volume followed by group as the independent variables, is shown in brackets.

[§] The addition of age as an additional independent variable makes little alteration to these figures, producing a GROUP F change of 5.6 (p = 0.02).

TABLE 16 REPEAT ANALYSIS: CEREBRAL & SULCAL VOLUMES
(excluding eleven images of poorer contrast)

REGRESSION UPON INTRACRANIAL VOLUME, HEIGHT AND GROUP.

| <u>Dependent Variable</u> | <u>Independent variable</u> (in order of entry) | <u>F change</u> ¹ | <u>P value of the</u> <u>F change</u> ¹ |
|------------------------------|--|------------------------------|---|
| Cerebral Volume | Intracranial volume | 303.2 | < 0.0001 |
| | Height | 8.1 | 0.006 |
| | Group | 8.0 (13.5) | 0.006 (0.0005) |
| Sulcal Fluid | Intracranial volume | 26.6 | < 0.0001 |
| | Height | 20.6 | < 0.0001 |
| | Group | 8.2 (11.7) | 0.006 (0.001) |
| Cortical volume [§] | Intracranial volume | 95.4 | < 0.0001 |
| | Height | 12.7 | 0.0007 |
| | Group | 7.9 (5.8) | 0.007 (0.02) |
| Subcortical tissue | Intracranial volume | 110.1 | < 0.0001 |
| | Height | 0.02 | 0.90 |
| | Group | 0.5 (1.7) | 0.47 (0.19) |

¹ Figures in brackets are analyses run with only the 67 cases that show close agreement on the fluid cutoff value (see main text).

[§] The addition of age as an additional independent variable produces a slightly more significant GROUP effect.

The exclusion of height from the analyses makes little alteration.

TABLE 17 GROUP DIFFERENCES IN VOLUMES FROM THE
"UNIFORM" BLOCK OF SLICES ONLY

(see text for explanation)

REGRESSION UPON INTRACRANIAL VOLUME, HEIGHT AND GROUP.

| <u>Dependent Variable</u> | <u>Independent variable</u> (in order of entry) | <u>F change</u> ¹ | <u>P value of the</u> <u>F change</u> ¹ |
|------------------------------|--|------------------------------|---|
| Cerebral Volume | Intracranial volume | 651.0 | < 0.0001 |
| | Height | 7.6 | 0.007 |
| | Group | 12.5 (9.1) | 0.0007 (0.003) |
| Sulcal Fluid | Intracranial volume | 29.8 | < 0.0001 |
| | Height | 4.2 | 0.04 |
| | Group | 7.7 (5.8) | 0.007 (0.02) |
| Cortical volume [§] | Intracranial volume | 173.7 | < 0.0001 |
| | Height | 8.6 | 0.004 |
| | Group | 3.1 (2.3) | 0.08 (0.13) |
| Subcortical tissue | Intracranial volume | 196.1 | < 0.0001 |
| | Height | 0.1 | 0.71 |
| | Group | 2.4 (1.9) | 0.13 (0.17) |

¹ as in Table 11.

[§] The addition of age as an additional independent variable produces a GROUP F change of 3.7 (p = 0.06).

TABLE 18 INTRACRANIAL VOLUME: PATIENTS & CONTROLS
(full supratentorial volume from the transverse slices)

MULTIPLE REGRESSION - EFFECTS OF GENDER, RACE AND HEIGHT

| <u>Independent variables</u> (in order of entry) | <u>F change</u> | <u>R² change</u> | <u>Significance</u> <u>of F change</u> |
|---|-----------------|-----------------------------|---|
| Gender | 47.1 | 0.39 | < 0.0001 |
| Height | 3.4 | 0.03 | 0.07 |
| Race | 21.7 | 0.14 | < 0.0001 |
| Group | 0.7 | < 0.01 | 0.42 |

TABLE 19 GROUP DIFFERENCES IN REGIONAL VOLUMES

REGRESSION UPON INTRACRANIAL VOLUME AND GROUP.

