A COMPUTERIZED TOMOGRAPHIC EVALUATION OF BRAIN MORPHOLOGY
IN FIRST EPISODE PSYCHOTIC PATIENTS

by

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M.A., University of British Columbia, 1984

A THESIS IN PARTIAL FULFILMENT OF THE
REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY
THE FACULTY OF GRADUATE STUDIES
DEPARTMENT OF PSYCHOLOGY

We accept this dissertation as conforming
to the required standard

The University of British Columbia
August 1986
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Date 14 August 86
A growing body of computerized tomography (CT) research suggests that a significant proportion of schizophrenic patients have enlargement of the third and lateral cerebral ventricles and of the cortical sulci. Preliminary results indicate that these anomalies are present at the onset of schizophrenia and are associated with variables putatively linked to poor prognosis. Evidence of ventricular dilation in nonschizophrenic psychotic patients suggests that these morphological anomalies are not specific to the diagnosis of schizophrenia. There is much variability in the estimated prevalence of ventricular and sulcal dilation and several recent studies report no enlargement. Differences between studies in methodology, in the severity of illness of the patients, and in control group selection have been proposed as probable biases contributing to inconsistencies in the research literature. The purpose of the present study was to test a number of hypotheses suggested by the previous research. The first three predict that first episode schizophrenic and nonschizophrenic psychotic patients have 1. Enlarged lateral ventricles, 2. Enlarged third ventricle, and 3. Dilated cortical sulci. The fourth hypothesis predicts that these three brain anomalies are associated with variables putatively linked to poor prognosis (poor premorbid adjustment, negative symptoms, disrupted smooth-pursuit eye movements). The fifth hypothesis predicts that medical
patients chosen from radiology records have smaller ventricles and sulci than do healthy control subjects. Measurements were taken from the CT scans of a representative sample of carefully diagnosed first episode, functionally psychotic patients. There were 31 schizophrenic, 20 schizo-phreniform, 18 bipolar, 16 depressed, three paranoid, and three schizoaffective patients. A volunteer control group of 44 healthy individuals was used for comparison. In order to evaluate possible biases due to the type of control subjects that are used, a second group comprised of 30 medical patients was obtained from radiology records. The results of this study indicate significant enlargement of the third ventricle in schizophrenic patients but failed to detect significant lateral ventricular enlargement or cortical atrophy in this patient group. No brain anomalies were found in schizo-phreniform, bipolar or depressed patient groups and no significant association was found between variables putatively associated with poor prognosis and any brain measure for any patient group. The third ventricle and cortical sulci were significantly smaller in the medical group than in the volunteer control group. The results are discussed in terms of the implications they have for previously reported findings and for future research. The present findings also underscore some methodological difficulties associated with using medical control subjects.
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ACKNOWLEDGMENTS

I would like to extend special thanks to Dr. W. G. Iacono for his invaluable guidance and encouragement with my dissertation research and throughout my graduate studies. I am very grateful to Dr. D. Papageorgis for his generous assistance with and helpful comments on my dissertation. My appreciation also goes to Dr. R. Tees for his help with my dissertation and to Dr. M. Moreau for her frequently unusual and insightful contributions. The process of locating participants and collecting data in this study was a team effort. In addition to Drs Iacono and Moreau, I am grateful to Dr. M. Beiser, Dr. S. Lin, Dr. J. Flemming, to the research team Dr. N. Kyle, K. Keetley, J. Husted, and D. Erickson, and the staff of the Greater Vancouver Mental Health Service. I also thank Dr. B. Flak for his advice on neuroradiological issues.
Diagnostic Heterogeneity in Schizophrenia

The introduction of DSM-III (American Psychiatric Association, 1980) has made the diagnosis of schizophrenia more reliable than ever before. Nevertheless, this diagnosis is still based on course and presenting state as defined by the patient's verbal report of subjective experiences and behavioral observations made by others. This system allows many individual differences between persons who receive this diagnosis (for a review of variables putatively related to schizophrenia, see Carpenter, Bartko, Carpenter, & Strauss, 1976; Perris, Struwe, & Jansson, 1981; Seidman, 1983). These differences, for the most part, are not considered when making the diagnosis of schizophrenia. There is also much variability across schizophrenic patients in response to treatment regimens and prognosis (for a review, see Neale & Oltmanns, 1980).

In addition to the many differences between patients who are diagnosed schizophrenic, there are many similarities between schizophrenia and other disorders. Affective disorders, for example, are defined in such a way that it is frequently difficult to specify whether an individual has schizophrenia or an affective disorder (American Psychiatric Association, 1980). This decision is made on the basis of which symptoms occurred first and/or which symptoms are prominent. Unless a patient presents himself at the first sign of any problems, the decision as to which symptoms occurred first is frequently difficult to make. For example, the decision as to which symptoms are prominent is confused
by the symptom overlap between the two diagnostic categories and the prevalence of depression in diagnosed schizophrenics (American Psychiatric Association, 1980). There are also a number of organic disorders such as epilepsy, cerebral tumor, and encephalitis that may present with symptoms that are indistinguishable from those found in schizophrenia (Davidson & Bagley, 1969).

These diagnostic problems suggest that researchers should not assume that the diagnosis of schizophrenia identifies patients who have a common pathological process. Indeed the preponderance of heterogeneous results in the studies of schizophrenia suggests that this diagnosis reflects a number of disorders rather than a single illness (Meltzer, 1979; Wyatt et al., 1981). One method of systematically investigating this diagnostic heterogeneity is to incorporate biological variables into the diagnosis of schizophrenia in an attempt to identify homogeneous subtypes. Biological variables have the advantage of providing objectively verifiable factors and thus lead to more easily testable research hypotheses. Among biological variables that have received a great deal of attention in recent years, neuroanatomical indicators have produced some of the most provocative results. These include findings of lateral ventricular enlargement (LVE), enlargement of the third ventricle, and cortical atrophy. The research literature concerning these variables in schizophrenia and in other psychotic disorders will be reviewed in the following
sections.

There is a rapidly growing body of research concerning these morphological anomalies. These studies may be categorized using a number of distinctions. These include the part of the brain that is being studied (lateral ventricles, third ventricle, cortex), and the diagnosis of the patients (schizophrenia, schizophreniform, bipolar, depressed). The present review will be divided into sections according to these distinctions. Those studies that do not fall easily into any one section have been cited more than once. Table 1 provides an overview of the studies reviewed and their particular focus.

**Lateral Ventricular Enlargement**

Lateral ventricular enlargement, as with many morphological anomalies in the human brain, may result from a number of causes. These include degeneration of brain tissue (Bird, 1982), obstruction of cerebrospinal fluid flow (TerBrugge & Rao, 1983), or changes in fluid, electrolyte and nutritional status (Bentson, Reza, Winter, & Wilson, 1978).

Brain changes may be focal or diffuse. Some specific causes of focal changes are trauma, infarction, inflammation, and vascular abnormalities. These disorders frequently involve dilation of a part of the ventricular system or atrophy in an area of the cortex and often spare other brain areas (TerBrugge & Rao, 1983). Numerous other conditions can have diffuse effects on brain morphology. These include
Table 1
Previous CT Studies of Brain Anomalies in Psychotic Patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Diagnostic System</th>
<th>Number of Patients</th>
<th>Control</th>
<th>LVE&lt;sup&gt;a&lt;/sup&gt;</th>
<th>TVE&lt;sup&gt;b&lt;/sup&gt;</th>
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<td>Andreasen et al., 1982b</td>
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<td>52</td>
<td>Med 47</td>
<td>VBR Yes</td>
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<td>-</td>
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<tr>
<td>Benes et al., 1982</td>
<td>Feighner</td>
<td>11</td>
<td>Med 26</td>
<td>VBR No</td>
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<td>-</td>
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<tr>
<td>Boronow et al., 1985</td>
<td>RDC</td>
<td>30</td>
<td>Med 26</td>
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<td>DeLisi et al., 1986</td>
<td>DSM-III</td>
<td>26</td>
<td>Norm 20</td>
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<td>DeMeyer et al., 1984</td>
<td>DSM-III</td>
<td>8</td>
<td>Med 15</td>
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<td>Linear No No No</td>
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<td>30</td>
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<td>Med 50</td>
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<sup>a</sup>LVE = Lateral Ventricular Enlargement.  
<sup>b</sup>TVE = Third Ventricular Enlargement.

Diffuse changes in brain morphology may involve primarily the ventricles with little effect on the cortex whereas in other illnesses this pattern is reversed. Huntington's chorea, for example, reflects a diffuse form of atrophy characterized by enlargement of the lateral ventricles and may not be associated with dilation of the cortical sulci until later stages of the disease process (TerBrugge & Rao, 1983). Likewise, hydrocephalus normally presents with enlargement of the ventricles in the absence of sulcal dilation (TerBrugge & Rao, 1983). In contrast, diffuse cortical atrophy, disproportionate to the degree of ventricular dilation has been reported in cerebral anoxia (TerBrugge & Rao, 1983). Other disorders such as Alzheimer's disease frequently involve both the ventricles and the cortex but either of these structures may be affected in isolation (TerBrugge & Rao, 1983). Thus, lateral ventricular enlargement is not limited to any single pathological process and is observed in a number of different types of illness. In addition, because enlargement of the lateral ventricles is frequently found with other morphological brain changes, it cannot be assumed to be an isolated finding in the absence of
extensive investigations.

There is some evidence that enlargement of the lateral ventricles may be reversible in some cases. Bentson et al. (1978) reported that cessation of steroids in long term steroid users resulted in the reduction in ventricular size in some patients. Other studies (Largenstein, Willig, & Kuhne, 1979; Okuna, Ito, Konishi, Yoshioka, & Nakamo, 1980) have reported enlargement of the ventricles in some patients when corticotrophin therapy was initiated and decreased ventricular size when this treatment was terminated. Abstinence in recently recovered alcoholics has also been shown to result in a reduction in the size of the ventricles (Carlen et al., 1984). In addition, a number of medical disorders can result in a decrease in ventricle size. These include head trauma, hematoma, astrocytomas, and vasospasms (Schneider, Kahn, Crosby, & Taren, 1982).

Two studies have investigated the possibility of changes in ventricular size in schizophrenia. Weinberger and Wyatt (1982a) re-scanned five schizophrenics for LVE after a two- to three-year interval and found no changes for any patient. Although this result suggests that there are no fluctuations in ventricular size in schizophrenics, the small sample size indicates that caution is needed in generalizing from these results.

In a second study, Nasrallah, Olsen, McCalley-Whitters, Chapman and Jacoby (1986) repeated a CT scanning procedure on 11 male schizophrenics. The second CT scan was performed
three to four years after the first and no significant overall changes in ventricle size were detected. However, the retest reliability of the measure of ventricle size was low (rho = .26). This instability suggests either that the method of measurement is highly unreliable or that there were random changes in ventricle size.

These two studies provide preliminary evidence suggesting that there are no clear changes in lateral ventricle size in schizophrenics over two to four years. However, the poor retest reliability obtained by Nasrallah et al. (1986) and the small number of subjects used in these studies suggest that it is premature to conclude that ventricle size is a stable characteristic in schizophrenic patients. It is necessary to rescan larger, representative groups with reliable methods of assessment in order to confirm these preliminary results.

**LVE in Postmortem Studies**

Postmortem investigations have tended to reveal no significant ventricular enlargement in the brains of schizophrenics. However, the premortem events, changes that occur in brain tissue with death, and postmortem extraction and fixation procedures may obscure ventricular enlargement especially if the enlargement is modest (Messert, Wannamaker, & Dudley, 1972). In addition, the brain tends to shrink after death thereby further obscuring subtle morphological changes (Jacobs, Kinkel, & Heffner, 1976).

**LVE in Pneumoencephalographic Studies**

Haug (1962) reviewed the early literature and found more
than 30 studies that reported enlarged ventricles in schizophrenic individuals. Haug noted, however, that these studies are difficult to interpret because most have used biased patient selection, inadequate controls, unspecified or inadequate diagnostic criteria, and poorly defined standards for normal ventricular size. Weinberger and Wyatt (1982a) reviewed the literature since 1962 and concluded that whereas more recent studies have many of the problems of the earlier investigations, there have been consistent reports of LVE in schizophrenics. This consistency suggests that there are morphological anomalies in the brains of some schizophrenic patients.

**LVE in Computerized Tomographic Studies**

In recent years, researchers have begun to use computerized tomography (CT) as a non-invasive, reliable method for assessing neurological anomalies during life (Gyldensted, 1977; Jacobs et al., 1976). This method of assessment directs X-rays, from sources located in a thin band around the circumference of the head, through the brain at various angles. The X-radiation is attenuated to some degree by the density of the neurological tissue it passes through. Receptors, also located around the head, convert the attenuated X-radiation to electrical signals. The electrical signals are then used to mathematically reconstruct an image of one cross-section (slice or scan) of the brain. Serial cross-sections of the brain are scanned to produce a number of images of the brain at a number of
different levels.

A number of different methods have been used to assess the size of the lateral ventricles. The simplest method involves the linear measurement of various aspects of the ventricles. The most commonly used technique includes the measurement of the area of the ventricles and of the brain from a single CT scan.

**Linear Measures.** The linear measures that are most commonly used are Evans' ratio, cella media ratio, bicaudate ratio, and frontal horn ratio (for definitions of these terms, see Appendix A). Most of these measures are designed to be obtained from the frontal projection of a pneumoencephalogram (Penn et al., 1978). Whereas these measures are relatively clear on a frontal projection of the brain, they are influenced by the level of the cut in the horizontal plane of a CT scan. The rapidly sloping ventricle walls are likely to obscure the true distances used in these linear measures and result in imprecise estimates of ventricle size (Penn et al., 1978).

In a study comparing linear measures with ventricular volume, Penn et al. (1978) reported that the linear indices correlated poorly with the actual volume. There was considerable variability in the linear measures especially when the size of small ventricles was being estimated. Furthermore, because ventricle size is a volume measure (x), a small linear (x) increase in already large ventricles represents a larger increase than a similar change in small ventricles. Thus, although linear measures are more easily
derived than other measures they are less reliable, are imprecise for small ventricles, and underestimate the size of ventricular enlargement in large ventricles. There is also considerable normal variability in the shape of the frontal horns of the lateral ventricles (LeMay & Kido, 1978) and this is likely to further reduce the value of linear measures that make use of this aspect of the brain. The imprecision of linear indices and the fact that few schizophrenia researchers use these measures makes it difficult to interpret results from studies that employ these methods.

**Ventricle to Brain Ratio.** Most CT studies of psychiatric patients involve a method of measurement that was developed by Synek and Reuben (1976). This manual method involves planimetric measurement of the area of the lateral ventricles in the scan that shows the ventricles at their largest. The ventricular area is divided by the area of the total brain in the same slice and the result is multiplied by 100. The resulting quotient is called the ventricle to brain ratio (VBR) and represents the percent of brain space that is taken up by the lateral ventricles from a single CT slice. This estimate of ventricle size is highly reliable and correlates extremely well with computerized methods for assessing volume (Jacobs, Kinkel, & Painter, 1978; Penn, Belanger, & Yasnoff, 1978). With computer assisted measures of ventricular volume, the area of the ventricles is automatically assessed at each slice and all of these areas are combined in order to compute the overall volume. Because of the complexity of this
method and the fact that it offers no significant advantages over the VBR (Weinberger, Wagner, & Wyatt, 1983) few researchers have made use of it.

Differences in the criteria that are used to define the ventricle walls can result in large between-study differences in reported mean VBR size (Maser and Keith, 1983; Jernigan et al., 1982). This variability underscores the need for control samples for each study and for the consecutive assessment of CT patient and control subject scans. Published normal values should not be substituted for a control group.

Prevalence of LVE in Schizophrenia

A large number of studies of ventricular enlargement in schizophrenic patients has been published. In the following discussion, those studies in which linear measures were used will be considered first followed by those investigations in which the ventricle to brain ratio (VBR) was reported.

Linear Measures

Famuyiwa, Eccleston, Donaldson, and Garside (1979) compared the CT scans of 45 chronically hospitalized schizophrenic patients with published normal values. The mean duration of hospitalization was 14.6 years. Diagnoses were made using Fieghner criteria and 17 patients were reported to have tardive dyskinesia. Three linear measures were used to assess lateral ventricle size (Huckman, cella media, and ventricular indices). The results indicated that 31 (65%) of the patients were outside the normal range. The facts that this group was chronically hospitalized,
relatively old (mean age was 48 years), a control group was not included, and linear measures were used to estimate ventricle size, makes the significance of these findings difficult to determine. This study does, however, provide preliminary evidence indicating that there may be significantly enlarged lateral ventricles in chronically ill schizophrenic patients.

Enlargement of the lateral ventricles was also reported by Okasha and Madkour (1982). The cella media index was used to estimate ventricle size in 43 chronic schizophrenics and 39 medical patients. All schizophrenics had been ill for more than five years and their age ranged from 15 to 59 years. Moderate ventricular enlargement was found in 20 (46%) patients. This study included patients with a wider age range than the schizophrenics in the study by Famuyiwa et al. (1979) and thus, because of the large number of subjects with ventricular enlargement, suggests that brain anomalies are present in both young and old patients.

Nyback, Wiesel, Berggren, and Hindmarsh (1982) also obtained evidence for the presence of ventricular enlargement in young schizophrenics. A linear measure using the frontal horns of the lateral ventricles, was used to estimate the size of the ventricles in 46 schizophrenic patients (17 to 44 years) and 46 volunteer controls. Of the patient group, 19 had recently experienced their first psychotic episode and 27 had been hospitalized two or more times previously. Separate analyses were not computed for these two groups. The patient
group had significantly larger ventricles than did the control group. A scatter plot of ventricle size by age indicated that some of the youngest patients had LVE. This finding supports that of Okasha and Madkour (1982) and suggests that ventricular enlargement may be found in schizophrenics of all ages.

Woods and Wolf (1983), using linear estimates (bicaudate index, and bifrontal index) of ventricular size, also reported ventricular enlargement in young schizophrenics. Mean age was 23 years. A group of 19 patients, diagnosed according to Research Diagnostic Criteria (RDC, Spitzer, Endicott, & Robins, 1978) were compared to 29 medical patients over lateral ventricle size. The mean duration of illness for these patients was four years. The degree of enlargement is described as slight but the actual extent of LVE is difficult to ascertain from the information given. Whereas the results of this study support those of Okasha and Madkour (1982) and Nyback et al. (1982) in indicating LVE in young patients, the degree of enlargement reported by Woods and Wolf (1983) appears to be lower than in these other studies.

Tanaka, Hazama, Kawahara, and Kobayashi (1981) report findings that suggest LVE is part of a degenerative process. Tanaka et al. (1981) compared 49 schizophrenic patients to a control group of 38 age matched medical patients. Seven linear measures were obtained and the data indicated significantly enlarged ventricles in patients aged 41 to 60
as compared to an age-matched control. There was, however, no significant difference between younger patients (21-40) and controls over ventricle size. Unfortunately, Tanaka et al. (1981) fail to describe their patient sample, diagnostic criteria, or selection procedure. Nevertheless, the findings of this study provide some support for those of Famuyiwa et al. (1982) and Okasha and Madkour (1982) in indicating LVE in chronic schizophrenics. The absence of LVE in young patients contradicts the findings of Nyback et al. (1982) and Woods and Wolf (1983) in suggesting that LVE is not present in the early stages of schizophrenia.

Two published studies that have used linear measures from CT scans report no significant ventricular enlargement in chronic schizophrenic patients. Trimble and Kingsley (1978) used Evans' ratio to estimate the size of the lateral ventricles of 11 chronic schizophrenics. The age of these patients ranged from 17 to 66 years (M = 34 years). No information is given regarding diagnostic criteria or selection procedures but it is noted that some were receiving outpatient treatment. Using a normal limit of .30 for Evans ratio, these authors report no significant ventricular enlargement. However, Evans (1942, cited in Weinberger & Wyatt, 1982a) used the figure of .25 to diagnose early or questionable atrophy. If this figure is used, seven of the 11 patients have enlarged ventricles. Given that LVE in schizophrenics is generally small compared to that of dementing or hydrocephalic patients, the possibility of early
atrophy (when using the .25 cutoff) must be considered.

A finding of no significant enlargement was also reported by Gluck, Mundt, and Gerhardt (1980). The distance between the outer tips of the frontal horns of the lateral ventricles was measured from the CT scans of 68 chronic schizophrenic patients and 68 medical control subjects. The method of diagnosis is not given but it is noted that 14 of the schizophrenics "did not communicate with the environment either verbally or emotionally". The duration of illness was greater than five years for all patients and age ranged from 22 to 66 years. The facts that some patients were relatively old, all had been ill for more than five years, and all were hospitalized suggests that this patient sample was probably as impaired as those of the studies where positive results were reported. This finding suggests that LVE may be less prevalent than appears from the earlier investigations. However, the method of measurement used in this study is unusual and may account for the failure to obtain significant results.

Summary of Studies in which Linear Measures were Used

Overall, the results of those investigations in which linear measures of the lateral ventricles were obtained suggest significant enlargement. Four of the five studies involving chronic schizophrenic patients indicate LVE. The variety of methods of measurement that were used makes comparison between these studies difficult but suggests that the finding of LVE is relatively robust. The results from
the studies in which young patients were included are less consistent. Of the three studies involving young patients, one reported clear LVE (Nyback et al., 1982), one reported only slight enlargement (Woods and Wolf, 1983), and one reported no enlargement (Tanaka et al., 1981). Further studies are needed to resolve this issue.

**Ventricle to Brain Ratio**

Reports of Significant LVE. In the first studies of schizophrenia using computerized tomography, Johnstone, Crow, Frith, Husband, and Kreeal (1976) and Johnstone et al. (1978b) reported significantly larger lateral ventricles in a group of 18 chronic schizophrenics than in a group of ten chronically hospitalized medical patients. Fourteen (94%) of 15 patients had ventricles larger than those of any control subject. No significant relationship between ventricular size and past treatment or age was found. These results have been criticized on a number of grounds. The mean duration of hospitalization was 32 years, most patients had been receiving neuroleptic medication for a number of years, and patients were relatively advanced in age (M = 58 years). Any of these factors may have accounted for the results that were obtained (Barron, Jacobs, & Kinkel, 1976; Jellineck, 1976; Marsden, 1976). In addition to these problems, the patient and control group sizes were small, and four leucotomized schizophrenic patients were included.

Weinberger, Torrey, Neophytides, and Wyatt (1979a) replicated the finding of Johnstone et al. (1976) with a
larger, younger sample of 65 schizophrenics and 56 normal controls (relatives of patients with Huntington's Chorea). Patients were under 50 years of age ($M = 29$ years), and had a mean duration of illness of 10.6 years. The schizophrenic group received RDC diagnoses and contained 42 patients who were chronically ill and 23 for whom the present episode was less than two years in duration. Most patients ($n = 58$) responded poorly to treatment. None had any indication of neurological disorder. The VBR was used to estimate the size of the lateral ventricles. Of the schizophrenic group, 52% were found to have significantly enlarged ventricles. No significant differences were found between chronically ill schizophrenics and those who had been continuously ill for less than two years. No relationship was observed between age, length of illness, duration of hospitalization, or number of ECT treatments and ventricular enlargement.

Golden et al. (1980) reported ventricular enlargement in 60% (25/42) of a group of patients who met the DSM-III criteria for chronic schizophrenia. The mean age of patients was 32 years and the average duration of illness was 10 years. Published normal values were used instead of a control group. This large proportion of abnormal scans may be influenced by the fact that 22 of the patients were referred for "suspicion of brain dysfunction". In addition, methodological differences in assessing VBR are likely to occur among studies: e.g., ventricular size may vary depending on the definition of the ventricular margin, the CT
machine that is used, and the angle of the CT slice (Weinberger et al., 1983; Revely, 1985). These methodological differences make it unwise to use normal values from one study to evaluate the proportion of abnormal scans in another. It was also reported by Jernigan, Zatz, Moses, and Berger (1982) that the method of assessing the VBR used by Golden et al. (1980) was atypical and resulted in inflated estimates of LVE. The fact that Golden et al. (1980) used published norms instead of a control group and an atypical method of assessing the VBR makes it difficult to interpret the results of this investigation.

A large proportion of patients with LVE were also reported by Kling, Kurtz, Tachiki, and Orzeck (1982/83). In this study the ventricle to brain ratio was measured on 26 chronic schizophrenic patients, 22 patients with either alcoholic or neurological problems, and 20 medical controls. Medical control scans were taken from radiology records and only those read as "grossly normal" were used. This selection procedure suggests that only scans that showed small ventricles were used. If this is the case, spuriously low "normal" values would be obtained and LVE in schizophrenic patients could be overestimated in this study. Schizophrenic subjects were diagnosed using DSM-III criteria and all were nonresponsive to treatment. The mean age of schizophrenic patients was 36 years (range 23 to 45 years) and mean duration of illness was 10 years. The schizophrenic group had significantly enlarged ventricles and
50% exceeded the largest value obtained by a control subject. No significant correlations were obtained between ventricle size and age or duration of illness. These findings support earlier studies and indicate that a large number of chronic schizophrenics have significantly enlarged ventricles. Patients in this study, like those of Weinberger et al. (1979a), were nonresponsive to medications.

Several studies have indicated that the prevalence of LVE in chronic schizophrenics may be less than 50 or 60%. Pearlson and Veroff (1981) reported fewer patients with enlarged ventricles than have been reported in the studies reviewed above. In this study, there were 22 schizophrenics, 16 manic-depressives, and 35 age- and sex-matched psychiatric controls. Diagnoses were made using DSM-III criteria. Patients were described as acutely ill but the mean age and duration of illness were not reported. Using the VBR as a measure of ventricular size, 41% (9/22) of the schizophrenics and 12% (2/16) of the manic-depressives were found to have significantly larger ventricles than those of the control group. Ventricle size did not correlate with age, age at onset, or duration of hospitalization but age was positively related to ventricular size in the control group.

Nasrallah, Jacoby, McCalley-Whitters, and Kuperman (1982a) compared 55 consecutively admitted chronic schizophrenic men with 27 age-matched medical controls. The mean age of patients was 30 years (range 20 to 45 years) and mean duration of illness was 6.3 years. Diagnoses were made
using DSM-III criteria. The VBR was used to assess the size of the lateral ventricles. Of the schizophrenic group, 34% (19/55) had significantly enlarged ventricles. Ventricle size was not significantly related to age or duration of illness.

Weinberger et al. (1982) evaluated the CT scans of 17 chronic schizophrenics, 35 schizophreniform patients, 50 patients with other psychiatric disorders, and 26 medical controls. The mean age of the schizophrenic patients was 28 years (range 17 to 50), for schizophreniform patients was 21 years (range 13 to 40), and for other psychiatric patients was 30 years (range 18 to 50). The duration of illness is not given for the schizophrenic or other psychiatric patients but is, by definition, less than six months for the schizophreniform patients. Diagnoses were made using DSM-III criteria. Twenty-four percent (4/17) of the chronic schizophrenics, and 20% (7/35) of the schizophreniform patients had lateral ventricles that were significantly larger than those of the control group. No enlargement was reported for the non-schizophrenic psychiatric patients. It is notable in this study that the prevalence of enlarged ventricles in chronic schizophrenics is much less than in the previous study by this research team (Weinberger et al., 1979a). In the earlier study, using the same methodology, the percentage of chronic patients with LVE was twice that of the 1982 study. It is not clear whether or not this discrepancy is due to differences in patient samples. No correlations were reported between age or duration of
illness and ventricle size. However, the fact that 20% of the schizophreniform patients had significantly enlarged ventricles suggests that LVE is present at the onset of psychosis in some patients and is not the result of somatic treatment, prolonged illness, or advanced age.

The finding of LVE in first episode patients was replicated by Schulz et al. (1983). In this study, 53% (8/15) of teenage schizophreniform/schizophrenic patients (diagnosed according to DSM-III criteria) had lateral ventricles that were significantly enlarged when compared to those of either a medical control group (n = 18) or of a group of borderline patients (n = 8). The estimated prevalence of LVE is greater than has been reported in most other studies with schizophrenics. The mean age of the patients was 16 years and the average duration of illness was 13 months (range five to 24 months). No significant correlation was obtained between duration of illness and ventricle size. The relationship between age and ventricle size was not reported. It is possible that early onset may indicate a more severe illness and poor prognosis. However, it is noteworthy that mean ventricle size in the control group is smaller than that reported in any other study. This suggests control group bias and thus the prevalence of LVE in schizophrenia that is reported may be an overestimate of the true prevalence. Schulz et al. (1983) note that the high prevalence of LVE in their sample may result from the fact that patients were obtained
from a facility where severely affected patients were admitted. The results of this study support those of Weinberger et al. (1982) and suggest that ventricular enlargement probably occurs at or before the onset of psychosis in some patients.

Findings of minimal ventricular enlargement were reported by Williams, Kolakowska, Arden, and Mandelbrote (1985). Only six (15%) of 40 chronic schizophrenic patients had lateral ventricles that were significantly enlarged when compared to 40 medical control subjects. RDC diagnoses were made and patients ranged in age from 20 to 50 years (M = 32 years). The VBR was used to assess ventricle size. Twelve patients were described as poor outcome, 16 as intermediate outcome, and 12 as good outcome. Ventricle size was not associated with age but was significantly related to "poor outcome" and chronic negative symptoms. This finding supports the earlier results of Johnstone et al. (1976), Weinberger et al. (1979a), and Kling et al. (1982-83) and suggests that ventricular dilation is greatest in patients who respond poorly to treatment and/or require long periods of hospitalization. The duration of illness ranged from two to 20 years but no association between duration of illness and ventricle size was reported. Most of the schizophrenics included in this study were outpatients.

Pandurangi et al. (1984) used the VBR to estimate the size of the lateral ventricles of 23 chronic schizophrenics and 23 medical controls. The mean age of patients was 28
years (range 20 to 40). All patients met DSM-III criteria for schizophrenia, and none had been hospitalized for extended periods. The duration of illness ranged from 2 to 19 years. Three of 23 patients (13%) had significantly enlarged ventricles. There were no significant correlations between ventricle size and age or duration of illness.

A small proportion of schizophrenics were also found to have LVE in a study by Luchins et al. (1984). In this study, the VBR was used to assess ventricle size in 45 schizophrenic, 20 affective disorder, and 50 medical patients. RDC diagnoses were used to classify patients. Thirty-one of the schizophrenic patients were chronically ill. Ages ranged from 18 to 59 (M = 29 years). Five (11%) of the 45 schizophrenic and four (18%) of the affective patients had lateral ventricles that were larger than the control mean plus two standards deviations. Ventricular size was not related to age. The correlations between ventricle size and duration of illness were not reported. Luchins et al. (1984) note that the low frequency of LVE in these patients may be due to the fact that these patients are less impaired than those of some other studies; i.e., the patients in the Luchins et al. (1984) study were able to function for much of the time in the community. It is also interesting to note that a significant relationship was obtained between ventricle size and response to neuroleptics. This further supports the contention that LVE is found most frequently in chronically hospitalized patients and/or
patients who respond poorly to treatment.

Luchins and Melzer (1986) followed up their earlier study (Luchins et al., 1984) by using 11 of their original schizophrenics, 11 of the medical controls, and adding 11 chronic, long term hospitalized schizophrenics. The two groups of schizophrenics were matched over age ($M = 28$ years) and duration of illness ($M = 8$ years). However, whereas the 11 schizophrenics from the original study were hospitalized for an average of 10% of their illness, the 11 patients who were added had been hospitalized for an average of 60% of their illness. Diagnoses were made according to DSM-III criteria and the VBR was used to assess ventricle size. The mean age of the controls was 36 years. The long term hospitalized patients had a mean ventricle size significantly greater than both the short term hospitalized patients and the control subjects. Seven of these schizophrenics (64%) had significant ventricular dilation (lateral ventricles greater than the control mean plus two standard deviations). As with the original study (Luchins et al., 1984), the 11 patients in the acute psychiatric wards also had significantly larger mean ventricle size than the control subjects. However, only three (27%) had significantly enlarged ventricles. The high prevalence of LVE in chronically hospitalized patients and the difference between the chronically hospitalized and short term hospitalized patients strongly suggest that patients who do not respond well to treatment or are unable to function in the community
are likely to have LVE. This notion is supported by the fact that whereas no relationship was obtained between VBR size and duration of hospitalization or duration of illness, a significant positive relation was found between VBR size and the percent of illness spent in hospital. Luchins and Melzer (1986) indicate that the control group may be biased because of the exclusion of individuals with "abnormal" scans; i.e., subjects with normal but large ventricles may have been excluded. Thus, the absolute number of patients with enlarged ventricles may be overestimated in this study. Nevertheless, this study does provide evidence for a relationship between severity of illness and ventricle size.

Rieder et al. (1983) reported that 7% (2/28) of a group of chronic schizophrenic patients had significantly enlarged lateral ventricles when compared to published normal values. A normal control group was not included in this study. It was also reported that one (7%) of 15 schizoaffective and two (10%) of 19 bipolar patients had LVE. Patients were classified according to RDC diagnoses. The mean age of the schizophrenic patients was 26 years. A significant relationship was obtained between age and ventricle size over the total patient sample (r = .42, p < .001). The duration of illness and relationship between ventricle size and duration of illness were not reported. Patients used in this study are described as including a high proportion of treatment-resistant cases. Because Reider et al. (1983) failed to include a control group, these findings are
difficult to interpret. There are systematic methodological differences between studies that influence obtained VBR values (Maser and Keith, 1983) and, thus, it is possible that the results of Reider et al. (1983) may reflect measurement artifact. Nevertheless, these findings concur with a number of previous reports and thus provide tentative corroborating evidence.

Andreasen, Smith, Jacoby, Dennert, and Olsen (1982b) also reported significant group differences between schizophrenic and control subjects over ventricle size. The VBR was assessed in a group of 52 chronic schizophrenic inpatients (diagnosed according to RDC and DSM-III criteria) and 47 medical control subjects. All patients had spent most of their illness as outpatients. The mean age of patients was 30 years and the mean duration of illness was 5 years. Using a comparable definition to that of Weinberger et al. (1979), Andreasen et al. (1982b) reported that only 6% (3/52) of schizophrenic patients had ventricles that were significantly enlarged; i.e., greater than the control mean plus two standard deviations. This number is low compared to that reported in other studies.

In another recent study, Owens et al. (1985) examined ventricular enlargement in 110 chronically hospitalized, 18 outpatient, and 8 first break schizophrenics. Two other groups comprised 32 manic depressives and 19 "neurotic" outpatients. Schizophrenics were diagnosed according to the CATEGO computerized diagnostic system--this system is based
on items derived from the Present State Examination (PSE; Wing, Cooper, & Sartorius, 1974). Manic and neurotic patients were diagnosed according to Feighner diagnostic criteria. Ages ranged from 22 to 87 years with a mean of 55 years for the schizophrenic group. The average age of the manic and neurotic patients was not given and mean duration of illness was not reported for any patient group. A significantly greater mean ventricle size was reported for the schizophrenic group over the manic and neurotic groups. The proportion of patients with significantly enlarged lateral ventricles (the control mean plus two standard deviations) is not given. A significant relationship was reported between age and ventricle size. Ventricle size was relatively constant across all age groups and increased in patients who were in the sixth or seventh decade of life.

Finally, a significantly enlarged mean ventricle size (VBR) was reported by DeLisi et al. (1986). In this study, CT scans were performed on 26 in- and out-patient schizophrenics, 10 well relatives of the schizophrenic patients, and 20 normal volunteers. Schizophrenic diagnoses were made according to DSM-III criteria and the average duration of hospitalization for these patients was 3.2 years. The mean age of the schizophrenic patients was 32 years, of the relatives was 33 years, and of the controls was 31 years. Whereas there was a significant difference over mean ventricle size between the schizophrenic patients and the control subjects, there was no difference between the
relatives of the schizophrenic patients and either the schizophrenic group or the control group. Using the definition of Weinberger et al. (1979a; control mean plus two standard deviations) to determine the number of patients with significant ventricular enlargement, only one (4%) schizophrenic had enlarged ventricles (VBR > 14.39). DeLisi et al. (1986) also measured the area of the frontal horns of the lateral ventricles and reported results from a frontal horn-brain ratio. Using this index of ventricular enlargement, three (12%) of the schizophrenics had frontal horns that were greater than the control mean plus two standard deviations. The minimal enlargement that was obtained in this study may be attributable, in part, to the fact that 11 of the normal controls were found to have psychiatric problems. Because there are reports of ventricular enlargement in some nonschizophrenic psychiatric patients (see Prevalence of LVE in Affective Disorders below) it is possible that this control group may be biased towards enlarged ventricles.

Reports of No Significant LVE. There are several reports of no LVE in schizophrenic patients. Benes et al. (1982) reported that none of ten young schizophrenic patients had significantly enlarged lateral ventricles when compared to 26 medical control subjects. This was the case whether linear or VBR measures were used. Feighner criteria were used to make diagnoses. The mean age of patients was 21 years and the mean duration of illness was four years.
Correlations between ventricle size and age or duration of illness are not reported. These patients showed varying degrees of cognitive impairment and the CT scans were done to evaluate the presence of organic brain disease. In addition, there was a period of seven years between the time the first and last patients were scanned. The fact that the CT scans were obtained over a number of years suggests that the selection criteria and the CT scanners and scanning procedures may be different for different subjects.