| <u>Dependent Variable</u> | <u>F change on entry of the GROUP effect¹</u> | <u>P value of the F change¹</u> |
|---------------------------|--|--|
| Right Sylvian fissure | 7.0 (8.7) | 0.009 (0.004) |
| Left Sylvian fissure | 12.5 (14.2) | 0.0007 (0.0003) |
| Right temporal lobe | 9.4 (9.6) | 0.003 (0.003) |
| Left temporal lobe | 0.4 (0.5) | 0.51 (0.48) |
| Right temporal GM | 4.1 (5.7) | 0.05 (0.02) |
| Left temporal GM | 0.0 (0.2) | 0.93 (0.70) |
| Right temporal WM | 5.1 (4.2) | 0.03 (0.04) |
| Left temporal WM | 1.0 (0.6) | 0.32 (0.44) |
| Right lateral ventricle | 0.5 (0.6) | 0.47 (0.44) |
| Left lateral ventricle | 2.4 (2.5) | 0.12 (0.12) |

¹ Figures in brackets refer to results obtained if height is included as a second independent variable before entering the group effect (see main text). For the temporal grey matter volumes the inclusion of age does not alter the results.

TABLE 20 THE VOLUMES FROM EACH HEMISPHERE: SULCAL, CEREBRAL, CORTICAL AND TEMPORAL LOBE

A. THE INTER-HEMISPHERIC DIFFERENCES
(mean and standard deviation; right minus left)

| <u>Variable</u> | <u>Controls (cm³)</u> | <u>Patients (cm³)</u> | <u>p value</u> |
|-----------------|----------------------------------|----------------------------------|----------------|
| Cerebral volume | 11.63 ± 8.06 | 6.25 ± 10.3 | 0.10 |
| Cortical volume | 3.86 ± 6.46 | -1.04 ± 6.79 | 0.03 |
| Sulcal fluid | -1.76 ± 4.24 | -4.58 ± 5.42 | 0.10 |

B. COMPARISON OF THE TWO GROUPS FOR EACH SIDE SEPARATELY

| <u>Variable</u> | <u>Controls (cm³)</u> (n = 16) | <u>Patients (cm³)</u> (n = 20) | <u>p value¹</u> |
|--------------------|--|--|----------------------------|
| Right cerebrum | 262.2 ± 24.8 | 264.8 ± 21.2 | 0.09 |
| Left cerebrum | 250.6 ± 28.4 | 258.6 ± 22.9 | 0.37 |
| Right cortex | 127.6 ± 14.4 | 127.6 ± 8.0 | 0.09 |
| Left cortex | 123.7 ± 17.1 | 128.6 ± 10.9 | 0.97 |
| Right sulcal fluid | 20.9 ± 6.3 | 27.2 ± 17.1 | 0.60 |
| Left sulcal fluid | 22.7 ± 6.7 | 31.7 ± 19.3 | 0.19 |

¹ Group testing using multiple regression as above to allow for intracranial volume.

TABLE 20 (contd.)

C. TEMPORAL LOBE INTER-HEMISPHERIC DIFFERENCES
(mean and standard deviation; right minus left)

| <u>Variable</u> | <u>Controls</u> (cm ³) | <u>Patients</u> (cm ³) | <u>p value</u> (t-test) |
|------------------|---------------------------------------|---------------------------------------|----------------------------|
| Temporal lobe | 5.95 ± 3.57 | 4.15 ± 4.46 | 0.05 |
| Temporal lobe GM | 3.55 ± 2.61 | 2.16 ± 3.17 | 0.04 |
| Temporal lobe WM | 2.26 ± 1.48 | 1.65 ± 1.93 | 0.12 |
| Hippocampus | 0.15 ± 0.37 | 0.33 ± 0.41 | 0.03 |
| Sylvian fissure | 0.87 ± 0.86 | 1.42 ± 1.19 | 0.02 |
| Temporal horn | 0.002 ± 0.16 | 0.02 ± 0.15 | 0.70 |

TABLE 21 SCAN MEASUREMENTS AND CLINICAL OUTCOME

| <u>Deviation from normal predicted volume*</u> (standardized residual) | <u>Favourable outcome</u> (n = 14) | <u>Intermediate outcome</u> (n = 20) | <u>Poorer outcome</u> (n = 14) | <u>K-W test¹</u> (p value) |
|---|---|---|---------------------------------------|--|
| Cerebrum | - 0.74 | - 1.20 | - 1.51 | 0.56 |
| Sulcal fluid | + 0.26 | + 1.01 | + 0.84 | 0.21 |
| Cortex | - 0.41 | - 0.82 | - 0.74 | 0.61 |
| Left Sylvian fissure | + 0.68 | + 0.84 | + 1.08 | 0.53 |
| Right temporal lobe | - 0.63 | - 0.63 | - 0.78 | 0.93 |
| Left temporal lobe | + 0.29 | - 0.25 | - 0.59 | 0.21 |

¹ Kruskal-Wallis test.