A well-conducted study that produced negative results was reported by Jernigan et al. (1982). In this study, the ventricular volume and VBR of 30 chronic schizophrenic in- and out-patients and 36 normal volunteers were measured from CT scans. Diagnoses were made using DSM-III criteria. No significant differences were obtained between the schizophrenic and control groups whether the VBR or ventricular volume was used to assess ventricle size. The mean duration of illness was 10 years and patients ranged in age from 23 to 58 years ($M = 32$ years). No significant correlations were obtained between ventricle size and duration of illness or age. Patients in this study were screened for neurological deficits and serious medical problems. No subject had a deficit in any of these areas. All of the patients in this study are described as employed or employable. The selection criteria used in this study suggests that this group of patients may be less impaired and have a better prognosis than the samples described in other
studies (Luchins, 1982). In order to determine whether these negative results were due to methodological factors, Jernigan et al. (1982) had the CT scans assessed by the research teams of Golden and Weinberger. Each of these groups reported a different mean ventricle size from that of Jernigan et al. (1982) but the relative rank order of subjects and mean group differences were very similar across all three research teams. No research group obtained significant LVE for these data. The results of this study suggest that LVE is less likely to be found in mildly impaired chronic schizophrenic patients than in patients who have a severe course of illness.

Smith and Maser (1983) also reported no significant enlargement of the lateral ventricles. In this study, 30 RDC diagnosed schizophrenics were compared to 14 medical controls. Age and duration of illness are not given nor are the correlations between ventricle size and age or duration of illness. Some patients are described as chronic nonresponders to treatment but it is unclear how many fall into this category. The results of this study, because chronic nonresponders to treatment are included, contradict many of the findings reviewed above. This finding suggests that LVE may not be apparent in some severely impaired patients. However, the absence of detailed information on subject characteristics and selection procedures prevents any firm conclusions.

Using a small sample (n = 8) of DSM-III diagnosed
schizophrenics, DeMeyer et al. (1984) reported no difference in lateral ventricular size between the patient group and a medical control group. The schizophrenic patients reportedly had a history of severe psychosis and were relatively unresponsive to neuroleptic medication. The mean age of the patients was 26 years. Duration of illness was not reported nor were the correlations between ventricle size and age or duration of illness. It is possible that the small size of the sample resulted in a nonrepresentative group. However, the severity of illness in these patients suggests that they were at least as impaired as patients used in other studies where highly significant findings were reported. This finding supports that of Smith and Maser (1983) and suggests that some patients who are severely impaired (i.e., respond poorly to treatment) do not have significant lateral ventricular enlargement.

Largen et al. (1984) also reported no lateral ventricular enlargement in a group of 35 hospitalized schizophrenics when compared to 17 medical controls. Most patients were chronically ill but four patients had recently experienced their first psychotic episode. The average age of patients was 30 years and the duration of illness ranged from two weeks to 24 years. Ventricle size was assessed using the VBR and RDC diagnoses were made. It is reported that most patients were relapsing psychotics and were able to live in the community between episodes. This study adds support to earlier negative findings and suggests that some
chronic patients have no significant enlargement of the lateral ventricles. However, the fact that these patients were able to live in the community suggests that they responded to treatment and were not as impaired as the chronically hospitalized patients used in some studies where positive results were obtained.

Shima et al. (1985) used the VBR to assess lateral ventricular size in 46 chronic schizophrenic inpatients. The mean age of the patients was 37 years (range 23 to 48 years) and average duration of illness was 13 years. Diagnoses were made according to DSM-III criteria. A control group of 38 healthy volunteers was used for comparison. A nonsignificant trend towards larger ventricles in the schizophrenic group is reported. Unlike previous studies, significant correlations were obtained between ventricle size and both age and duration of illness. It is difficult to determine the level of impairment in these patients from the information given. Nevertheless, this result provides support for other negative results and suggests that some chronic patients do not have enlarged ventricles.

Finally, Boronow et al. (1985), in a well-described study, reported a nonsignificant trend towards enlarged lateral ventricles in 30 chronic schizophrenic patients when compared to 26 medical patients. The mean age of the schizophrenics was 25 years and the average duration of illness was five years. No significant correlations were obtained between ventricle size and either age or duration of
illness. RDC diagnoses were made and ventricle size was assessed using the VBR. This study is particularly noteworthy in that schizophrenic patients were described as severely ill chronic schizophrenics. This result further questions the assumption that lateral ventricular enlargement is present in a significant proportion of chronic schizophrenics.

Summary of the Studies of LVE in Schizophrenia

From the preceding review, some conclusions can be drawn. The consistency of LVE in the older pneumoencephalographic studies and in the CT studies where linear measures were employed has been supported by many findings from CT studies where the VBR was used. The findings from these studies suggest that enlargement of the lateral ventricles is found in both young and old schizophrenic patients and some preliminary results suggest that ventricular enlargement may be present at the onset of psychosis in some schizophrenics. There is, however, much variability in the reported prevalence of this anomaly. Estimates of the prevalence of LVE have ranged from 7% to 94% with a median of 29% and seven studies indicate no significant enlargement. In addition, there is much variability in the mean size of the lateral ventricles that is reported. These VBR values range from 4.1 (Luchins et al., 1984) to 18.7 (Johnstone et al., 1976) for patients and 2.7 (Schulz et al., 1983) to 10.8 (Owens et al., 1985) for control subjects.

Procedural factors probably account for some of the variability in the size of the lateral ventricles that has
been reported (Maser & Keith, 1983). In particular, differences in the definition of the ventricle walls that are used when tracing the perimeter of the lateral ventricles have been shown to result in large differences in the estimated size of this aspect of the brain (Jernigan et al., 1982). However, if the same procedures are used for patients and control subjects, then this factor should not influence the prevalence of LVE that is found and would not account for the failure to find enlargement in several studies. A more serious methodological problem would be one that affects subject groups differently. An example would be a bias in subject selection that leads to unrepresentative schizophrenic or control samples.

Differences between studies in the severity of impairment of schizophrenic samples has been widely recognized as a likely contributing factor to the inconsistencies in the CT research findings. If this is the case, then LVE could be limited to those patients with severe pathology; i.e., patients who respond poorly to treatment and/or require prolonged hospitalization. Overall, research results support this contention and suggest that severely impaired patients are more likely to have LVE than are less impaired patients. However, there is some preliminary evidence (Boronow et al., 1985; DeMeyer et al., 1984; Largen et al., 1984) to indicate that even in some severely ill patients, there may not be significant ventricular enlargement.
In addition, it is not always clear from the descriptions of subjects to what extent, or in what areas of functioning, patients are impaired. Patients are likely to differ significantly between centers over such variables as response to treatment, type of symptoms, the presence of associated personality disorders, and the role of precipitating factors (Maser & Keith, 1983). At the present time, there is not a commonly agreed upon definition of level of impairment. Thus, whereas most research findings suggest that patients who are severely impaired are more likely to have LVE, some studies do not support this hypothesis and the absence of a common definition of severity precludes meaningful comparison of subjects between studies over this variable.

Whereas differences in the populations from which schizophrenics are drawn is recognised by most researchers as a probable contributing factor to the wide variability in findings, little attention has been drawn to the fact that CT studies also differ with respect to the selection of control groups. The control groups that have been used include psychiatric patients, various types of medical patients, and normal volunteers. As was noted above (Lateral Ventricular Enlargement), a number of physical disorders may result in enlarged ventricles or in decreased ventricular size. Thus, the characteristics of the medical population that is sampled from can potentially influence the obtained mean ventricle size and, as a consequence, the prevalence of LVE that is detected in psychiatric patients.
In addition, normal variability in brain morphology is poorly understood (Maser & Keith, 1983) and the extent of this variability is likely to go unrecognized by diagnosticians who normally examine CT scans to detect neuropathology. This factor is particularly pertinent to the studies of LVE in schizophrenia because many investigators use medical patients as control subjects. Selection of "normal" CT scans could lead to the systematic exclusion of patients with normal but large ventricles and the inclusion of subjects who, because of neuropathology, have abnormally small ventricles. This would exaggerate the prevalence of LVE in schizophrenic patients.

If, as is usually hypothesised, ventricular enlargement is a feature of the schizophrenic illness in a small to moderate proportion of severely ill patients, then those studies that indicate LVE (i.e., those that include a significant proportion of patients who have enlarged ventricles) should report greater mean VBR values than those studies that detect no LVE. Control subjects, on the other hand, should have relatively similar VBR values across studies regardless of the results of the investigation. In order to test this hypothesis, all studies that assessed the prevalence of LVE in schizophrenia and included a control group were included. Because linear measures cannot easily be compared across studies, only those investigations that included the VBR were used in this analysis. Twenty-three studies used the VBR as a measure of ventricle size and
included a control group (Table 2). The mean VBR for all subjects in 14 studies where positive results were obtained was compared to that of the subjects in the seven studies where no LVE was reported. Because Johnstone et al. (1976) and Owens et al. (1985) used old subjects and reported VBR values far greater than those of other researchers, these studies were not included in the following calculations. All but one of the remaining reports provide group means and standard deviations for VBR measures, making it possible to calculate means and standard deviations across groups of studies and to compute t-statistics to evaluate significant differences. For the one investigation that did not report standard deviations, they were estimated from other studies that used similar subject groups.

As can be seen in Figure 1, the mean values for the schizophrenic groups are very similar across positive (M = 6.84, n = 454) and negative (M = 6.74, n = 190) results. The mean values for the control subjects, on the other hand, differ substantially between those reporting LVE (M = 3.97, n = 444) and those finding no LVE (M = 6.34, n = 182; t = 10.14, p<.001). As Figure 1 indicates, there is little overlap in range between those studies reporting positive results and those with negative findings. If the mean VBR value for all control subjects (M = 4.69) is used to dichotomize control groups into those with large (M VBR > 4.69) and those with small (M VBR < 4.69) lateral ventricles, then most (11/14, 79%) control groups in the studies that
## Table 2

**Ventricle Size in Studies Where the VBR was Used**

<table>
<thead>
<tr>
<th>Reports of LVE</th>
<th>Schizophrenic</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>#</td>
<td>VBR</td>
</tr>
<tr>
<td>Andreasen et al., 1982a</td>
<td>52</td>
<td>6.0</td>
</tr>
<tr>
<td>DeLisi et al., 1986</td>
<td>26</td>
<td>8.2</td>
</tr>
<tr>
<td>Johnstone et al., 1976</td>
<td>18</td>
<td>18.7</td>
</tr>
<tr>
<td>Kling et al., 1982/83</td>
<td>26</td>
<td>8.4</td>
</tr>
<tr>
<td>Luchins et al., 1984</td>
<td>45</td>
<td>4.1</td>
</tr>
<tr>
<td>Nasrallah et al., 1982</td>
<td>55</td>
<td>8.7</td>
</tr>
<tr>
<td>Owens et al., 1985</td>
<td>136</td>
<td>11.9</td>
</tr>
<tr>
<td>Pandurangi et al., 1984</td>
<td>23</td>
<td>5.4</td>
</tr>
<tr>
<td>Pearlson &amp; Veroff, 1981</td>
<td>22</td>
<td>7.5</td>
</tr>
<tr>
<td>Pearlson et al., 1984</td>
<td>19</td>
<td>6.2</td>
</tr>
<tr>
<td>Reveley et al., 1982</td>
<td>7</td>
<td>8.6</td>
</tr>
<tr>
<td>Schulsinger et al., 1984</td>
<td>7</td>
<td>9.8</td>
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<td>Schulz et al., 1983</td>
<td>15</td>
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</tr>
<tr>
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<td>8.7</td>
</tr>
<tr>
<td>Weinberger et al., 1982</td>
<td>52</td>
<td>5.5</td>
</tr>
<tr>
<td>Williams et al., 1985</td>
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<td>4.6</td>
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<tr>
<td><strong>Average Ventricle Size</strong></td>
<td>545</td>
<td>6.8</td>
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</table>

**Reports of No LVE**

<p>| | | | | | |</p>
<table>
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<td>26</td>
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<tr>
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<td>5.7</td>
<td>26</td>
<td>4.9</td>
<td>Medical</td>
</tr>
<tr>
<td>DeMeyer et al., 1984</td>
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<td>5.8</td>
<td>15</td>
<td>4.3</td>
<td>Medical</td>
</tr>
</tbody>
</table>

Continued on the next page.
Table 2 (Continued)

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<th>Control</th>
</tr>
</thead>
<tbody>
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<td></td>
<td>#</td>
<td>VBR</td>
</tr>
<tr>
<td>Jernigan et al., 1982</td>
<td>30</td>
<td>5.2</td>
</tr>
<tr>
<td>Largen et al., 1984</td>
<td>35</td>
<td>6.7</td>
</tr>
<tr>
<td>Shima et al., 1985</td>
<td>46</td>
<td>8.2</td>
</tr>
<tr>
<td>Smith &amp; Maser, 1983</td>
<td>30</td>
<td>6.8</td>
</tr>
<tr>
<td><strong>Average Ventricle Size</strong></td>
<td>190</td>
<td>6.7</td>
</tr>
</tbody>
</table>

\(^a\) LVE = Lateral Ventricular Enlargement

\(^b\) The studies of Johnstone et al., (1976) and Owens et al., (1985) were not included in these calculations.
Figure 1. Mean VBR Values for Each Study and Overall Mean Values for Schizophrenic and Control Subjects in Studies of Lateral Ventricular Enlargement.
reported LVE have small ventricles and most (6/7, 86%) of the studies reporting no LVE have control groups with large ventricles (p<.01, Fisher exact test).

Clearly the findings from the previous studies fail to support the hypothesis that the type of schizophrenic sample accounts for the variability in the estimated prevalence of LVE. Overall, the significance of obtained CT results depends on the mean size of the ventricles in the control subject but not in the schizophrenic patients. It is possible that the control groups in those studies where no LVE was reported have inflated VBR values or control subjects in investigations where positive results were obtained could have spuriously small ventricles; i.e., either the prevalence of LVE has been overestimated or underestimated. As was noted above, ventricle size in medical patients can be influenced by physical disorders or biased selection criteria. However the mean VBR for all healthy volunteer controls should reflect ventricle size in the normal population. If the studies that have reported LVE in schizophrenia are accurate, then the medical control subjects from these studies should have a mean VBR value similar to that of normal individuals. If, on the other hand, the ventricles of schizophrenics are not normally enlarged, then the mean VBR of control subjects in the studies that report no LVE should approximate that of normal control subjects.

The data from the studies reviewed here are equivocal. The VBR value for normal individuals (M = 5.3, n = 225) falls
between medical patients from studies where enlargement was reported ($M = 3.6$, $n = 263$) and those from investigations where no LVE was found ($M = 6.2$, $n = 103$). Furthermore, whereas five studies that included normal control subjects reported LVE in schizophrenic patients (DeLisi et al., 1986; Pearlson et al., 1984; Reveley et al., 1982; Schulsinger et al., 1984; Weinberger et al., 1979a), two well conducted studies (Jernigan et al., 1982; Shima et al., 1985) used normal subjects and found no ventricular enlargement in schizophrenic patients.

Differences in control group samples may result from biased selection criteria. Unfortunately, this issue is difficult to investigate because most studies provide sparse information about the composition of control groups and few describe fully how subjects were selected. It is possible that there are differences between control groups containing medical patients and those composed of normal individuals. As noted above, ventricle size in medical patients can be increased or decreased by physical disorders or influenced by biased selection criteria. Seventy-one percent (5/7) of the studies failing to find enlargement and 64% (9/14) of those reporting LVE used CT scans from medical or psychiatric patients. Medical patients in investigations reporting negative results produced larger VBRs ($M = 6.22$, $n = 103$) than those from studies with positive results ($M = 3.63$, $n = 263$; $t = 8.38$, $p < .001$); and normal subjects in those reports failing to find LVE had larger ventricles ($M = 6.51$, $n = 79$).
than did normal people in studies reporting LVE (M = 4.61, n = 146; t = 5.15, p < .001). Hence, problems with control groups cannot be explained in a simple way by considering the health or patient status of the control samples.

It is worth noting that across all studies, there is a tendency for healthy volunteers to have larger VBRs (M = 5.28, n = 225) than medical patient controls (M = 4.36, n = 366; t = 3.80, p < .001). If the median VBR for all the control groups is used to divide these samples, 86% of the normal groups fall above the median and 62% of the medical patient groups fall below or at the median (p < .05, Fisher exact test). Unfortunately, it is not possible, from the information provided in these reports, to determine the extent to which authors may have used biased selection criteria and excluded medical patients with normal but large ventricles.

In summary, a number of studies have indicated that schizophrenic patients have dilated lateral ventricles. There is, however, no consensus on the prevalence of this phenomenon and some recent research has failed to detect significant ventricular enlargement. The CT research tentatively suggests that it is those patients who are most impaired who tend to have dilated ventricles. Because of the absence of a common definition of severity, this issue is difficult to resolve from the present data. An analysis of the studies in which VBR values have been reported suggests that differences in the reported size of ventricles in
control subjects account for many of the inconsistencies in the literature. It is unclear, however, whether differences in VBR values across control groups are due to differences in populations, selection criteria, or methodological factors but it does appear that control groups composed of healthy volunteers have larger ventricles than those composed of various types of medical patients. Systematic research into this issue is clearly needed.

There is some additional research dealing with factors that are associated with lateral ventricular enlargement. The findings from this research can help resolve some of the ambiguities in CT research.

Variables Associated with LVE in Schizophrenia

Genetic and Obstetric Factors. As was noted above, LVE has been reported in both first episode and in young schizophrenics. If some patients have dilated ventricles at the onset of psychosis, then ventricular enlargement could have resulted from genetic factors, obstetric complications, nutritional factors or from disease or injury sustained during childhood or adolescence.

A great deal of research has established a genetic contribution in the etiology of schizophrenia (for a review, see Gottesman & Shields, 1982). The relationship between family history of psychiatric problems and schizophrenia is, however, far from perfect. It is likely that environmental factors interact with genetic predisposition to produce a schizophrenic illness. Obstetric complications have been
proposed as one such contributing factor in schizophrenia (McNeil & Kaij, 1978). In support of this notion, there is evidence of a relationship between perinatal complications, minimal brain damage, and poor outcome in schizophrenia (Parnas, et al., 1982a; Parnas, Schulsinger, Schulsinger, Mednick, & Teasdale, 1982b). A number of investigators have looked at ventricular enlargement in relation to both family history of schizophrenia and to birth complications in schizophrenic patients in order to investigate the possibility that LVE is present before the onset of schizophrenia.