* See text for explanation.

APPENDICES

APPENDIX A**RESEARCH DIAGNOSTIC CRITERIA (RDC) FOR SCHIZOPHRENIA**

Criteria A through C are required for the period of illness being considered, and these criteria can be equally applied to multiple episodes in order to derive a longitudinal diagnosis instead of an episodic one.

A. During an active phase of the illness (may or may not now be present) at least two of the following are required for a definite diagnosis:

1. Thought broadcasting, insertion, or withdrawal.
2. Delusions of being controlled (or influenced), other bizarre delusions, or multiple delusions.
3. Somatic, grandiose, religious, nihilistic, or other delusions without persecutory or jealous content lasting at least one week.
4. Delusions of any type if accompanied by hallucinations of any type for at least one week.
5. Auditory hallucinations in which either a voice keeps up a running commentary on the subject's behaviours or thoughts as they occur, or two or more voices converse with each other.
6. Non-affective verbal hallucinations spoken to the subject.
7. Hallucinations of any type throughout the day for several days or intermittently for at least one month.
8. Definite instances of marked formal thought disorder accompanied by either blunted or inappropriate affect, delusions or hallucinations of any type, or grossly disorganized behaviour.

B. Signs of the illness have lasted at least two weeks from the onset of a noticeable change in the subject's usual condition (current signs of the illness may not now meet criterion A and may be residual symptoms only, such as extreme social withdrawal, blunted affect or inappropriate affect, mild formal thought disorder, or unusual thoughts or perceptual experiences).

C. At no time during the active period (delusions, hallucinations, marked formal thought disorder, bizarre behaviour etc.) of illness being considered did the subject meet the full criteria for either probable or definite manic or depressive syndrome to such a degree that it was a prominent part of the illness.

Symptoms are further defined elsewhere in the RDC manual. The presence of symptoms from criterion A only during alcohol or drug abuse is not sufficient, and the presence of a probable organic pathology excludes the diagnosis. All sources of information can be used in making a diagnostic assessment.

Criterion C extends to cover multiple episodes. It excludes schizo-affective disorder but permits the category of depressive syndrome superimposed on schizophrenia.

Subtypes based on duration of illness or phenomenology can also be distinguished within the RDC if required.

APPENDIX B**INTERVIEW CHECKLIST OF OBSTETRIC/PERINATAL ITEMS**

Briefly explain the purpose of the interview, and which pregnancy it is concerned with, before asking the following questions. Tick each item where it is positive, use a cross if negative and a question mark if unknown.

| | <u>Item</u> | <u>Comments</u> |
|---|----------------------------|--------------------------------|
| * How old were you at that time? Age yrs | | |
| * Was that your first pregnancy? Record number of previous live births | | |
| * Was it a twin birth? | twin | complicated? |
| * Have you ever had any miscarriages or stillbirths? Details of number and circumstances: | | |
| * Do you remember if delivery was in hospital or at home? If in hospital can you say which one: | | |
| * Were you happy during the pregnancy, or was it a difficult or unpleasant time? Record details: | | |
| * Were you physically well during the pregnancy? If not, did you have any of the following: | | |
| a) Bleeding during the pregnancy Details..... | ante-partum haemorrhage | |
| b) Infection eg German measles | rubella | |
| c) Threatened miscarriage Details..... | threatened abortion | |
| d) Anaemia | rhesus incompatab. | |
| e) High blood pressure | pre-eclampsia | induction or hospital stay? |

| | <u>Item</u> | <u>Comments</u> |
|--|-----------------------------|----------------------------------|
| * Did you have to go into hospital for any reason before delivery actually started? Record details:..... | | |
| * Did you take any medicines during the early months of that pregnancy? Details: | | |
| * Was the delivery full-term? If not, how early or late was it weeks. | > 3/52 early > 2/52 late | |
| * Did labour begin naturally or was it induced?..... (did membranes burst > 24 hours before delivery?) | > 24 hours | |
| * What was the labour like? How long did it last altogether:..... hrs. | under 3 hrs over 36 hrs | "difficult" or "rapid" labour |
| * Did you require a forceps delivery or a Caesarian section? | difficult forceps | |
| If Caesarian, was it done as an emergency? | emergency | |
| Complications?..... | complicated | |
| * Was the baby delivered head first or not? (face, breech or shoulder?.....) | abnormal presentation | |
| * Did a doctor or midwife attend the delivery?..... Did they say there was anything unusual or difficult about it, such as cord around the neck? Details | | |
| (possible cord prolapse?.....) | prolapse | |
| Was the baby every in danger? If so, give details: | | |
| * How much was the birthweight? lb oz | < 4.5 lb. | |