In an attempt to assess the relative contributions of genes and environment to lateral ventricle size in chronic schizophrenia, Reveley, Reveley, Clifford, and Murray (1982) compared CT scans of 11 normal monozygotic (MZ) and eight normal dizygotic (DZ) twins with those of seven pairs of MZ twins that were discordant for schizophrenia (aged 22 to 60 years). Patients were classified according to RDC diagnoses. The ventricle size in normal MZ twins was highly correlated ($r = .98$) whereas the correlation for normal DZ twins was considerably lower ($r = .45$). The mean interpair difference in ventricular size was also lower for the normal MZ (.36 VBR units) than for the DZ twins (1.90 VBR units). The MZ twins discordant for schizophrenia, like the normal MZ twins, showed a high correlation for ventricle size ($r = .87$) but had a much greater interpair difference (2.6 VBR units) than the normal MZ twins. In all but one case, the schizophrenic twin
had the larger ventricles.

The similarity in ventricle size between normal twins suggests that the size of the ventricles is highly influenced by genes but that the influence of some third variable results in LVE in the schizophrenic twins of discordant monozygotic twin pairs. It is interesting to note in this study that whereas some schizophrenic MZ twins do not have ventricles that would normally be considered as enlarged, they do have larger ventricles than their co-twin. This suggests that much ventricular enlargement in schizophrenics may go unnoticed because ventricles are not enlarged beyond the normal range.

The results of this study indicate an interaction between genes and environment in causing enlarged ventricles. Whereas ventricle size appears to be genetically determined in normal individuals, some other factor appears to influence this characteristic in schizophrenics.

Using a sample of schizophrenic patients from a previous study (Weinberger et al., 1979a), Weinberger, DeLisi, Neophytides, and Wyatt (1981) investigated the possibility that lateral ventricle size is under genetic control. Ventricle size (VBR) was compared across ten schizophrenic patients (diagnosed according to RDC criteria), 12 well siblings of these patients (at least one for each patient), and a control group of 17 asymptomatic individuals. The control subjects came from seven sibships with at least two siblings from each family. Mean ventricle size in the
The schizophrenic group was significantly greater than that of their siblings and of the control group. In addition, lateral ventricle size was very similar within each control sibship but not for the sibships that included a schizophrenic patient. In each family, the schizophrenic patient had largest ventricles. These findings support those of Reveley et al. (1982) and indicate that whereas lateral ventricle size tends to be genetically determined in the normal population, some additional factor affects ventricle size in schizophrenic patients.

In a further attempt to study genetic aspects of ventricular enlargement, Nasrallah, Kuperman, Hamra, and McCalley-Whitters (1983) investigated the relationship between LVE and family history of schizophrenia. Ventricles were defined as enlarged if the VBR was greater than the control group mean plus two standard deviations. The control group comprised 27 age and sex matched medical patients. A significantly higher frequency of family history of schizophrenia was reported in a group of 19 chronic schizophrenic patients with LVE than in 36 patients with normal ventricles. Six (32%) of the 19 patients with LVE and only two (6%) of 36 patients with normal ventricles had a family history of schizophrenia. Ventricular enlargement was not associated with age at onset of schizophrenia, or duration of treatment. The results of this study suggest that schizophrenics with a family history of schizophrenia are more likely to have enlarged ventricles (6/8, 75%) than
are individuals with no family history (13/47, 28%). However, most of the patients in this study who had enlarged ventricles had no family history of schizophrenia. This result provides some support for the findings of Reveley et al. (1982) and Weinberger et al. (1981) and suggests a genetic factor is involved in determining ventricle size. The results of Nasrallah et al. (1983) also suggest that a family history of schizophrenia may predispose individuals to LVE but a family history is not necessarily associated with LVE in schizophrenic patients.

In a complex study, Reveley, Reveley, and Murray (1984) assessed the relationship between ventricle size, birth complications and family history of psychiatric disorders in 21 schizophrenics and 18 healthy controls. All subjects were from MZ twin pairs. Patients were diagnosed according to RDC criteria. Six (28%) of the 21 patients and eight (44%) of the 18 controls had birth complications and no family history of psychiatric disorders. Seven (33%) of the 21 schizophrenics had a family history of psychiatric disorder and no birth complications. The remaining eight schizophrenics and ten control subjects had neither a family history of schizophrenia nor birth complications. No patient had both family history of psychiatric disorder and birth complications.

Schizophrenics with a family history of psychiatric disorder (n = 7) had significantly smaller ventricles than patients without this family history (n = 14). However,
because no patient with a family history of psychiatric disorder had birth complications, and six of the 14 patients without a family history had obstetric complications, small ventricles in these individuals may be due to the normal birth rather than family history of psychiatric problems. This possibility is made more likely by the finding that controls with normal births had significantly smaller ventricles than controls with birth complications. No relationship was found between ventricle size and birth complications for the six schizophrenics with birth problems. There was no relationship between LVE and duration of illness, duration of hospitalization, or age. There was a significant negative relationship between age at onset of schizophrenia and ventricular size; i.e., patients who were young when they developed schizophrenia tended to have large ventricles.

These findings are difficult to interpret but suggest that birth complications frequently result in enlarged ventricles in normal individuals and that this may not be the sole determinant of ventricular enlargement in schizophrenia. Unlike the study of Nasralah et al. (1983), no relationship was found between LVE and family history of psychiatric disorder.

DeLisi et al. (1986) included schizophrenic patients and their nonschizophrenic siblings in an effort to investigate the influence of perinatal problems on ventricular enlargement. Both lateral ventricle size (VBR) and the size
of the frontal horns of the lateral ventricles were assessed. CT scans were obtained on 26 schizophrenics from 11 sibships (two or more patients from each family), Nine nonschizophrenic siblings (one or more individual from each of nine families), and 20 normal unrelated volunteers. DSM-III criteria were used to diagnose patients. Schizophrenic patients were found to have larger lateral ventricles and frontal horns than did the control subjects. There was no difference in ventricle size between the schizophrenics and their siblings. In addition, a significant relationship was reported between birth complications and frontal horn size for schizophrenics. None of the nonschizophrenic siblings or the control subjects had a history of birth complications. The results of this study are in conflict with those of Reveley et al. (1984) and suggests that perinatal complications may contribute to ventricular enlargement in schizophrenia.

The relationships between LVE and both perinatal complications and family history of schizophrenia were investigated by Pearlson et al. (1985). In this study, mean lateral ventricle size for 19 schizophrenic patients was found to be larger than that for 19 normal volunteers. Diagnoses were made according to DSM-III criteria. No significant relationships were found between LVE and either birth complications or family history of schizophrenia. However, only four patients had birth complications and whereas these four individuals tended to have larger
ventricles and an earlier onset of schizophrenia than patients without perinatal problems, these differences failed to reach statistical significance.

An interesting study of a group of patients followed up from the 1962 Copenhagen High-Risk Project (Mednick & Schulsinger, 1965) was conducted by Schulsinger et al. (1984). All subjects in this study were taken from the initial high-risk project (i.e., all had a family history of schizophrenia). The sample comprised 10 schizophrenics, 10 borderline schizophrenics, and 16 individuals described as free of mental illness. Diagnoses were made using ICD-8 criteria. The schizophrenic group had the largest mean ventricular size, followed by the controls, with the borderline group having the smallest ventricles. This finding of small ventricles in borderline patients was also reported by Schulz et al. (1983). Ventricle size in the controls was not significantly different from that of the borderline patients. No relationship was found between perinatal complications and LVE. The findings of this study support the findings of Reveley et al. (1984) and Pearlson et al. (1985) and indicate that ventricular size is not related to birth complications. The absence of LVE in borderline patients and individuals with no mental illness, all of whom have a family history of schizophrenia, suggests that enlarged ventricles may be necessary before the full schizophrenic syndrome appears in some patients with a genetic predisposition.
The preceding studies suggest that ventricle size is genetically determined in normal individuals but that other factors contribute to ventricular dilation in schizophrenics. There is a relationship between LVE and obstetric complications in normal individuals but this finding appears to be attenuated in psychotic patients. Most investigators report a relationship between LVE and a family history of psychiatric problems in schizophrenic patients. The nature of this relationship is in dispute at the present time and further research is needed to clarify the issue. The research into genetic and perinatal complications has not resolved the issue as to whether LVE predates the onset of schizophrenia.

A second line of research has focussed on the relationship between LVE and premorbid adjustment. If ventricular enlargement occurs before the onset of psychosis, it is possible that the brain anomalies would be associated with poor premorbid functioning. Thus, a relationship between LVE and poor premorbid adjustment would support the contention that ventricular dilation occurs before the onset of schizophrenia.

Premorbid Adjustment. Poor premorbid adjustment has proven to be the most powerful predictor of poor prognosis in schizophrenia (Neale & Oltmanns, 1980, p.28). If, as the research evidence suggests, LVE is associated with poor prognosis, then it is possible that LVE and poor premorbid adjustment are related. In order to investigate this
possibility, Weinberger, Canon-Spoor, and Potkin (1980b) assessed ventricular enlargement and premorbid status in 51 schizophrenic inpatients and 78 normal volunteers. These researchers constructed their own inventory to assess premorbid adjustment. The schizophrenic group had significantly poorer adjustment in their early adult years than did the controls. A small but significant premorbid deficit was reported in the schizophrenics with enlarged ventricles compared with the schizophrenics who had normal ventricles. The nine patients with the poorest adjustment all had enlarged ventricles as compared with only three of the 14 with the best adjustment scores.

Jeste et al. (1982) used the same inventory as Weinberger et al. (1980b) and used a median cutting score to dichotomize the schizophrenic group into good and poor premorbid adjustment. Of the schizophrenic subjects who were judged to have good premorbid adjustment, 77% (17/22) had normal ventricles. Those schizophrenics who were judged to have poor premorbid adjustment were as likely to have normal ventricles (12/22) as LVE (10/22).

DeLisi et al. (1986) also used the scale constructed by Weinberger et al. (1980b) but found no relationship between lateral ventricle size (VBR) and level premorbid adjustment. CT scans were obtained on 26 schizophrenics and diagnoses were made according to DSM-III criteria. The results of the three studies of premorbid adjustment and ventricular enlargement suggest that the scale constructed by Weinberger
et al. (1980b), has limited value for predicting LVE. Two of the three studies provide preliminary evidence suggesting either that good premorbid adjustment decreases the risk of developing LVE or possibly that ventricular enlargement is an indication of an early developmental brain disorder that interferes with social development in schizophrenics.

The confidence we can have in even these very tentative conclusions is limited by the unknown validity of the premorbid adjustment scale developed by Weinberger et al. (1980b). The scale was constructed from items selected from the Phillips Premorbid History Scale and the Premorbid Asocial Adjustment Scale (for a review, see Kokes, Strauss, & Klorman, 1977). Weinberger's scale consists of 28 items divided among five subscales. No reliability checks were made on this scale. The format of the items, scoring range, and distribution of scores are not given. It is reported that some of the items could not be answered for some schizophrenics, although no analysis was made concerning which subjects failed to answer which questions. It is unclear how the unknown psychometric properties of this scale affected the results of these studies. Further investigations are needed, using psychometrically sound instruments in order to further evaluate these interesting findings of Weinberger and his colleagues.

A more widely accepted method of assessing premorbid adjustment is the short version of the Phillips Premorbid History scale (PMH, Harris, 1975, see Appendix B). The PMH
has been accepted as a reliable and valid measure of premorbid adjustment and has gained widespread use (Kokes et al., 1977). The reliability of this measure is reportedly high \( r = \text{mid .80s to mid .90s} \) and there is high concurrent validity with the long version of the PMH \( r = .95 \) for males and .85 for females; Kokes et al., 1977). The long version of this measure was found to be significantly related to percent of lifetime spent in psychiatric hospitals \( r = .42 \) to .45; DeWolf, 1968, reported in Kokes et al., 1977).

**Negative Symptoms.** A number of symptoms that are indicative of poor prognosis in schizophrenia were reported in the early work of Kraepelin and Bleuler (Neale & Oltmanns, 1980). Some of these symptoms were long accepted as fundamental characteristics of schizophrenia and indicative of an early dementing process. These characteristics have recently been termed negative symptoms (Crow, 1980) and include such symptoms as flat affect, psychomotor retardation and poverty of speech. Florid psychotic symptoms, on the other hand, have not been associated with poor prognosis and have been labeled positive symptoms (Crow, 1980). Positive symptoms have been linked to disturbed dopaminergic transmission (see Crow, Cross, Johnstone, & Owen, 1982b, for a review). These facts led Crow (1980) to hypothesize two types of schizophrenia. Patients with type I syndrome are characterized by positive symptoms and are likely to respond to neuroleptic medications. Type II patients, characterized by negative symptoms, are likely to respond poorly to
neuroleptics, have enlarged lateral ventricles, and have poor prognosis. Evidence concerning this distinction will be reviewed below.

There have been two studies that have examined the relationship between negative symptoms and enlarged ventricles in schizophrenia. In the first study, Johnstone et al. (1978b) reported a significant relationship between negative symptoms (flat affect, psychomotor retardation, and poverty of speech) and enlarged ventricles in a group of 17 chronic schizophrenics. There was no relationship between LVE and positive symptoms. The patients in this study were chronically hospitalized and thus the negative symptoms may have developed as a result of prolonged illness, institutionalization and/or neurological dysfunction.

In order to clarify this issue, a second study, using less impaired patients was conducted (Andreasen, Olsen, Dennert, & Smith, 1982a). Two groups of schizophrenics (eight with normal ventricles and eight with LVE) were evaluated for presence of negative symptoms. Patients were diagnosed using both DSM-III and RDC diagnostic systems. The patients with LVE tended to have more negative symptoms but this difference did not reach statistical significance.

The negative symptoms that were identified by Andreasen et al. (1982a) were flattened or blunted affect, impoverished thinking, avolition or apathy, asociality, and impaired attention. The reliability and validity of these criteria were evaluated by Andreasen (1982) and Andreasen and Olsen
Andreasen (1982) reported an overall reliability of .92, and .70 to .92 for the individual ratings. Andreasen and Olsen (1982) reported that these symptoms are significantly related to Phillips Premorbid History ratings, Mini Mental Status scores, and Global Adjustment Scale (GAS) ratings. In Andreasen's preliminary work (1982; Andreasen & Olsen, 1982), she appears to have identified a useful set of symptoms that have potentially high interrater reliability and she has provided preliminary evidence for construct validity. Nevertheless, at the present time, there is no consensus in the literature regarding what symptoms should be classified as negative and no agreement regarding what constitutes a negative symptom syndrome (Sommers, 1985). Although the work of Andreasen (1982, Andreasen & Olsen, 1982) represents a useful starting point for testing the usefulness of negative symptoms in the understanding of schizophrenia, much systematic research remains to be done.

Other investigators have suggested that negative symptoms are indicative of normal or low dopamine activity and that positive symptoms indicate increased dopamine activity (Crow, 1981; Johnstone et al., 1978a). In order to test this hypothesis, Angrist, Retrosen and Gershon (1980) administered a dopamine agonist (amphetamine) and, at a later date, a dopamine antagonist (phenothiazine) to two groups of schizophrenics (one with predominantly positive and one with negative symptoms). Individuals with predominantly negative symptoms showed little response to either drug, whereas
individuals with predominantly positive symptoms were significantly more agitated after amphetamines and less agitated after neuroleptics were administered. These findings support those of Crow (1981) and Johnstone et al. (1978b) and suggest that schizophrenics with positive but not negative symptoms have increased dopamine receptor levels.

If neuroleptic medications are relatively ineffective for patients with negative symptoms, and if negative symptoms are associated with LVE then neuroleptic medications should be relatively ineffective for patients with LVE. A number of researchers have investigated the differential effectiveness of neuroleptics and its relationship to LVE in schizophrenic patients.

Response to Neuroleptics. Weinberger et al. (1980a) investigated the relationship between ventricle size and response to neuroleptic medication in 20 chronically hospitalized schizophrenics. Improvement was monitored using the Brief Psychiatric Rating Scale. Patients were grouped according to whether their VBR was inside or outside two standard deviations of the control mean of 62 similarly aged healthy volunteers that were used in a previous study (Weinberger et al., 1979a). Ten patients had LVE and ten had normal ventricles. The groups were matched for age, age at onset of illness, years of illness and duration of hospitalization. An initial drug free trial was conducted after which drug dosage and plasma neuroleptic concentration were monitored and equalized across groups. The initiation
of medication resulted in a significant improvement in the group with normal ventricles and no change in the group with enlarged ventricles. This well controlled study suggests that, in chronically ill schizophrenic patients, LVE is associated with poor response to neuroleptic medication. This observation was supported by Kling et al. (1982/83) who reported that a large proportion (50%) of schizophrenics who were not responsive to medication had significantly enlarged ventricles.

In another controlled medication study, Luchins et al. (1984) compared 19 schizophrenics who had ventricular enlargement to 24 schizophrenics with normal ventricles. Ventrices were described as enlarged if they were at least one standard deviation greater than the control group mean. The control group comprised 62 similarly aged medical patients. Level of adjustment was assessed at the end of a medication washout period, and after three and five weeks of medication. A highly significant interaction was reported between VBR and global adjustment over the three assessment times. There was no difference in adjustment ratings between the two groups after the drug washout period. However, whereas patients with normal ventricles showed much improvement after five weeks of medication, patients with LVE showed a nonsignificant deteriorating trend over the same time.

Jeste et al. (1982) conducted a medication study using the same well controlled procedure as that of Weinberger et
al. (1980a). Of the 20 chronic schizophrenics that underwent this procedure, eight were defined as responsive and 12 as nonresponsive to neuroleptic medication. The Brief Psychiatric Rating Scale was used to assess adjustment before and during medication treatment. Seven of the eight patients who responded favorably to the medication had normal ventricles (VBR greater than the mean plus two standard deviations of a control group used in a previous study, Weinberger et al., 1979a). The situation with the schizophrenics who did not respond favorably to medication was less clear. Eight of the 12 nonresponders had LVE and, although this trend is in the predicted direction, there were four of the nonresponders who had normal ventricles.

The results of this study are in agreement with all previous studies of LVE and response to medication, and suggest a negative correlation between these variables. The findings of Jeste et al. (1982), however, suggest that whereas ventricular enlargement in schizophrenia may be indicative of poor response to medication, a number of individuals with normal sized ventricles may also respond poorly to neuroleptics.

One recent study (Smith et al., 1985) failed to detect a relationship between lateral ventricle size and response to neuroleptic medications. The schizophrenic subjects used in the study of Largen et al., (1984, n = 39) were given a one to three week drug free trial followed by fixed doses of medications. RDC diagnoses were made and the mean age of
subjects was 31 years. Lateral ventricular size was assessed using the VBR and level of adjustment was determined using the Brief Psychiatric Rating Scale. There was no significant relationship between lateral ventricle size and level of adjustment before the medication trial or during the drug trial. It is possible that because Largen et al., (1984) reported no significant ventricular enlargement with these patients, this group is biased towards good prognosis individuals. In addition, the administration of fixed doses of medication is likely to result in variations in plasma neuroleptic concentrations and could have obscured any relationship between medication response and ventricular size.