| | <u>Item</u> | <u>Comments</u> |
|--|-----------------------------------|-----------------|
| <p>* Was the baby well straight after delivery or was anything different the first few weeks?</p> <p>a) blue for longer than 5 minutes?</p> <p>.....</p> <p>b) jaundice for longer than 1 week?</p> <p>.....</p> <p>c) needing special or intensive care?</p> <p>.....</p> <p>d) failure to gain weight?</p> <p>.....</p> <p>e) fits in the first few months?</p> <p>.....</p> | | |
| <p>Other details:</p> <p>.....</p> | <p>incubator > 4 weeks</p> | |
| <p>* Do you mind if we try to fill in any missing details by contacting your GP?</p> <p>Record i) name</p> <p>ii) tel no</p> <p>iii) address</p> <p>.....</p> <p>.....</p> <p>.....</p> | <p>Do not contact</p> | |

APPENDIX CCOMPILED RATING FROM ALL SOURCES OF INFORMATION

(coded for data entry on to computer)

| | <u>Code</u> | <u>Line position</u> |
|--|-------------|----------------------|
| Subject number | | 1-5 |
| Informants (1=mother; 2=father; 3=sibling; 4=son/daughter; 5=spouse; 6=friend; 7=nurses; 8=other; 9=no informant) | | 6 7 |
| Date of last admission (code 01xxxx if only the month and year are known) | | 8-13 |
| Date of last discharge (code 000000 if still an I.P.) | | 14-19 |
| Date of subject assessment | | 20-25 |
| ----- | | |
| <u>Demographic</u> | | |
| Sex (1=male; 2=female) | | 26 |
| Race of father) 1=Afro-Caribbean,2=European,3=black) African, 4=Indian/Pakistani,5=near/ Race of mother) middle East,6=far East,7=other. | | 27 28 |
| British born (1=yes; 2=no) | | 29 |
| Date of birth | | 30-35 |
| Marital state: 0=single or cohabiting under 1 year; 1=married or cohabiting over 1 year; 2=separated (if married) or apart from common law spouse with chance of return; 3=divorced or permanently left common law spouse; 4=widow/widower. | | 36 |
| Employment status: 1=full time; 2=part time (1-30 hrs); 3=unemployed over 1 month for any reason; 4=off sick over 1 month, job kept open; 5=retired from ill-health; 6=full time housework; 7=student. | | 37 |

| | <u>Code</u> | <u>Line position</u> |
|---|-------------|--------------------------|
| Occupation level (as for Goldthorpe & Hope, plus 66=unemployed; 77=student; 88=housewife; 99=N/K) | | 38-39 |
| Unemployment in past 5 years due to psychopathology (code as for SADS-L; 0=not expected to work or unemployment unrelated to psychopathology; 1=no time off work; 2=up to 1 month; 3=up to 6 months; 4=up to 1 year; 5=up to 2 years; 6=up to 3 years; 7=up to 5 years; 8=all the time; 9=N/K) | | 40 |
| Highest previous occupation level (code as above) | | 41-42 |
| <u>Education</u> | | |
| Years in full time education from age 5 (99=N/K) | | 43-44 |
| Educational achievement (0=no qualification; 1= CSE's obtained; 2= "O" levels obtained; 3= "A" levels obtained; 4=college/university but did not qualify; 5=college/university with qualifications) | | 45 |
| Learning difficulties requiring remedial teaching or special school (0=no; 1=uncertain; 2=yes) | | 46 |
| <u>Medical History and Drug Use</u> | | |
| Meningitis or encephalitis (0=never; 1=mild; 2=serious or complicated) | | 47 |
| Head injury (0=none; 1=injury, no LOC or admission; 2=LOC or hospital admission but no PTA; 3=PTA up to 1 hour; 4=PTA 1-12 hrs; 5=PTA 13-24 hrs; 8=PTA occurred but duration uncertain) | | 48 |
| Any perceptual or communication difficulty (0=no; 1=visual(excl myopia); 2=hearing loss; 3=speech impairment from deafness; 4=stammer; 5=other dysarthria; 6=dysphasia; 7=other; 8=myopia; 9=more than one of the above) | | 49 |
| Developmental disorder or delay (0=no; 1=yes NOS; 2=language; 3=motor(not walking before 18/12); 4=other specific disorder;5=global delay;9=N/K) | | 50 |

| | <u>Code</u> | <u>Line position</u> |
|---|-------------|----------------------|
| Systemic physical disorder (0=no; 1=yes, before schizophrenia onset; 2=yes after schizophrenia onset; 3=yes, relation to schizophrenia unclear) | | 51 |
| Physical disability unrelated to drug treatment (0=no; 1=yes, independent of schizophrenia; 2=yes, secondary to schizophrenia; 3=yes, relation to schizophrenia unclear) | | 52 |
| Overdose (0=none; 1=overdose without LOC; 2=overdose, LOC unlikely to relate to CNS damage; 3=overdose with possible CNS damage) | | 53 |
| Childhood infections | Measles | 54 |
| (0=no; 1=mild and uncomplicated; 2=severe or complicated; 9=N/K) | Mumps | 55 |
| | Chickenpox | 56 |
| Migraine/febrile fits (0=neither; 1=migraine; 2=febrile fits in childhood; 3=both) | | 57 |
| <u>Alcohol and drug abuse</u> | | |
| Regular drinker (0=not at all;1=drinks irregularly; 2=yes) | | 58 |
| - units of alcohol per week at present | | 59-60 |
| - independent evidence of drinking over 56 units weekly (0=definitely no; 1=uncertain; 2=definitely yes) | | 61 |
| - previous drinking over 56 units weekly for over a year, rated from all sources (0=definitely no; 1=uncertain, probably not; 2=uncertain, probably yes; 3=definitely yes) | | 62 |
| Illegal drugs (0=none; 1=cannabis only & infrequently; 2=cannabis only & regularly; 3=opiates; 4=amphetamines or cocaine; 5=psychedelics; 6=solvents; 7=barbiturates; 8=other; 9=more than one from groups 3-8) | | 63 |
| Relationship of drug intake to schizophrenia (0=no drugs; 1=no relationship; 2=possible precipitant; 3=probable precipitant) | | 64 |

| | <u>Code</u> | <u>Line position</u> |
|--|-------------|--------------------------|
| Age of regular drug abuse (code 99 if N/A) | | 65-66 |
| Current use of cannabis (0=none; 1=infrequent, less than daily; 2=daily intake) | | 67 |
| For groups 3-8 above specify past frequency of use (0=never; 1=once or twice; 2=occasional and irregular; 3=regularly, at least twice weekly) | | 68 |
| Current use of groups 3-8 (0=none; 1=any use at all) | | 69 |
| ----- | | |
| Member of special subcultural group before illness onset (specify religious, political, occupational, sexual or nationality.....) Code 0=no; 1=yes, little personal importance or cultural deviance; 2=yes, of great importance or culturally extreme; 8=uncertain) | | 70 |
| First language English? (0=yes; 1=bilingual; 2=no) | | 71 |
| ----- | | |
| <u>NMR Exclusion Criteria</u> | | |
| Exclude from scanning (0=no; 1=anorexia nervosa; 2=hypertension; 3=past overdose with likely CNS damage) | | 72 |
| Exclude from parts of scan analysis, due to the scanner (0=no; 1=all ratings incl. visual; 2=T1 values only; 3=area measurements only; 4=T1 & area measurements) | | 73 |
| Exclude from parts of scan analysis, due to the patient (0=no; 1=all ratings incl. visual; 2=T1 values only; 3=area measurements only; 4=T1 & area measurements) | | 74 |
| Card Number | 1 | 80 |

| | <u>Code</u> | <u>Line position</u> |
|--|-------------|--------------------------|
| Subject Number | | 1-5 |
| <u>Premorbid Personality</u> (code 9 if N/K) | | |
| Social-early | | 6 |
| -late | | 7 |
| Peer -early | | 8 |
| -late | | 9 |
| Scholastic-early | | 10 |
| -late | | 11 |
| School adaptation-early | | 12 |
| -late | | 13 |
| Interests-early | | 14 |
| -late | | 15 |
| Sociosexual | | 16 |
| Social isolation | | 17 |
| Affect | | 18 |
| Sensitivity | | 19 |
| Thought content | | 20 |
| Speech | | 21 |
| Antisocial behaviour (social) | | 22 |
| Antisocial behaviour (asocial) | | 23 |
| <u>Course of Illness</u> (code 99 if N/K) | | |
| Age at puberty | | 24-25 |
| Age at onset of identifiable psychiatric syndrome (post-pubertal) | | 26-27 |
| Age first medical contact for psychiatric reasons | | 28-29 |