Overall, the studies of medication effects in schizophrenia suggest that neuroleptic medication has its effect at the level of the dopamine receptors. This treatment is most useful for ameliorating florid psychotic symptoms and less useful in the treatment of negative symptoms. The effectiveness of neuroleptics in treating schizophrenia appears to be attenuated in individuals with LVE. However, whereas the reduced effectiveness of this treatment is associated with LVE it is probably not limited to individuals with significantly enlarged ventricles.

On the basis of the findings concerning LVE, type of symptoms, and dopaminergic activity, Crow (1980) postulated that the underlying pathological process for individuals with predominantly positive symptoms (Type 1 schizophrenics) is a
disturbance in dopaminergic transmission. Negative symptoms (Type 2 schizophrenia) on the other hand, are more closely related to the dementias and result from structural changes as evidenced in LVE and poor response to neuroleptic medications. This hypothesis has gained support from one other source in addition to those reviewed above.

Eye Blinks. There is considerable evidence from the animal and human literature linking blink rate with dopaminergic activity (Kleinman et al. 1984). The fact that high blink rates have been reported in schizophrenics (Stevens, 1978) and low blink rates in patients with Parkinson's disease (Karson, Berman, & LeWitt, 1983) suggests that blink rates may reflect dopamine activity in man. If, as Crow (1980) has hypothesized, type 1 schizophrenia reflects a disturbance in dopamine transmission and no cerebral atrophy then a normally high blink rate in these patients should be significantly reduced by the administration of dopamine antagonists (neuroleptic medication). Type 2 schizophrenia, because it is associated with structural brain changes (LVE) rather than excessive dopaminergic activity, should present with a low or normal blink rate that is not reduced as much as that of patients with excessive dopamine activity.

In order to test this hypothesis, Kleinman et al. (1984) assessed the blink rate and VBR in 55 chronic schizophrenic inpatients (19 to 51 years). The control group of Weinberger et al. (1979a) was used for comparison. RDC and Feighner
diagnoses were made. Two groups were formed on the basis of ventricle size: There were 13 patients with LVE and 42 with ventricles within the normal range. The cut-off was equal to the mean VBR of the control group plus two standard deviations. The blink rate in patients with normal ventricles was significantly higher than that of the controls and was significantly reduced by neuroleptic medication. The patients with enlarged ventricles also had a higher blink rate than the controls but this was not significantly affected by the medication. These findings support the hypothesis of Crow (1980) and suggest that there may be two distinct groups of schizophrenic patients and that these groups require different treatment approaches.

In summary, negative symptoms have been associated with a dementing course and poor prognosis in schizophrenia. There is also some preliminary evidence linking negative symptoms to structural brain anomalies (LVE). Other studies have reported an association between LVE, low or normal dopaminergic activity, and poor response to neuroleptic medication. These findings have led to the hypothesis that there is a distinct subgroup of poor prognosis patients with negative symptoms and ventricular enlargement.

**Smooth-Pursuit Eye Movements.** Smooth-pursuit eye movements make use of diverse neurological pathways and require the integration of a number of sources of information. Disrupted eye movements have been shown to reflect specific and widespread neuropathology in
nonpsychiatric patients (Daroff & Troost, 1978). Although there is only preliminary evidence linking smooth-pursuit dysfunctions and neurological anomalies in schizophrenics, there is an extensive literature on both neurological anomalies (e.g., LVE) and disrupted smooth pursuit eye movements in schizophrenia.

The early works of Holzman and his associates (Holzman, Proctor, & Hughes, 1973; Holzman et al., 1974) reported disrupted smooth pursuit eye movements in some schizophrenics. A great deal of research has been done on eye-movements since these initial studies. The eye-tracking impairment has been identified consistently and involves numerous saccadic (fast) eye movements intruding upon a smooth following movement. This tracking deficit has been found in remitted schizophrenics (Iacono, Peloquin, Lumry, Valentine, & Tuason, 1982; Salzman, Klein, & Strauss, 1978), in both young (Kuechenmeister, Linton, & Mueller, 1977), and older schizophrenics (Holzman, Kringlen, Levy, Proctor, & Haberman, 1978) and the subject's sex has not been shown to significantly influence the deficit (Iacono & Koenig, 1983; Iacono, Tuason, & Johnson, 1981). Neuroleptic medication does not seem to influence this anomaly (Holzman et al., 1974, 1975; Mialet & Pichot, 1981; Shagass, Amadeo, & Overton, 1974). Finally, attentional demands of the task probably do not account for the deficit. Only extremely distracting tasks disrupt pursuit movements (Lipton, Frost, & Holzman, 1980; Pass, Salzman, Klorman, Kaskey, & Klein,
1978), and the deficit has been found by numerous investigators using various methodologies (see Iacono, 1983, for a review).

Because disrupted smooth pursuit eye movements are consistently reported in a proportion of schizophrenics and this anomaly is frequently associated with brain damage in neurological patients, it is possible that those schizophrenics who have enlarged ventricles are the same individuals who have disrupted eye movements.

Weinberger and Wyatt (1982b) report some preliminary results that address this issue. The eye movements of 20 chronic schizophrenic patients with normal ventricles were compared with those of 14 patients with LVE. Significantly more patients with LVE had disrupted eye-movements (9/14, 64%) than did patients with normal ventricles (6/20, 30%). No information is given regarding the patients that were used, the selection criteria or the methodology. However, these findings provide preliminary evidence suggesting an association between LVE and disrupted pursuit eye-movements.

In a second study, Bartfai, Levander, Nyback, Berggren, and Schalling (1985) assessed the relationship between SPEM and lateral ventricle size, third ventricle width, and sulcal dilation. Measures were taken on 17 RDC diagnosed schizophrenics. The mean age of patients was 30 years (range 23 to 42). A control group was not included. A linear index of lateral ventricle size was used (frontal horn ratio, see Appendix A) and no significant relationship was found between
lateral ventricular dilation and a rating of SPEM. Likewise, no relationship was found between SPEM ratings and third ventricle width or sulcal dilation. Little information is given regarding the CT results. The facts that no control group was used, only a linear measure of the lateral ventricles was employed, and insufficient information concerning CT results is given make these results difficult to interpret. The results of Weinberger and Wyatt (1982b) and Bartfai et al. (1985) are inconclusive. Further research is needed to investigate this relationship more systematically.

Summary of Variables Associated with LVE in Schizophrenia

Many CT studies of LVE in schizophrenia indicate that some schizophrenics have enlarged lateral ventricles. Research with first episode patients and patients who are relatively young tentatively suggests that ventricular dilation may be present at the time of the onset of psychosis. There are, however, contradictions in this literature. Further investigations have failed to provide consistent evidence linking obstetric complications with LVE. There is some evidence for an association between a positive family history of schizophrenia and LVE but the nature of this relationship is in dispute at the present time. Finally, there is preliminary evidence suggesting that poor premorbid adjustment is positively associated with ventricular enlargement. Together, this body of research tentatively suggests that dilation of the lateral ventricles
may occur before the onset of psychosis in some patients. This conclusion is preliminary and further research is needed to confirm this hypothesis.

In addition to suggesting that LVE may be present at the onset of psychosis, the CT studies reviewed above (see The Prevalence of LVE in Schizophrenia) suggest that enlarged ventricles may be more common in severely ill patients. Whereas there is not a commonly agreed upon index of severity, there is evidence to indicate that patients who respond poorly to neuroleptic medications tend to have larger lateral ventricles than do patients who respond well. This finding suggests that individuals with LVE will be more symptomatic than those with normal ventricles. There is also preliminary evidence linking negative symptoms and disrupted smooth-pursuit eye movements with LVE. These findings tentatively suggest neurological deficits. Together, this research supports the hypothesis that LVE is most common in severely impaired patients; i.e., patients who do not respond well to neuroleptic treatment and/or patients who tend to spend extended periods of time in psychiatric hospitals.

Whereas there is relatively good evidence indicating that lateral ventricular enlargement is present in some schizophrenic patients, it is not clear whether this characteristic is specific to schizophrenia. If enlarged ventricles are also present in nonschizophrenic psychiatric patients, it would suggest that LVE reflects a single neuropathological process with diverse clinical expressions.
or that various forms of neuropathy result in psychiatric disorders.

The Prevalence of LVE in Affective Disorders

In recent years, researchers have begun to measure lateral ventricular size in nonschizophrenic psychiatric patients in order to determine whether LVE is specific to schizophrenia. Relatively few studies have been conducted and these are limited in scope.

Bipolar Disorder. Pearlson and Veroff (1981), and Pearlson, Veroff, and McHugh (1981) compared the lateral ventricles of 22 schizophrenic and 16 bipolar manic patients with those of 35 age- and sex-matched patients diagnosed as having adjustment or personality disorders. Ages ranged from 16 to 50 years. All schizophrenic and bipolar patients had reported hallucinations and/or delusions and all were diagnosed using DSM-III criteria. The mean ventricle to brain ratio of the schizophrenic and bipolar groups was not significantly different and both groups had mean VBR's that were significantly greater than those of the controls. Forty-one percent (9/22) of the schizophrenics and 12% (2/16) of the bipolar patients were reported to have ventricles greater than the control group mean plus two standard deviations. The selection criteria required the elimination of individuals with signs of neurological problems or "lowered IQ" and thus may have biased this sample in favor of good prognosis individuals. Pearlson et al. (1981) report that there is no relationship between ventricle size and age,
age at onset of illness, duration of hospitalization, or neuroleptic dosage.

Using groups of 24 bipolar manic patients with psychotic symptoms, 55 chronic schizophrenics, and 27 age- and sex-matched medical controls ($M = 32$ years, range 20-45), Nasrallah, McCalley-Whitters, and Jacoby (1982b) replicated the findings of Pearlson and Veroff (1981). Diagnoses were made according to DSM-III criteria. The mean VBRs of the bipolar and schizophrenic patients were not significantly different from each other and both groups had significantly larger lateral ventricles than those of the controls. Seven (29%) of 24 bipolar and 19 (34%) of 55 schizophrenic patients were reported to have significantly enlarged ventricles. As with the study of Pearlson et al. (1981), all bipolar patients in this study had psychotic symptoms.

Reider et al. (1983) assessed lateral ventricular size in 28 chronic schizophrenic, 15 chronic schizoaffective, and 19 manic patients. RDC diagnoses were used to classify patients and the VBR was used as a measure of ventricular size. A normal control group was not included in this study. The mean age of the schizophrenic group was 26 years, of the schizoaffective group 25 years, and of the manic group 44 years. No significant differences in ventricle size were found between the three groups. Using the recommended VBR cut-off of 10, used by Weinberger et al. (1979a), 7% (2/28) schizophrenic, 7% (1/15) schizoaffective, and 10% (2/19) bipolar patients were reported to have significantly enlarged
ventricles. There are systematic differences in measuring ventricles across studies (Weinberger and Wyatt, 1982a) and, therefore, the use of a control group from a separate study makes the results of Reider et al. (1983) difficult to interpret.

In a further study, Pearlson et al. (1984a, 1984b) reported a prevalence of LVE in bipolar patients with psychotic features that was similar to that reported by Nasrallah et al. (1982b). Subjects were 27 bipolar patients and 27 age- and sex-matched normal controls. The mean age of the patients was 31 years (range 18 to 40) and mean duration of illness was 10 years. Diagnoses were made using DSM-III criteria. The mean VBR of the bipolar patients was significantly greater than that of the controls. Eight of the 27 bipolar patients (30%) were reported to have significantly enlarged lateral ventricles. No significant relationship was found between ventricle size and age. There was a significant positive correlation between LVE and both persistent unemployment and number of hospitalizations. No patients in this study had been chronically hospitalized and all were living in the community at the time of testing.

Nasrallah, McCalley-Whitters and Pfohl (1984) replicated the finding of Pearlson et al. (1984a, 1984b) with 24 consecutively admitted bipolar manic males (aged 20 to 45 years). Diagnoses were made according to DSM-III criteria. A control group was comprised of 27 car accident victims. Nasrallah et al. (1984) reported that eight (33%) of the
bipolar patients had significantly enlarged lateral ventricles. Ventricular enlargement was not related to age at onset, duration of illness, or response to drug treatment. Finally, in a recent study of LVE in schizophrenia (Owens et al., 1985), 32 manic patients were included for comparison. Diagnoses were made according to Feighner diagnostic criteria. A control group of 19 "neurotic" outpatients was also included. The age of the manic group is not given. However, the total patient sample was old compared to that of other studies (range 22 to 87 years, M = 56 ± 12.7 years). The findings of this study that relate to the manic group are difficult to interpret from the information given. The ventricular size of the manic patients did not differ significantly from either the schizophrenic or control patients. However, the VBR values reported in this study are far greater than those found in other studies. The majority of patients are over 50 years of age and no information is given regarding the age range in each group. Thus, it is possible that the absence of differences between groups in this study is influenced by ventricular enlargement due to aging.

Major Depression. Other studies have examined the prevalence of lateral ventricular enlargement in major depression. Scott, Golden, Ruedrich, and Bishop (1983) examined 10 patients diagnosed as having major depression according to DSM-III criteria and 10 age-matched medical controls. The mean age of patients was 39 years. Depressed
subjects were inpatients and all exhibited mood-congruent hallucinations and/or delusions. The depressed group had a mean VBR significantly greater than that of the control group. The proportion of patients with significantly enlarged ventricles is not reported. This study provides preliminary evidence for ventricular enlargement in some patients who have major depression with psychotic features.

A finding of enlarged ventricles in depressed patients was also reported by Targum, Rosen, DeLisi, Weinberger, and Citrin (1983). The VBR was obtained from 38 patients who received DSM-III diagnoses of major depression with melancholia (20 were delusional and 18 nondelusional) and 26 neurological patients. The mean age of delusional and nondelusional groups of patients was 31 years. The mean VBR of the delusional patients was significantly greater than that of the control patients but not that of the nondelusional group. There was no significant difference between the nondelusional patients and the control group. Five (25%) of the 20 delusional patients had VBR's greater than the control mean plus two standard deviations whereas none of the nondelusional patients reached this criterion. The results of this study support those of Scott et al. (1982) and suggest a proportion of depressed patients with psychotic features have enlarged ventricles.

Mixed Affective Disorder Patients. Two other studies have included affective disorder patients as controls for comparison with schizophrenic patients. Weinberger et al.
(1982) used a group of 23 patients with "acute affective disorder" in addition to groups of schizophrenic and neurological patients. DSM-III criteria were used in making diagnoses but no specific diagnostic information is given for the affective group. The mean VBR of the affective group is not significantly different from that of the control group but is significantly smaller than the mean of the schizophrenic group. Without further information about the affective disorder patients, no specific conclusions can be made from this study. However, these results do suggest that, whereas LVE may be present in some severely ill patients who have affective disorders with psychotic features, this anomaly may be absent in patients with less severe affective symptoms.

Significantly enlarged ventricles in affective disorder patients were reported by Luchins et al. (1984). In this study, a group of 22 individuals with affective disorders were compared to 45 schizophrenic patients and 50 headache control subjects. All psychiatric subjects were inpatients and received RDC diagnoses. Of the affective disorder group, 14 were depressed and 6 were manic. Ages ranged from 18 to 59 ($M = 35$ years). There was no significant difference in mean VBR size between the schizophrenic and affective disorder groups and both of these groups had significantly larger mean VBR values than the control group. Four (18%) of the 22 affective disorder and five (11%) of the 45 schizophrenic patients had significantly enlarged lateral
ventricles. In support of the other studies that included manic and depressed patients, enlarged ventricles were found to be associated with delusional symptoms.

**Summary of Studies Examining Affective Disorder Patients**

The studies that have included manic and depressed patients indicate that ventricular enlargement is present in some patients with affective disorders and is, therefore, not specific to schizophrenia. The prevalence of LVE in manic or depressive patients is difficult to ascertain from the few studies that have been conducted. In bipolar patients, the prevalence has ranged from zero to 33% (median value = 21%) and LVE has been observed in five of the six CT studies that have included manic patients. Three studies reported that patients had psychotic symptoms and LVE. The remaining three studies did not indicate whether or not patients were psychotic. The results of both of the CT studies of depressed patients have indicated that a proportion of these individuals have enlarged ventricles. Both studies included depressed patients who have psychotic features. The one study that compared psychotic with nonpsychotic patients reported that LVE was limited to depressed patients with psychotic features. One of the two studies that used affective disorder samples not broken down into manic and depressed groups reported significant ventricular enlargement. The patients in this study were psychotic. Together the results of these studies indicate that LVE is not specific to schizophrenia. These findings do, however,
suggest that LVE may be specific to psychosis. If this is the case, enlarged lateral ventricles may be associated with a form of psychosis that cuts across traditional diagnostic divisions.

The research findings reviewed above suggest that a significant proportion of schizophrenic and nonschizophrenic psychotic patients have LVE. However, a central question that is not addressed by this research is whether or not the observed brain changes are specific to the structures around the lateral ventricles or whether they are part of more diffuse brain changes. In order to determine whether there are changes elsewhere in the brain, a number of researchers have investigated the third ventricle.

**Enlargement of the Third Ventricle**

A number of medical conditions may result in enlargement of the third and lateral ventricles (see Lateral Ventricular Enlargement above). A number of investigators have also reported enlargement of the third ventricle in schizophrenic patients. Gluck, Radu, Mundt and Gerhardt (1980) reviewed the pneumoencephalographic studies of schizophrenic patients and noted that 80% of these studies report enlargement of the third ventricle. The difficulties associated with the pneumoencephalogram (see LVE in Pneumoencephalographic Studies above) suggest that these studies should be interpreted with caution. More recently, researchers have made use of computed tomography to measure the size of the third ventricle.
Methodological Issues.

All of the ten studies that have assessed the size of the third ventricle in schizophrenic patients have measured the width of this ventricle at its widest point. In four studies, the width is measured from an image on a cathode ray tube, in one study a magnified rule was used, and in one a measure was taken from an image projected and enlarged 40 times. Four of the ten studies fail to describe how the width of the third ventricle was measured. It is not clear from the studies of the third ventricle whether the distances reported are actual life size or are the distances measured from the CT scans. This ambiguity makes it difficult to compare measures between studies. The film that is used to display CT images usually shows the brain at approximately one third life size. Because of this, the actual distance that is measured on the scan ranges from approximately 0.33mm to 2.50mm. Therefore some magnification is needed to accurately measure the third ventricle. The variability between studies in the reported width of the third ventricle ($M = 0.95 \pm 0.44$mm to $M = 7.4 \pm 1.6$mm) suggests either that there may be some measurement error due to the method used and/or some investigators report measures directly from the CT scan whereas others convert these measures to life size. Future studies need to use well-described and reliable procedures.

Enlargement of the Third Ventricle in Schizophrenia

Dewan et al. (1983) investigated the diencephalic region
of the brains of 23 chronic schizophrenics and 23 medical control subjects by measuring the width of the third ventricle. Diagnoses were made according to DSM-III criteria. The width of the third ventricle was significantly greater for the schizophrenics than for the medical patients. This measure was not significantly related to age or duration of illness in the schizophrenic patients. However, age was significantly related to third ventricle width in the medical control group.