| | <u>Code</u> | <u>Line position</u> |
|--|-------------|--------------------------|
| Age at first psychotic symptoms | | 30-31 |
| Age at onset of psychiatric symptoms contiguous with first psychotic episode | | 32-33 |
| Insidious onset (>6/12) of symptoms before delusions or hallucinations (0=acute onset; 1=only negative symptoms; 2=only neurotic/ affective symptoms; 3=both negative & neurotic symptoms; 4=behavioural change NOS; 9=N/K) | | 34 |
| Age at first psychiatric contact | | 35-36 |
| Age at first admission | | 37-38 |
| Total number of admissions | | 39-40 |
| Total duration as inpatient in weeks (up to the date of scanning) | | 41-44 |
| Puerperal onset (0=parous,no puerperal psychosis; 1=parous,puerperal psychosis up to two months post-partum; 8=male or nulliparous female subject) | | 45 |
| Persistently poor compliance with depot neuroleptics (0=no; 1=uncertain; 2=yes) | | 46 |
| Neuroleptic response on positive symptoms, overall (0=no effect; 1=partially effective; 2=complete removal; 3=makes them worse; 4=n/k, behaviour normal; 5=n/k, behaviour partly improved; 6=n/k, behaviour unchanged or worse; 9=cannot assess) | | 47 |
| Maximum duration of DSM-III-R schizophrenic symptoms (0=none over 6 months; 1=just prodromal/residual symptoms over 6 months; 2=hallucinations or delusions over 6 months) | | 48 |
| Best level of functioning over past 5 years (or from schizophrenia onset if under 5 years)-coded as for SADS-L | | 49 |
| Patient showing any DSM-III-R symptoms of schizophrenia at time of assessment i.e. excl. affective symptoms but incl. residual ones (0=no; 1=yes) | | 50 |

| <u>Treatment</u> | <u>Code</u> | <u>Line position</u> |
|---|-------------|----------------------|
| Lifetime | | |
| - oral neuroleptics (0=none; 1=under 6 months; 2=under 2 years; 3=over 2 years) | | 51 |
| - depot: duration in months | | 52-54 |
| - total dose in gm. CPZ equivalents (0=none; 1=under 15; 2=15 to 150; 3=over 150; 9=N/K) | | 55 |
| - lithium (1=definitely yes; 0=otherwise) | | 56 |
| - tricyclic antidepressant (or derivative) (code as for Li ⁺) | | 57 |
| - MAOI (code as for Li ⁺) | | 58 |
| - benzodiazepines (0=none;intermittent use regular use less than 6 months; 1= regular use over 6 months) | | 59 |
| - ECT (0=never; 1=uncertain; 2=up to 12 treatments; 3=over 12 treatments) | | 60 |
| Current medication, at time of scan (0=no;1=yes) | | |
| i) Neuroleptics (code 0000 if on no neuroleptic) | | |
| CPZ equivalent dosage over past month (gm./10) | | 61-64 |
| ii) Anticholinergics: Dosage..... | | 65 |
| iii) Benzodiazepines: Dosage..... | | 66 |
| iv) Antidepressants (tricyclic): Dosage..... | | 67 |
| v) Lithium: Dosage..... | | 68 |
| vi) Other: Dosage..... | | 69 |
| Card number | 2 | 80 |

| | <u>Code</u> | <u>Line position</u> |
|--|-------------|----------------------|
| Subject number | | 1-5 |
| <u>Disability Assessment Schedule (8=N/A;9=N/K)</u> | | |
| Work role (work performance incl. housewife's or interest in getting a job) | | 6 |
| Sexual (two marital items or sexual interest) | | 7 |
| Social withdrawal | | 8 |
| General interest | | 9 |
| Underactivity | | 10 |
| Participation in household | | 11 |
| Self care | | 12 |
| Adjusted score (section 1) | | 13-14 |
| Adjusted score (section 2) | | 15-16 |
| Global evaluation | | 17 |
| <u>Negative Symptom Rating Scale (NSRS)</u> | | |
| Grooming | | 18 |
| Motion | | 19 |
| Motivation | | 20 |
| Emotional response | | 21 |
| Expressive relatedness | | 22 |
| Speech content | | 23 |
| Judgement/decision | | 24 |
| Memory | | 25 |
| Attention | | 26 |
| Orientation | | 27 |