Only two studies (Nyback et al., 1982; Okasha & Madkour, 1982) have reported enlargement of lateral and third ventricles. Nyback et al. (1982) reported significant enlargement of both the third and lateral cerebral ventricles in young (17 to 44 years) schizophrenics. RDC diagnoses were made. There was a significant positive correlation between the size of the third and lateral ventricles in both the patients (r = .46) and volunteer control subjects (r = .52). In addition, a significant positive relationship was reported between age and the width of the third ventricle. Unfortunately, linear measures of the lateral ventricles were used and the method used to measure the third ventricle was not given. As a result the findings of this study are difficult to interpret. These findings support the earlier pneumoencephalographic results and suggest that enlargement of the third ventricle may be a part of general ventricular enlargement in schizophrenia. The results of Nyback et al. (1982) are, however, in conflict with those of Dewan et al.
who did not find a positive relationship between third ventricular width and age.

Enlargement of the third and lateral ventricles was also reported by Okasha and Madkour (1982). In this study, a group of 43 chronic schizophrenics (mean age was 33 years) had significantly larger third and lateral ventricles than did a group of 39 medical controls. As with Nyback et al. (1982), Okasha and Madkour (1982) used a linear measure of the lateral ventricles and did not describe how the third ventricle was measured. In addition, diagnostic criteria were not specified and the patient sample was incompletely described. There is also no indication whether enlarged lateral ventricles were associated with an enlargement of the third ventricle. Thus, while these results support those of Nyback et al. (1982), the methodological limitations of this study warrant caution in drawing conclusions.

Tanaka et al. (1981) also used linear measures of the lateral ventricles but failed to find either third or lateral ventricular enlargement in 32 young schizophrenics (aged 20 to 44 years). A second group of 14 older patients (aged 41 to 60 years) was found to have significantly enlarged third and lateral ventricles. This finding contradicts that of Nyback et al. (1982) who reported ventricular enlargement in a group of relatively young patients. Unfortunately, Tanaka et al. (1981) did not describe their patient sample, diagnostic criteria, or selection procedures. The association between age and third ventricle size that was
reported by Nyback et al. (1982) was supported by the findings of this study. Tanaka et al. (1981), however, did not report a correlation coefficient for this relationship.

Several recent studies indicate no lateral ventricular enlargement but report enlargement of the third ventricle. Smith and Maser (1983) measured the lateral and third ventricles of 30 schizophrenic patients (diagnosed according to RDC criteria) and 14 medical patients. A small but statistically significant increase in the width of the third ventricle was reported. No information was given regarding how the third ventricle was measured. The ventricle to brain ratio (VBR) of the lateral ventricles was reported to be no different for the schizophrenic and medical control groups. Smith and Maser (1983) report that "a few" of their patients were chronic nonresponders to medication. In all previous studies that have used patients who respond poorly to medication (Jeste et al., 1982; Kling et al., 1982/83; Luchins et al., 1984; Weinberger et al., 1980a) significant enlargement of the lateral ventricles was reported. It is thus unusual that Smith and Maser (1983) did not obtain a significant effect. No information was given regarding the relationship between third and lateral ventricular size.

Pandurangi et al. (1984) reported little lateral ventricular enlargement in 23 chronic schizophrenics when compared to 23 medical patients. In support of the findings of Smith and Maser (1983), the schizophrenics had a small but significant enlargement of the third ventricle. The size of
the third ventricle was positively correlated with age but not with lateral ventricular size. This positive relationship between age and size of the third ventricle supports the findings of Nyback et al. (1982) and Tanaka et al. (1981) and is consistent with the possibility that enlargement of the third ventricle may be a sequela or iatrogenic effect.

DeMeyer et al. (1984) reported that a small group (n=8) of schizophrenics (diagnosed according to DSM-III criteria) had significant enlargement of the third ventricle but not of the lateral ventricles (VBR) when compared to 15 medical patients. A second group of individuals, including patients with organic hallucinosis, pervasive developmental disorder, and mental retardation, was added for further analyses. This addition makes it difficult to interpret subsequent results of this study. Nevertheless, the findings of this study support those of previous investigations and suggest that a proportion of chronic schizophrenics have enlargement of the third ventricle.

The finding of enlargement of the third ventricle was also reported in a recent, well described study (Boronow et al., 1985). The size of the third ventricle was significantly greater for a group of 30 chronic schizophrenic patients (RDC diagnosed) than for a group of 26 medical patients. There was a nonsignificant trend towards larger lateral ventricles (VBR) in the schizophrenic group. It is noteworthy in this study that no significant correlations were obtained between
third and lateral ventricular size, nor between third or lateral ventricular size and age, age at onset of psychosis, duration of illness, cumulative hospitalization, or premorbid adjustment. Boronow et al. (1985) suggest that, while the patients in this study manifested serious psychopathology, had been frequently rehospitalized, and for the most part were unable to hold regular jobs, they did not require continuous hospitalization and thus did not represent the most impaired of schizophrenics.

There have been two reports of no significant enlargement of the third ventricle in schizophrenic patients. Gluck et al. (1980) took linear measures of the lateral and third ventricles from 68 chronic schizophrenic patients (22 to 68 years) and 68 medical patients (matched on age, sex and inner diameter of the skull) were used for controls. A nonsignificant trend towards smaller third and lateral ventricles in the schizophrenic group was reported. Gluck et al. (1980) reported that the measures obtained from the schizophrenic and control groups were comparable to published normal pneumoencephalographic values (Huber, 1961, reported in Gluck, 1980). Selection procedures and diagnostic criteria were not given. In addition, the use of a linear measure of the lateral ventricles makes it difficult to interpret these results.

Nasrallah, Jacoby, Chapman, and McCalley-Whitters (1985) also reported no significant enlargement of the third ventricle in 55 chronic schizophrenics (diagnosed according
to DSM-III criteria). Significant enlargement of the lateral ventricles were reported for the same group of patients (Nasrallah et al., 1982a). The dimensions of the third ventricle was obtained after projecting the X-ray images onto a screen at 40x magnification and tracing the brain image on paper. This procedure results in much loss of definition and thus may have resulted in measurement error. Nasrallah et al. (1985) do, however, report a significant relationship between the width of the third ventricle and the VBR of the lateral ventricles. This finding supports that of Nyback et al. (1982) but contradicts those of Boronow et al. (1985) and Smith and Maser (1983). In support of Boronow et al. (1985), Nasrallah et al. (1985) found no significant relationship between age and the width of the third ventricle.

Summary of Studies of the Third Ventricle

Most published studies indicate that schizophrenics tend to have enlargement of the third ventricle. Eight of the ten studies that measured the width of the third ventricle reported significant widening. Only four of the ten studies measured the relationship between third and lateral ventricular size. Of these four, two reported a significant relationship and two reported no relationship. Two of four studies that correlated age and the width of the third ventricle reported a significant relationship and two reported no relationship. No studies have been done to investigate third ventricle size in first episode
schizophrenic patients or in any nonschizophrenic psychiatric patients.

Many investigators who have studied the lateral ventricles failed to measure the third ventricle and, of those who included the third ventricle many failed to measure the ventricular bodies in a comparable fashion. Various linear measures of the lateral ventricles have been used in these studies and the method of measuring the third ventricle is frequently not specified or idiosyncratic. Whereas the majority of reports indicate significant enlargement of the third ventricle in schizophrenic patients, there is considerable variability in the reported size. Finally, there is no conclusive evidence linking enlargement of the third ventricle with enlargement of the lateral ventricles.

Systematic investigations are needed with clearly defined patient samples and well-described, reliable methods of measuring the ventricular bodies. None of the studies of enlargement of the third ventricle were done with first episode patients, patients at risk, or discordant monozygotic twins. Until this type of research is conducted, it cannot be known whether enlargement of the third ventricle is related to the onset of psychosis or is a sequela of the illness process. Apart from the study of Boronow et al. (1985), no studies have investigated the correlates of the width of the third ventricle. Systematic investigations into clinical variables associated with this anomaly are needed at the present time. Finally, none of the CT studies with
nonschizophrenic, psychotic patients has included a measure of the third ventricle. Thus, it is not known whether this enlargement of the third ventricle is specific to schizophrenia or whether it is also found in other psychotic illnesses.

Atrophy of the Cerebral Cortex

Cortical atrophy is a common result of a number of medical conditions (see Lateral Ventricular Enlargement above). These include cerebral tumor, cerebral infection, Alzheimer's disease, Huntington's chorea, and anoxia (TerBrugge & Rao, 1983). Depending on the etiology, cortical atrophy may be focal or diffuse and may or may not involve ventricular enlargement. In a review of the literature, TerBrugge and Rao (1983) noted that all studies of cortical atrophy and normal aging have shown an increase in the size of the cortical sulci with increasing age.

Methodological Issues

The measurement of cortical atrophy from CT scans is a complex and controversial issue (Bird, 1982). One common procedure involves measuring the width of the individual sulci on the two or three highest CT scanning cuts. The proponents of this method admit that this measure is relatively imprecise and assesses only specific areas of the cortex rather than obtaining an overall rating (Bird, 1982). The positioning of the head and the level of the uppermost cuts are sources of great variation with this type of measurement (Bird, 1982). Opponents of this method of
assessing atrophy suggest that measuring sulcal width from CT scans is too inaccurate and unreliable to be of use (Jacoby, Levy, & Dawson, 1980). As an alternative, several authors have proposed global ratings of atrophy based on a three-point (Reider, Donnelly, Herdt, & Waldman, 1979), four-point (Boronow et al., 1985), or five-point scale (Largen et al., 1984). Even with these scales, there is much variability across studies regarding the amount of sulcal dilation that is present for each rating of atrophy. Ratings made using these scales, like the sulcal measures, are influenced by the level of the cuts that are chosen. None of the studies of cortical atrophy in schizophrenia specify which CT cuts are used and many fail to describe the procedures employed. The variability in methodology, inaccuracy in assessment methods, and lack of procedural information present major difficulties to the interpretation of results.

Prevalence of Cortical Atrophy in Schizophrenia

A finding of significant cortical atrophy in schizophrenic patients was reported by Nasrallah, Kuperman, Jacoby, McCalley-Whitters, and Hamra (1983). In this study, 55 chronic schizophrenic patients were compared to 27 medical controls. Cortical atrophy was assessed using a four-point global rating scale. Twenty two of 55 schizophrenic patients (40%) were found to have sulcal widening compared to one control subject (4%). The patients with cortical atrophy had significantly worse cognitive test scores than the patients without atrophy.
Three studies have included measures of both cortical atrophy and lateral ventricular enlargement (Kling et al., 1982/83; Weinberger, Torrey, Neophytides, & Wyatt, 1979b; Weinberger et al., 1982). Weinberger et al. (1979b) evaluated sulcal dilation in 75 chronic schizophrenics and 62 healthy volunteers. A number of linear measures of cortical sulci from three separate CT cuts were taken to assess atrophy. Separate analyses were done for each measure. The Sylvian fissure, interhemispheric fissure, and mean width of cortical sulci were all significantly larger in the patient group. There was no significant relationship between these measures and age, length of illness, or duration of hospitalization. These patients also had significantly enlarged lateral ventricles (Weinberger et al., 1979a) but there was no relationship between sulcal width and ventricular size.

In a second study by the research team of Weinberger (Weinberger et al., 1982) sulcal width in addition to lateral ventricular size was assessed in 35 schizophreniform patients and 26 medical patients. Cortical atrophy was assessed using a three-point global rating scale. Five of the 35 schizophreniform patients (14%) and none of the control subjects were reported to have cortical atrophy. There was no relationship between cortical atrophy and LVE. This finding suggests that cortical atrophy is present at the onset of psychosis in some patients and is independent of ventricular enlargement.
The results of Weinberger et al. (1979a, 1979b, 1982) were replicated by Kling et al. (1982/83). The width of the Sylvian fissure was significantly wider and ventricles were larger in 26 chronic schizophrenic patients than in 20 medical control patients. However, unlike the study of Weinberger et al. (1979b, 1982), Kling et al. (1982/83) reported that increased ventricular size was significantly associated with Sylvian fissure widening.

Dewan et al. (1983) assessed third ventricular and sulcal enlargement in 23 chronic schizophrenics and 23 medical patients. The width of the Sylvian fissures was used to assess cortical atrophy. Both the third ventricle and Sylvian fissure were significantly enlarged in the schizophrenic group. These two measures were significantly related. This finding provides tentative support for the results of Kling et al. (1982/83) and suggests that there may be general atrophy of the brain rather than separate focal atrophies as was suggested by Weinberger et al. (1979a, 1979b, 1982).

Several studies have included measurements of cortical atrophy, and third and lateral ventricular enlargement in an attempt to map the extent of the atrophic process in schizophrenia. Smith and Maser (1983) reported no LVE but significant enlargement of the third ventricle and cortical sulci in 30 chronic schizophrenic patients. The method of assessing cortical atrophy and the relationships between lateral ventricular size, third ventricle width, and cortical
atrophy are not reported.

Pandurangi et al. (1984) reported minimal enlargement of the lateral ventricles but enlargement of both the third ventricle and cortical sulci. Subjects were 23 chronic schizophrenics and 23 medical patients. Cortical atrophy was assessed by measuring the width of the Sylvian fissure and the maximum width of the largest cortical sulcus. The relationships between the various morphological measures are not reported.

Largen et al. (1984) compared 35 chronic schizophrenics with 17 medical controls over the lateral and third ventricles and cortical sulci. A global rating of atrophy was made on a five-point scale. No significant enlargement of the third or lateral ventricles was found but there was significantly more cortical atrophy in the schizophrenic patients than in control subjects. No correlations between these measures were reported.

Tanaka et al. (1981) compared a group of 32 young schizophrenic patients (aged 21 to 40) and 14 older schizophrenics (aged 41 to 60) with 38 age matched medical controls. Cortical atrophy, in addition to third and lateral ventricular size, was measured. Cortical atrophy was assessed by measuring the width between the Sylvian fissure and the skull, the width of the interhemispheric fissure, and the width of the broadest cortical sulcus. Linear measures of the lateral ventricles were used. The older group showed significant enlargement of the cortical sulci, the third, and
lateral ventricles. The younger group showed no differences over any of these measures. The patient sample, diagnostic criteria, and selection procedures were not reported. These limitations make it difficult to compare these results with those of other studies. Unlike the results of Weinberger et al. (1982), the findings of Tanaka et al. (1981) suggest that cortical atrophy is not present in young patients but develops with the illness.

None of the four studies of the third and lateral ventricles and cortical atrophy assessed the relationship between these variables. In three studies, no enlargement of the lateral ventricles was found, and in one there was no enlargement of the third ventricle. The consistent finding of cortical atrophy in the absence of these other anomalies and in spite of the differing methodologies supports earlier results (Dewan et al. 1983; Kling et al., 1982/83; Weinberger et al., 1979b, 1982) and suggests that cortical atrophy is prevalent in chronic schizophrenia.

There have, however, been four reports of no cortical atrophy in chronic schizophrenia. In the first CT study of brain morphology in schizophrenia, Johnstone et al. (1976, 1978) reported no cortical atrophy in 17 chronically hospitalized patients. The area of cortical sulci (as opposed to the width that was used in other studies) in the uppermost CT cut was used as a measure of atrophy. Control subjects were eight chronically hospitalized medical patients. Given the extreme chronicity of the schizophrenic
subjects and the fact that atrophy is commonly reported in chronic patients it is surprising that no atrophy was found in this study. It is possible that the chronicity of the medical controls, the idiosyncratic method of assessing sulcal enlargement, or the choice of CT cut could have obscured any significant atrophy.

Gluck et al. (1980) reported no significant enlargement of the third or lateral ventricles or cortical sulci in 68 chronic schizophrenics when compared to 68 medical patients. Cortical atrophy was assessed by counting the number of enlarged sulci on the top two CT scans. This unusual method of measuring cortical atrophy may have contributed to the lack of significant results. In addition, selection procedures and diagnostic criteria were not reported.

Nyback et al. (1982) included a young group of patients in order to investigate whether structural brain abnormalities are present in the early stages of schizophrenia. Cortical sulci and third and lateral ventricles were assessed in 46 schizophrenic patients (aged 17 to 44 years) and 48 age matched healthy volunteers. A global rating of cortical atrophy was made using a four-point scale. Linear measures of the lateral ventricles were made. There was no significant cortical atrophy in the schizophrenic patients. Third and lateral ventricles were significantly larger in the schizophrenic patients than in the control subjects.

Finally, a finding of no cortical atrophy was reported
by Boronow et al. (1985). In this well described study, the third and lateral ventricles and cortical sulci were assessed in 30 chronic schizophrenics and 26 medical patients. The third ventricle but not the lateral ventricles or cortical sulci was significantly enlarged in the schizophrenic patients. Cortical atrophy was assessed using a four-point rating scale. Sulcal size was significantly related to age but not to third or lateral ventricular size, age at onset of psychosis, duration of illness, cumulative hospitalization, or premorbid adjustment.

In summary, although nine of the 13 studies of cortical atrophy in schizophrenia report positive results, the overall picture is inconclusive. Widely differing methodologies were used to assess atrophy and insufficient procedural information is reported. Five investigators assessed the relationship between cortical atrophy and ventricular enlargement. In one study, LVE was related to sulcal widening; in a second, enlargement of the third ventricle was related to cortical atrophy; and in the remaining three studies, no significant relationships were obtained. Of the three studies that have assessed cortical atrophy in the early stages of schizophrenia only one reported significant sulcal widening.

**Cortical Atrophy in Affective Disorders**

There have been two CT studies of cortical atrophy in bipolar affective disorder patients. Pearlson and Veroff (1981) and Pearlson et al. (1981) investigated cortical
atrophy and lateral ventricular size in 16 bipolar manic, 22 schizophrenic, and 35 personality disorder patients. All subjects were between 16 and 50 years of age. Sulcal width was assessed using a four-point rating scale. Two of the 16 bipolar patients (12%) and four of 22 schizophrenic patients (18%) had significant cortical atrophy when compared to the personality disorder patients. Sulcal widening was related to ventricular enlargement in the schizophrenic patients but not in the bipolar patients.

In a second study, Rieder et al. (1983) assessed cortical atrophy and ventricular size in 19 bipolar, 15 schizoaffective, and 28 chronic schizophrenic patients. A normal control group was not included. Cortical atrophy was assessed using a four-point global rating scale. No significant differences in cortical atrophy were reported between the three groups. However, the mean age of the manic patients was significantly greater than that of the other two groups. If patients over 50 years of age were excluded, none of the bipolar patients had significant cortical atrophy whereas some of the schizophrenic patients had atrophy.