| | <u>Code</u> | <u>Line position</u> |
|---|-------------|--------------------------|
| NSRS subtotals - thought process | | 28 |
| - cognition | | 29 |
| - volition | | 30 |
| - affect | | 31 |
| NSRS Total Score | | 32-33 |
| ----- | | |
| <u>Parental Data</u> (code 99 if N/K) | | |
| Age of mother at subject's birth | | 34-35 |
| Age of father at subject's birth | | 36-37 |
| Occupation of father (Goldthorpe & Hope) | | 38-39 |
| <u>Obstetric Complications</u> | | |
| Questionnaire (total score acc. to Lewis et al 1988) (0=no; 1=uncertain; 2=definite; 9=N/K) | | 40 |
| Antenatal complication (excl. delivery under 37/52) (score as above) | | 41 |
| Birthweight (kg) (code 99 if N/K) | | 42-43 |
| <u>RDC Family History overall coding</u> (code 9 if N/K) | | |
| - Schizotypal P.D. in 1st (code=1) or 2nd (code=2) degree rels. (if 1st and 2nd then code=1) | | 44 |
| - RDC Schizophrenia: No. of 1st degree rels. | | 45 |
| - RDC Schizophrenia: No. of 2nd degree rels., not 1st. | | 46 |
| - RDC Schizophrenia: No. of 3rd degree rels., not 1st/2nd. | | 47 |
| - RDC Major depressive disorder: No. of 1st degree rels. | | 48 |
| - RDC Major depressive disorder: No. of 2nd degree rels., not 1st. | | 49 |

| | <u>Code</u> | <u>Line position</u> |
|--|-------------|--------------------------|
| - RDC Bipolar disorder: No. of 2nd degree rels., not 1st. | | 50 |
| -Family history uncertain in 1st degree rels. | | 51 |
| -Family history uncertain in 2nd degree rels. | | 52 |
| -Family history of other RDC disorder (specify.....) | | 53 |
| <u>PSE Ratings</u> (rate 9 if interview inadequate for that item) | | |
| - Auditory hallucinations | | 54 |
| - Visual hallucinations | | 55 |
| - Somatic hallucinations | | 56 |
| - Thought alienation | | 57 |
| - Passivity experiences | | 58 |
| - Other delusions | | 59 |
| - Thought disorder | | 60 |
| - Depressive syndrome | | 61 |
| DSM III-R diagnosis | | 62-65 |
| <u>Handedness</u> (Annett scale) | | |
| - Handedness group (1-8) | | 66 |
| - Overall allocation (1=R.H.; 2=L.H.) | | 67 |
| - LH with no family history (0=all 1st degree rels RH; 1=either parent LH; 2=both parents RH but sib/child L.H.; 8=N/A; 9=N/K) | | 68 |
| - Foot dominance (1=right;2=left;3=equal) | | 69 |
| - Eye dominance (as above) | | 70 |

| | <u>Code</u> | <u>Line position</u> |
|---|-------------|--------------------------|
| <u>Soft neurological signs</u> | | |
| i) Face/hand test (1=right; 2=left; 3=both; 9=not done) | | |
| - missed one hand on ipsilateral test | | 71 |
| - missed one hand on bilateral hand or contralateral test | | 72 |
| - missed more than the above | | 73 |
| ii) Agraphesthesia (score 1 for each number wrong, and 9 if test not done) | | |
| - right hand | | 74 |
| - left hand | | 75 |
| <u>Involuntary movements</u> - AIMS severity score | | 76 |
| - No T.D. but akathisia (0=no; 1=yes) | | 77 |
| Card Number | 3 | 80 |

| | <u>Code</u> | <u>Line position</u> |
|---|-------------|----------------------|
| Subject Number | | 1-5 |
| <u>Data from CT scan</u> | | |
| - Date of CT scan | | 6-11 |
| - Scanner (1=1010; 2=9800) | | 12 |
| - Scan Number | | 13-17 |
| - Ventricular-brain ratio | | 18-21 |
| - Lateral ventricular area (9999 if N/K) (0-20 H.U.; sq. cm.) | | 22-25 |
| - Lateral ventricular area (9999 if N/K) (0-25 H.U.; sq. cm.) | | 26-29 |
| - Total intracranial area (9999 if N/K) (0-99 H.U.; sq. cm.) | | 30-33 |
| <u>Pre-morbid IQ (Nelson Adult Reading Test)</u> | | |
| - Error score (code 88 if omitted for cultural reasons; 99=N/K) | | 34-35 |
| - Verbal I.Q. | | 36-38 |
| - Full I.Q. | | 39-41 |
| <u>NMR scan</u> | | |
| NMR number for each subject | | 42-45 |
| NMR number for each image | | 46-50 |
| Date of scan | | 51-56 |
| Time of scan (24 hour clock; 00.00=N/K) | | 57-60 |
| Menstrual phase (0=week before; 1=menstruation; 2=week after; 3=2 nd week after; 7=amenorrhoea; 8=irregular; 9=N/A) | | 61 |
| Height (cm.) | | 62-64 |
| Card Number | 4 | 80 |

APPENDIX D

THE VOLUMETRIC MEASUREMENT METHOD : FURTHER DETAILS

1. The visual interactive method for deciding the fluid cutoff value.

It was found with this method that any visual judgement, being dependent on the exact appearance of the image, altered substantially with its relative illumination. This variable was controlled by the grey scale display range, as to whether the full grey scale range was used or only one particular part of it. The full range differed greatly from one scan to another so it was necessary to find a way of standardizing the appearance of different scans. This was satisfactorily dealt with by setting the maximum value of the display range equal to the mean CSF value.

2. Calculating the fluid cutoff value from the isolated CSF distribution.

This alternative method was based on observations made from those two scans (see Figure 7) where the total frequency distribution contained a distinct fluid component, since in these cases one definitely knew at what point the cutoff value between fluid and grey matter should be placed. Its position was found to be approximately 2.5 standard deviations (SD) below the mean fluid value. In the remaining subjects whose fluid volume was smaller, where increased overlap between sulcal fluid and grey

matter distributions would occur, a more conservative calculation of 2.0 SD below the mean was estimated to represent the correct cutoff point. Since each subject's edited image gave this mean and SD of the fluid the calculation was straightforward.

The validity of these mean fluid values taken from the edited images was supported by their consistent relationship with the modal values of grey and white matter on the total frequency distribution. Expressing these modal values as a percentage of the fluid mean, measured in 25 patients and 20 controls blind to diagnosis, this relationship was found to be very similar in both groups:

| | <u>WM mode</u> | <u>WM/GM cutoff</u> | <u>GM mode</u> |
|---------|----------------|---------------------|----------------|
| Control | 25.6% | 43.9% | 59.9% |
| Patient | 25.8% | 44.1% | 58.8% |

However, it was anticipated that in the small minority of scans with slightly poorer contrast the grey matter and fluid distributions would be even more closely merged, so this calculated cutoff would erroneously start to inflate the fluid compartment by including excessive grey matter. This was a further reason for regarding the visual interactive method as the more preferable of the two.

The reliability of this second method was examined by re-editing 23 scans and estimating the mean again, and the intraclass correlation coefficient proved to be 0.98. In eleven scans of the same individual this mean value showed a standard deviation of 2.7%, indicating that it remained stable over time.

3. Greater consistency in the automated edge-detector

Standardizing the grey scale display range by use of the mean CSF value also had one further substantial advantage, since it remained fixed during the entire measurement procedure of each scan. It enabled greater speed and consistency to be introduced into the automatic tracing of the boundary between cortical grey and white matter. The constant relationship between the mean CSF value and the cutoff value separating white and grey matter (see above) allowed the latter to be expressed as a simple percentage level of the display range. The edge-detection program could then be set to trace immediately at this level on each slice, rather than having to decide each trace in turn. Adopting the level of 44% shown above generated results that visually were entirely acceptable, and adjustment was still possible on those few occasions when it did not exactly match the observed anatomy.

4. Rejection of the use of "filtered" images

Filtered images (see p. 81) were found unsuccessful in trying to enhance the problematic boundary between grey matter and sulcal fluid. The volumes of the cortex and hippocampus were measured from six scans of the same individual, both in their original state and after a high frequency filter had been applied. There was no difference in their variance, indicating that no greater reliability in identifying this tissue boundary had been achieved as a result of the filter. The original unfiltered images were therefore retained for all measurements.