The limited data on cortical atrophy in affective disorder patients do not permit any firm conclusions. Because neither study included normal controls, these investigations are not well suited to determine the extent of cortical atrophy but are only suited to determine the amount of atrophy in one group relative to others. The study of Pearlson and Veroff (1981) suggests that a small proportion of
bipolar manic patients may have significant atrophy but the study of Rieder et al. (1983) contradicts this. Further studies are needed to determine whether cortical atrophy is limited to schizophrenia or whether it is also found in bipolar manic patients. Finally, no CT studies with depressed patients have included a measure of cortical atrophy.

**Summary of the Studies of Cortical Atrophy**

Research evidence suggests that some schizophrenic patients have cortical atrophy. Further research using patients who are relatively young is inconclusive. There is no clear evidence for a relationship between cortical atrophy and ventricular enlargement. Finally, the studies of sulcal widening in nonschizophrenic psychotic patients do not permit any conclusions at the present time.

**Summary of CT Literature**

Difficulties associated with the diagnosis of schizophrenia have led many researchers to search for biological concommitants that can be incorporated into existing diagnostic systems. A biological factor would have the advantage of providing an objectively verifiable, stable indicator of pathology. In addition, it could provide an important predisposing sign, have etiological significance, or be a sequela of the illness process. Three potential markers that have been the focus of a great deal of empirical research are lateral ventricular enlargement (LVE), enlargement of the third ventricle, and cortical atrophy.
Findings from CT Scan Studies

Many CT studies of the lateral ventricles in chronic patients indicate LVE. Other studies have included first episode patients in an attempt to determine whether LVE is present in the early stages of schizophrenia or whether it is a sequela of the illness process. This research tentatively suggests that enlargement of the lateral ventricles may occur at the time of or before the first psychotic episode. This hypothesis is supported by preliminary evidence linking poor premorbid adjustment with LVE. There are, however, some contradictory findings and further research using a representative sample of patients who have recently experienced their first psychotic episode is needed to resolve this issue. Studies of the prevalence of LVE in schizophrenic patients tentatively suggest that ventricular dilation is most likely to be found in severely impaired patients. This notion is supported by findings that have indicated an association between LVE and poor response to neuroleptic medication, percent of illness spent in hospital, negative symptoms, and disrupted smooth pursuit eye movements.

Several recent CT studies have focused on nonschizophrenic psychiatric patients in order to determine whether LVE is specific to schizophrenia or whether it cuts across traditional diagnostic divisions. This research suggests that a proportion of manic and depressed patients have enlarged lateral ventricles. In most studies, this
enlargement is associated with the presence of psychotic symptoms. The findings from these studies are, however, relatively limited and more research is needed to determine whether lateral ventricular enlargement is present at the onset of psychosis and what clinical factors LVE is related to in these patients.

In an attempt to determine whether brain changes extend beyond the lateral ventricles, a number of researchers have investigated changes specific to the diencephalic areas of the brain. This has been done by measuring the size of the third ventricle. Most of these studies indicate significant enlargement of this ventricle. It is unclear from this research whether third and lateral ventricular enlargement are related. In addition, no investigators have studied whether there is enlargement of the third ventricle at the onset of psychosis, whether this enlargement is specific to schizophrenia, or whether it is associated with symptoms indicative of poor prognosis. Further studies are needed to address these questions.

Several studies of ventricular enlargement have included a measure of cortical atrophy in an attempt to assess the extent of atrophic processes. The results of this research tentatively suggest that a proportion of schizophrenic patients has enlarged cortical sulci. It is unclear from the research whether cortical atrophy is related to enlargement of the third and lateral ventricles, whether it is associated with clinical characteristics suggestive of poor prognosis,
or whether it is specific to schizophrenia.

The CT research leaves a number of important questions unanswered. It is not clear what proportion of a representative sample of first-episode schizophrenic patients has enlargement of the lateral ventricles and cortical sulci, and whether enlargement of the third ventricle is present at the onset of psychosis. Investigations are also needed to determine whether lateral and third ventricular enlargement and sulcal atrophy are present at the onset of psychosis in nonschizophrenic psychotic patients as they are with schizophrenic patients. Finally, the relationship between morphological brain changes and clinical characteristics suggestive of poor prognosis needs to be investigated in first-episode patients to determine if a syndrome can be defined.

Summary of Methodological Issues

Three potential sources of error that were discussed in the preceding literature are biased patient samples, biased control samples, and procedural variability. Many of the early CT studies of schizophrenia appear to include severely ill, often chronically hospitalized patients. However, because there is no commonly agreed upon index of severity, it is frequently difficult to assess how impaired patient samples are. The fact that poor response to neuroleptic medications and the number of negative symptoms appear to be related to lateral ventricle size supports the contention that severely impaired patients have LVE. Nevertheless, the
absence of a common definition of severity has resulted in ambiguities in the research literature. Future studies must report more detailed information regarding the characteristics of the subjects and selection procedures in order that severity of impairment of subjects can be compared between studies.

The control group that is used in most studies is comprised of medical patients who received a CT scan for medical reasons. However, a number of medical problems are known to decrease or to increase ventricle size. In addition, the selection of "normal" scans from medical records could lead to the exclusion of patients with normal but large ventricles and the inclusion of subjects who because of neuropathology have abnormally small ventricles. The results from the studies of the prevalence of LVE in schizophrenia suggest that some factor associated with the control sample differentially affects the obtained findings; i.e., studies that report LVE in schizophrenia tend to use control subjects with small lateral ventricles and studies that indicate no ventricular enlargement in schizophrenics report large ventricles in control subjects. It is clear from the data available that many of the inconsistencies in the CT literature are due to the size of the ventricles in the control sample. It is unclear from previous reports whether the differences in VBR values across control groups are due to population differences, selection criteria, measurement biases, or CT scanning procedures. Future
researchers must be cognizant of the problems associated with control groups.

The method that is used to assess morphological brain changes can also result in variability in findings and makes it difficult to make comparisons across studies. Most studies of lateral ventricular size involve the ventricle to brain ratio (VBR); i.e., the percent of brain space that is taken up by the ventricles on the CT slice that shows the ventricles at their largest. This measure is taken manually from a CT film or semi-automatically from an image on a cathode ray tube. This estimate is highly reliable and correlates extremely well with more complex measures of ventricular volume. Even with the VBR, there are large differences between studies in the cut-off value that is used to define LVE. Some of this variability results from the definition of the ventricle wall that is used. At the present time there is no commonly agreed upon definition and thus it is difficult to use the VBR values from one study as a comparison for another study. Several investigators have used various linear measures of the brain. The use of these disparate measures does not allow the comparison of results between studies.

All studies of the third ventricle have used a measure of the width of this ventricular body. However, because the third ventricle is normally small and the image on CT film is usually reduced by a factor of approximately three, this measure is difficult to take without some magnification. In
half of the investigations of the third ventricle, no method of measurement is described. This makes it difficult to assess the degree to which variability in findings results from the method of measurement. In addition, investigators have failed to indicate whether measurements are life size or are reported directly from the CT film. Future studies should describe the procedure used to measure the third ventricle.

There is no consensus in the literature regarding the method of assessing cortical atrophy. The level of the uppermost CT cut that is chosen for measurement can influence considerably the likelihood of finding signs of cortical atrophy. Nevertheless, in all studies, the actual levels of the brain that are used to make these assessments are not reported, and some also fail to describe the procedures that were employed. The variability in methodology and lack of procedural information present major difficulties to the interpretation and comparison of results. Researchers need to include information regarding the level of CT cut and the procedure used when assessing cortical atrophy. In addition, an endeavour should be made to take ratings from CT scans other than those that show the upper limits of the cortex.

**Research Objectives**

The primary purposes of the present study are to determine whether 1. enlargement of the lateral ventricles, 2. enlargement of the third ventricle, and 3. enlargement of
the cortical sulci are present at the onset of psychosis in psychiatric patients and, if they are, to determine the prevalence of these anomalies. If these morphological anomalies are present at the onset of psychosis they may reflect predisposing factors or markers of susceptibility to psychosis. No enlargement, on the other hand, would suggest that the findings reported in the research literature are sequelae or iatrogenic phenomena. Specifically, the primary purposes of this study are to determine whether patients with schizophrenia, schizophreniform disorder, bipolar disorder or major depression have larger lateral ventricles, third ventricle, and cortical sulci than do normal control subjects.

A fourth purpose of this study is to investigate the relationship between specific morphological brain anomalies and other putatively related variables at the onset of psychosis in schizophrenic and affective disorder patients. A significant positive relationship between brain measures and clinical variables would suggest that a neuropathological process with clinical manifestations is present at the onset of psychosis in some patients. This finding could lead to the specification of a distinct syndrome with implications for etiological processes, treatment decisions, and prognosis. Specifically, the fourth purpose of this study is to determine whether lateral ventricular enlargement, enlargement of the third ventricle, and cortical atrophy are associated with poor premorbid adjustment, negative symptoms,
and disrupted smooth pursuit eye movements in first-episode schizophrenic and first-episode psychotic affective disorder patients.

A fifth purpose of this study is to determine whether the type of control group that is used influences the CT results that are obtained. Specifically, a medical control group, selected from radiology records, will be included together with a normal control group. This addition will allow the assessment of potential selection biases associated with using medical patients as control subjects.

Method

Subjects

The participants in this study included 91 psychiatric patients recruited as part of an extensive study to determine the incidence of first episode psychosis in the Vancouver area. This study included measures of psychosocial and biological characteristics of psychopathology. Patients ranged from 15 to 47 years and both sexes were represented. An objective of the initial study was to determine the incidence of first break psychosis in the Vancouver metropolitan area. Patients were referred from all psychiatric hospitals and community mental health centres in the Vancouver area as well as from private practice psychiatrists who agreed to assist the project. In addition, a random sample of one of every six general practitioners in the area was solicited to refer patients. All patients were recruited within three months of being treated for their
first psychotic episode. Subjects with signs of neurological problems or alcohol/drug dependence were excluded (see Appendix E). Of the 302 patients initially identified, 126 refused to participate in the epidemiological study. Of the remaining 176, 63 refused to participate in the CT evaluation, 16 moved out of the area before they could be asked to participate, four died before they could be recruited, and two could not be released from hospital for the CT scan. Three patients who participated in the CT scanning procedure refused the psychophysiological testing. Finally, there was insufficient information to make ratings of negative symptoms on two patients and of premorbid adjustment on ten patients.

Of the 91 patients who received a CT scan, there were 67 males and 24 females. The average age was 23.5 years (range 15 to 47). Table 3 gives the sex distribution and mean age for patients in each diagnostic group. At the time subjects were recruited, 81 were receiving inpatient treatment and ten were in outpatient care. All patients reported psychotic symptoms (delusions and/or hallucinations). Diagnostic decisions were based on DSM-III criteria. Other diagnostic systems, including Research Diagnostic Criteria (RDC, Spitzer et al., 1978) were also used to classify patients. Information that was used to make diagnostic decisions was obtained from a structured interview with the patient (Present State Exam; Wing, Cooper and Sartorius, 1974), from a review of the hospital chart, and, where possible, from an
Table 3

Demographic characteristics of Participants

<table>
<thead>
<tr>
<th>Groups</th>
<th>Number of Subjects</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>DSM-III Schizophrenia</td>
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<td>5</td>
</tr>
<tr>
<td>Schizophreniform</td>
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<td>3</td>
</tr>
<tr>
<td>Bipolar</td>
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<td>9</td>
</tr>
<tr>
<td>Major Depression</td>
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<td>5</td>
</tr>
<tr>
<td>Paranoid Disorder</td>
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<td>2</td>
</tr>
<tr>
<td>Schizoaffective</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Total Patients</td>
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<td>24</td>
</tr>
<tr>
<td>Volunteer Control</td>
<td>29</td>
<td>15</td>
</tr>
<tr>
<td>Medical Control</td>
<td>13</td>
<td>17</td>
</tr>
</tbody>
</table>
interview with family members and friends. A case conference including at least two diagnosticians (psychiatrists and clinical psychologists) was held for each patient. A consensus was reached for each symptom and symptom checklists were used to complete diagnoses (Appendix C). All patients were receiving psychotropic medication at the time they were recruited. Participants gave informed consent for each part of this study (psychophysiological testing and CT scan, see Appendix D) and were paid $20 for their participation in the CT scanning, and $10 for the psychophysiological testing.

A normal control group of 44 volunteers was recruited from family practice clinics, employment centres, community centres, and community colleges in the Vancouver area. There were 29 males and 15 females between the ages of 15 and 42. All volunteers were given a screening interview (Appendix E) and reported that neither themselves nor their first degree relatives had ever received psychiatric treatment or had an alcohol or drug abuse problem. In addition, all volunteers reported that they had no chronic illnesses. More male than female patients were recruited and the ratio of males to females was different for each diagnostic group (Table 3). The sex ratio in the volunteer control subjects approximated that of the total patient sample. Control subjects within the age range of the total patient sample were included at approximately the same age distribution as the patients; i.e., the age distribution was positively skewed.

A second control group was comprised of 30 individuals
who received a CT scan as part of a medical examination. There were 13 males and 17 females between the ages of 15 and 33. Reasons for referral to the CT scanner were to investigate headaches (n = 12), rule out space-occupying lesions (n = 9), rule out multiple sclerosis (n=4), investigate suspected seizure disorder (n = 3), investigate intracerebral calcification (n = 1), and assess post-injury head trauma (n = 1). All scans were reported to be within normal limits. The scanning procedure for these patients was the same as for the psychiatric patients and volunteer control subjects. All age-appropriate medical patients who received a CT scan in a three month period during which the psychiatric patients and volunteer control subjects were scanned and who had no significant radiological findings served as subjects in this control group. The age distribution of this group approximated that of the total patient sample.

Apparatus and Interviews

Computerized Tomography. All scans were performed using a third generation, high resolution, total body scanner (Siemens Somatom DR2). The window width was set at 80 and the level at 27 for all subjects during CT scanning. From 13 to 16 serial cross-sections of the brain, 8mm in thickness, were scanned parallel to the cantho-meatal line. Scans were made from the base of the skull to the top of the cranial vault. Scans for the psychiatric patients and volunteer control subjects were done without enhancement; i.e., without
having a contrast medium injected into the patient to make soft tissue such as tumors more visible on an X-ray scan. Eleven of the medical patients received scans without enhancement and 19 received only enhanced scans.

Data from all scans, represented in the form of a 256x256 matrix of tissue density values, were stored on magnetic disc cartridges and also reproduced on transparent X-ray film. Four or six CT scans, each measuring approximately 11.5cm x 8.5cm (98cm²), were printed on a single sheet of X-ray film. The CT scan that showed the lateral ventricles at their largest was selected for each subject and enlarged to a 23.5cm x 17.5cm format (411cm²); i.e., approximately four times the original scan size. A Sokkish 19908 compensating polar planimeter was used to measure the area of the lateral ventricles and the area of the brain from the enlarged scan. These measurements were taken while the CT scan was affixed to a horizontal, white translucent plastic table that was illuminated from below.

The width of the third ventricle at its widest was measured from a 11.5cm X 8.5cm CT scan using a Precision Tool and Instrument Co travelling microscope, type 2160. This instrument is comprised of a microscope fixed to a moveable table. The microscope may be moved to the left or right and forwards or backwards using adjustment screws. The magnitude of each of these movements is given on a vernier scale and is accurate to 0.001mm. The microscope has cross hairs on the lens and allows accurate positioning of the instrument along
the edges of the third ventricle. The frame that holds the moving table is mounted on a white translucent plastic table that was illuminated from below. The CT scan that showed the third ventricle at its largest was fixed to the illuminated table while the microscope was positioned and measurements were taken. Measurements were converted to life size by multiplying the obtained measure by a constant. This procedure resulted in the actual width of the third ventricle in mm.

A rating of cortical atrophy was made using a three point scale. One indicated no visible sulci, two indicated some sulci were visible but that they were not extensive, and three was reserved for scans where sulci were both visible and extensive. This rating was made using the CT scan three slices above the scan that showed the lateral ventricles at their largest. One 11.5cm x 8.5cm scan from each participant was matched to a sample of nine scans (three for each rating) that showed the variability allowed by each rating score (1, 2, or 3).

**Interviews.** A screening schedule was completed for each patient based on information obtained from the referring agency (see Appendix E). This schedule was used to determine an individual's suitability for inclusion in this study. For patients who satisfied the screening criteria and gave informed consent, the Present State Examination (PSE, Wing et al., 1974) was administered by a psychiatrist or clinical psychologist trained in the administration of this
instrument. The results of this interview were used as a basis for making diagnostic decisions.

Premorbid adjustment was assessed using the short form of the Phillips Premorbid History scale (PMH, Harris, 1975, see Appendix B). This measure is comprised of two separate seven-point scales (premorbid social adjustment and premorbid heterosexual adjustment). Each of these scales is normally scored from zero to six. Zero indicates very poor functioning and six indicates good functioning. In order to incorporate more information, these scales were adapted to form a continuous rating scale scored from one to 70; i.e., each of the original seven possible rating points was expanded to include values of zero to nine. This was done to allow finer distinctions to be made between the original ratings. The original scale descriptions were maintained as anchor points. The rating of heterosexual adjustment on the Phillips scale is designed to be used only with individuals aged 20 and older. In order to rate patients under 20 years of age, ratings from an adapted form of the heterosexual part of the Gittleman-Klein scale were substituted for the Phillips heterosexual adjustment scale ratings (Gittleman-Klein & Klein, 1969; Appendix B). This scale is designed to be used with individuals 16 to 20 years of age and is comparable to the Phillips scale in format and content.

Negative symptoms were evaluated according to the criteria used by Andreasen (1982). These symptoms are flattened or blunted affect, impoverished thinking, avolition
or apathy, asociality, and impaired attention. Ratings made during the PSE interview were used to assess these negative symptoms in the present study. A global rating of negative symptoms was made by summing PSE items 36, 54, 58, 107, 108, 110, 119, 128, 129, 130, 133, 134, and 138 (Appendix G).

**Eye Movement Apparatus.** Eye movements were monitored while each subject observed a target consisting of a 5mm circle of light with a dot in its center. The target moved with a sinusoidal motion, horizontally across the screen of a Tektronix type RM 15 single-beam oscilloscope. The subject's eyes were approximately 30cm from the centre of the screen. A Wavetek Digital VCG model 113 sine wave generator was used to drive the target. Silver/silver chloride electrodes (1cm in diameter) were attached to the abraded outer canthi for horizontal EOG recording. Electrodes placed above and below the right eye were used to monitor blinks. A ground electrode was attached to the left ear lobe. Signals from both the EOG and target were recorded simultaneously on a Beckman R612 Dynograph and on a magnetic tape using a Vetter FM Model A tape recorder. Modified type 9806A AC couplers, set to a time constant of three seconds, were used for the EOG and target input on the dynograph. AC coupling was used to reduce the contribution of baseline shift to the records. A time constant of .1 seconds was used to monitor blinks.

**Procedure**

For those participants who gave consent, the Present State Examination (PSE) was conducted by a psychiatrist or
A clinical psychologist trained in the use of this instrument. This interview was done at the time each subject was recruited. The PSE was used to assess the symptom picture for the month during which the patient was most symptomatic.

The CT scanning procedure was conducted as soon as possible after recruitment. A uniform scanning procedure was used. Scans were completed at the radiology department in the University of British Columbia Health Sciences Hospital. Each subject was asked to lie on a movable table attached to the CT scanner. A moulded head-rest was used to stabilize the participant's head until 13 to 16 consecutive CT scans had been made. This procedure took approximately 15 minutes.

A measure of eye movement integrity was obtained as close as possible to the time of the PSE interview. Participants were shown the apparatus and given an explanation of the procedures before the experiment began. EOG electrodes were attached and the subject's head stabilized in a chin and forehead rest. Tape recorded instructions were used to request that during the eye tracking tasks, the subject refrain from blinking, hold his or her head still, and follow the target closely. An oscillating sinusoidal target was presented at .4, .8, and 1.2Hz for 20 cycles at each frequency. Each task was separated by a 20 second rest period. A number of other measures were obtained after the eyetracking tasks were completed. The duration of the total psychophysiological session was from two to three hours.
Data Quantification

CT Scan Data. All measures were taken from the CT scans without knowledge of the subjects identity or diagnosis. Using the planimeter, the area of each of the lateral ventricles was traced three times and the area of the brain six times. The mean of the three measures was calculated for each ventricle. These mean values were added together and divided by the mean of the six measures of the brain. This ratio was multiplied by 100 to give the ventricle to brain ratio (VBR) as it is reported in most previous studies. This procedure is the same as that used by Weinberger et al. (1979a, 1982). The width of the third ventricle was measured at the widest point that a continuous ventricle wall could be seen. The degree of cortical atrophy was assessed using the three-point rating scale described previously. One indicated that no sulci were visible, two indicated that sulci were visible but not extensive, and three denoted sulci that were clearly visible and extensive.

Interview Data. The negative symptom rating was made by tabulating items from the PSE that indicated the presence of negative symptoms. The resulting score ranged from zero to 13. Zero indicates that no negative symptoms were judged to be present while 13 indicates severe incapacitation with negative symptoms. The Abbreviated Phillips Scale ratings range from one (very poor premorbid adjustment) to 70 (very good premorbid adjustment) for each of the subscales (social and heterosexual adjustment). A rating of premorbid
adjustment was made by adding the subscale scores. The total score ranges from two to 140. Two independent raters derived this score from information collected during a standardized interview (see Appendix B). The average of these two ratings was used in the analyses of results.

Eye Movement Data. Taped EOG and target channels from the smooth pursuit eye-tracking tasks were fed into a Digital Equipment Corporation LSI 11/23 digital computer. The computer was programmed to align the channels for phase differences and to set channels equal with respect to amplitude differences. The computer was also programmed to compute root-mean-square (RMS) error deviation of the EOG data channel from the target channel. This procedure involves the calculation of differences, in standard deviation units, between the target signal and the subject's eye movements. Conceptually, this measure represents the degree of fit between the target signal and tracking performance. The mean of the three obtained RMS values (one for each of the .4, .8, and 1.2Hz tracking tasks) was obtained for each subject. This procedure provides a highly reliable estimate of tracking integrity (Iacono & Lykken, 1981). Because the distribution of these data was positively skewed, the log of this value was used in the analysis of the data.

Results

The results of this research are divided into three sections. The first, entitled "Reliability of Measures and
Ratings", presents the interjudge reliability for the measures used in this study. The second section, entitled "Subject Characteristics", is divided into four subsections: "Sex of Subjects", "Age of Subjects", "Participants and Nonparticipants" and "Medical Control Group". The issues of age and sex differences across patient and control groups is addressed. In addition, this section also deals with comparisons between subjects who did not receive a CT scan and those who consented to participate in this study. The fourth subsection deals with the differences between those medical patients who had CT scans with a contrast medium and those who, like all other subjects in this study, received a CT scan without contrast medium. A contrast medium is injected into patients in order to make soft tissue such as tumors more visible on an X-ray scan. The third section of the results, "Analysis of CT Findings", is concerned with testing the research hypotheses. This section is divided into four subsections: "Lateral Ventricles", "Third Ventricle", "Cortical Atrophy" and "Relationships Between Morphological Measures". Between group differences are assessed for each morphological measure. The groups are schizophrenia, schizophreniform, bipolar, and major depression (diagnosed according to DSM-III criteria), and volunteer and medical control groups.

**Reliability of Measures and Ratings**

Pearson correlation coefficients were computed in the following analyses except where indicated. In order to assess
the concurrent validity of VBR measures, global ratings of ventricular dilation were compared with planimetry measures. The scans of 20 randomly selected subjects were rank ordered according to lateral ventricular size by a neuroradiologist. Planimetry measures were completed on the same scans by a second rater and the rankings and measurements were compared. The Spearman rank correlation for this comparison was high (\( r = .80 \)). Interjudge reliability was assessed by comparing the planimetry measures of two independent raters for 25 subjects. This measure of reliability was high (\( r = .93 \)).

The width of the third ventricle for 20 subjects was measured by two independent raters. The level of agreement between the two raters was very high (\( r = .97 \)). The ratings of cortical atrophy for all 166 subjects were done by two independent raters. There was full agreement on 150 (90%) of the 166 ratings. Discrepant ratings were resolved through mutual agreement. Two independent raters reviewed the information relevant to premorbid functioning and each assigned a score for each patient. The interjudge reliability for both the premorbid social adjustment scale and the premorbid sexual adjustment scale were high (\( r = .97, \) and \( r = .99 \) respectively). Group values for premorbid adjustment, negative symptoms and SPEM are given in Appendix J.

Subject Characteristics

A number of statistical tests were computed in order to provide a clear definition of the subject samples and were not used to test research hypotheses. In order to determine whether there were any systematic biases due to age, sex, or
attrition, liberal tests were used and a probability value of .05 was employed as a cut-off.

**Age of Subjects.** The mean age of the individuals who participated in the present study was similar for the total psychiatric patient sample and both of the control groups (Table 3, p. 104). There was a significant correlation between age and each CT measure for the schizophreniform patients. However, one individual with large ventricles was substantially older than the mean of this patient group (33 years versus $M = 20.6$ Years). With this subject outlier removed from the calculations, no CT measure was significantly related to age for any patient or control groups (see Appendix H).

**Sex of Subjects.** As Table 3 shows, there are more males than females in both the total patient sample and the volunteer control group. The predominance of males is also reflected in the sex ratio of schizophrenic, schizopreniform, and depressed patient groups. However, both sexes are equally represented in the bipolar patients and the medical control group has more females than males. Because the three major research hypotheses deal with the psychiatric patient groups and the volunteer control group, a chi square analysis was computed to determine if there were significant differences in sex ratio across these samples. In order to compensate for the small number of females in each patient group, Yates' correction was applied to this analysis. This test failed to detect a significant difference in the
p of males to females over these groups, $\chi^2(4, N = 129) = 7.11, p > .05$. The final research hypothesis deals with the medical control group and the volunteer control subjects. In order to test whether there are significant differences in the ratio of males to females across these groups, a chi square analysis was computed over sex and type of control group. This analysis was not significant, $\chi^2(1, N = 74) = 2.79, p > .05$ (Because there is one degree of freedom in this chi square analysis, Yates' correction was applied, Hays, 1973).

There were too few females in each diagnostic group to allow an accurate assessment of sex differences in ventricle or sulcal size for each diagnosis. However, an analysis of sex differences over the size of each of the CT measures (third and lateral ventricle size and cortical atrophy) failed to detect a significant effect for the total patient sample, range of $t_{s}(89) = 0.12$ to $0.74$, all $p_s > .1$, the volunteer control group, range of $t_{s}(42) = 0.16$ to $1.84$, all $p_s > .05$, and the medical control group, range of $t_{s}(28) = 0.47$ to $1.72$, all $p_s > .1$. All tests were two tailed. In summary, whereas there are differences in the ratio of males to females over the patient and control groups, no significant sex differences were detected over the size of the three CT measures (lateral ventricle, third ventricle, cortical sulci). Males and females were combined for all further analyses.
Participants and Nonparticipants. Of the 176 patients who were initially recruited, CT scans were not obtained on 85 individuals (see Table 4). More males than females were identified initially and this difference is also reflected in the patients who participated in the CT scanning procedure. There were however, slightly more female nonparticipants (26/50, 52%) than males (59/126, 47%). The mean age of the patients who did not receive a CT scan (M + SD = 28.4 + 5.8 years) was significantly greater than that of the participants (M + SD = 23.5 + 6.5 years), t(175) = 5.26, p<.001. A number of patients who did not participate in the CT scanning procedure were relatively advanced in age. Seven patients with paranoid disorder (M = 44.4 years) and one of the patients with major depression (aged 50) were notably older than the average age of the subjects who received a CT scan. There were some differences in the number of nonparticipants between diagnostic groups (Table 4). Proportionately fewer patients with affective disorders (bipolar or major depression) received a CT scan than did individuals with schizophrenia or schizophreniform disorders. A chi square analysis across subjects (participants, nonparticipants) and major patient groups (schizophrenic, schizophreniform, bipolar, depressed) failed to detect a statistically significant difference, $\chi^2 (3, N = 160) = 4.38$, p>.1. Of the 85 individuals who did not receive a CT scan 63 (74%) refused, 16 (19%) moved residence and/or could not be located, 4 (5%) died before they could be scanned, and 2 (2%)
Table 4

Demographic Characteristics of Nonparticipants

<table>
<thead>
<tr>
<th>DSM III Diagnoses</th>
<th>N</th>
<th>T</th>
<th>N</th>
<th>T</th>
<th>Not Scanned</th>
<th>M</th>
<th>SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia</td>
<td>15</td>
<td>41</td>
<td>5</td>
<td>10</td>
<td>20</td>
<td>51</td>
<td>(39%)</td>
<td></td>
</tr>
<tr>
<td>Schizophreniform</td>
<td>8</td>
<td>25</td>
<td>5</td>
<td>8</td>
<td>13</td>
<td>33</td>
<td>(39%)</td>
<td></td>
</tr>
<tr>
<td>Bipolar</td>
<td>14</td>
<td>23</td>
<td>7</td>
<td>16</td>
<td>21</td>
<td>39</td>
<td>(54%)</td>
<td></td>
</tr>
<tr>
<td>Major Depression</td>
<td>16</td>
<td>27</td>
<td>5</td>
<td>10</td>
<td>21</td>
<td>37</td>
<td>(57%)</td>
<td></td>
</tr>
<tr>
<td>Paranoid Disorder</td>
<td>4</td>
<td>5</td>
<td>3</td>
<td>5</td>
<td>7</td>
<td>10</td>
<td>(70%)</td>
<td></td>
</tr>
<tr>
<td>Schizoaffective</td>
<td>2</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>6</td>
<td>(50%)</td>
<td></td>
</tr>
<tr>
<td>Total Patients</td>
<td>59</td>
<td>126</td>
<td>26</td>
<td>50</td>
<td>85</td>
<td>176</td>
<td>(48%)</td>
<td></td>
</tr>
</tbody>
</table>

a Total number of patients who were recruited in the epidemiological study.
could not be released from hospital for the CT scan.

In summary, approximately 50% of the subjects recruited for the initial epidemiological study did not participate in the CT scanning procedure. The rate of nonparticipation was very similar across males and females. However, the nonparticipants tended to be older than the participants and there was a nonsignificant trend towards proportionately fewer participants with affective disorders to participate than for schizophrenic or schizophreniform disorder patients. Most individuals did not receive a CT scan because they refused or because they could not be located after they were released from hospital.

**Medical Control Group.** A comparison was made over the three CT measures (lateral ventricles, third ventricle, cortex) between medical patients who were injected with a contrast medium and those who, like the other subjects in this study, had noncontrast CT scans. There were no significant differences between these two groups over lateral ventricle size ($M \pm SD = 5.84 \pm 2.44$ Vs $5.56 \pm 2.83$), $t(28) = .14$, $p>.1$, third ventricle width ($M \pm SD = 2.93 \pm 0.68$ Vs $2.94 \pm 0.93$), $t(28) = .04$, $p>.1$, or cortical atrophy ($M \pm SD = 1.54 \pm 0.78$ Vs $1.30 \pm 0.47$), $t(28) = 1.07$, $p>.1$.

**Analysis of CT Findings**

The first section of the results ("Reliability of Measures and Ratings") indicates that the data were reliably collected. The second section ("Subject Characteristics") suggests that although there are differences in the ratio of
males to females between groups there is no indication that this disparity influenced the results. In addition, a large number of patients who were identified in the epidemiological study did not participate in the CT study. Whereas this could have biased the sample, there is no evidence of differential attrition over sex or diagnosis. Subsequent analyses will focus on testing the research hypotheses of the present study. Because the majority of previous researchers diagnosed patients according to DSM-III criteria, this diagnostic system is used to classify patients in the present study. Numerous CT studies have used RDC diagnoses and, in order to explore the possibility of the diagnostic system having an affect on the obtained results, the major hypotheses were also tested with patients classified according to RDC criteria (see Appendix I). The major hypotheses predict that psychotic patient groups will have enlargement of the lateral ventricles, third ventricle, and cortical sulci. Furthermore, these morphological brain changes should be related to poor premorbid adjustment, number of negative symptoms, and disrupted smooth pursuit eye movements. A further hypothesis based on previous research predicts that significant results are likely to be obtained if the control group is comprised of medical patients who are selected from radiology records.

**Lateral Ventricle.** In order to analyse lateral ventricle size, a one-way ANOVA was performed to compare VBR ratings across groups (schizophrenia, schizophreniform,
bipolar, depressed, volunteer control, and medical control). Psychiatric patients were diagnosed according to DSM-III criteria for this analysis. The size and distribution of the lateral ventricles were very similar across groups (Table 5, Figure 2). No significant group difference was found, $F(5, 153) = 0.51, p > .1$. Only one psychiatric patient (3%) exceeded the volunteer control mean plus two standard deviations ($VBR > 11.90$). Two volunteer control subjects (4%) exceeded this value. If the medical control group were used to determine the standard for normal ventricular size, two schizophrenic (6%), one schizophreniform (5%), and two volunteer control subjects (4%) had significantly enlarged lateral ventricles ($VBR > 10.87$).

A negative finding may be the result of type II error. In order to assess this possibility, a power analysis was computed. There is a wide range in the size of the effects that have been reported in the literature. These range from a high of 1.92 SD (Johnstone et al., 1976) to a low of 0.4 SD (Andreasen et al., 1982) with a median of approximately 0.7 SD. If true differences in the present study are as large as the median of previously reported studies then there is a probability of .95 that it would be detected in the present study. If, however, the population difference is as small as that reported by Andreasen et al. (1982), then there is a probability of 0.5 that it would have been detected in the present study. Thus, while moderate differences would probably be detected, small group differences could have been
Table 5
Mean Values for Ventricle and Cortex Measures for Each Group

<table>
<thead>
<tr>
<th>Group</th>
<th>Lateral Vent (VBR)</th>
<th>Third Vent (mm)</th>
<th>Cortex (Rating)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia</td>
<td>M 6.74</td>
<td>4.05</td>
<td>2.06</td>
</tr>
<tr>
<td>N = 31</td>
<td>SD 2.59</td>
<td>1.50</td>
<td>0.85</td>
</tr>
<tr>
<td>Schizophreniform</td>
<td>M 5.74</td>
<td>3.28</td>
<td>1.95</td>
</tr>
<tr>
<td>N = 20</td>
<td>SD 2.44</td>
<td>0.83</td>
<td>0.76</td>
</tr>
<tr>
<td>Bipolar</td>
<td>M 6.20</td>
<td>3.33</td>
<td>1.89</td>
</tr>
<tr>
<td>N = 18</td>
<td>SD 1.95</td>
<td>1.01</td>
<td>0.83</td>
</tr>
<tr>
<td>Depression</td>
<td>M 6.36</td>
<td>3.63</td>
<td>2.00</td>
</tr>
<tr>
<td>N = 16</td>
<td>SD 2.96</td>
<td>0.88</td>
<td>0.89</td>
</tr>
<tr>
<td>Total Patients</td>
<td>M 6.45</td>
<td>3.62</td>
<td>2.05</td>
</tr>
<tr>
<td>N = 91</td>
<td>SD 2.51</td>
<td>1.18</td>
<td>0.83</td>
</tr>
<tr>
<td>Volunteer Control</td>
<td>M 6.39</td>
<td>3.49</td>
<td>1.82</td>
</tr>
<tr>
<td>N = 44</td>
<td>SD 2.76</td>
<td>1.13</td>
<td>0.76</td>
</tr>
<tr>
<td>Medical Control</td>
<td>M 5.77</td>
<td>3.01</td>
<td>1.39</td>
</tr>
<tr>
<td>N = 30</td>
<td>SD 2.55</td>
<td>0.90</td>
<td>0.61</td>
</tr>
</tbody>
</table>

a A rating of 1 = no visible sulci, 2 = sulci are visible but not extensive, 3 = sulci are visible and extensive.
Figure 2. Distribution of Ventricle to Brain Ratios in Each Patient and Control Group.

Note 1. Lines above and below each bar denote the standard error of measurement.

Note 2. Sz = schizophrenic, Szm = schizophreniform, Dep = depression, Vol C = volunteer control, Med C = medical control.
missed.

Because of methodological differences between studies, the practice of using a predetermined cut-off should ideally be avoided. However, Weinberger et al. (1982) have recommended a VBR value of ten as a conservative cut-off point that may be used to define lateral ventricular enlargement.

Six of 91 psychiatric patients (7%) in the present study had VBR scores greater than ten. Four of these subjects were diagnosed schizophrenic (13%), one schizophreniform (5%), and one paranoid, according to DSM-III diagnostic criteria. Three of the six were male and three were female. Four were less than 30 years of age. There were also five of 44 volunteer control subjects (11%) and one of 30 medical control patients (3%) who had VBR values greater than ten. The five volunteer subjects with enlarged ventricles appeared to be no different from the remaining volunteers. There were three males and two females and all were working, in high school, or in college. Four were under 30 years of age and all reported active social lives. The medical patient with a VBR value greater than ten was a 24 year old female. She was referred for a CT scan to investigate an aneurism.

Because the premorbid ratings are measured on an ordinal scale, the relationship between premorbid adjustment and lateral ventricle size was assessed using Spearman rank correlations. The relationships between lateral ventricle size and both negative symptoms and smooth-pursuit eye
movements were assessed using Pearson correlations. In order to increase the statistical power of these analyses, bipolar and depressed patients were combined in one group.

There were no significant relationships between lateral ventricle size and premorbid adjustment, smooth pursuit eye-movements or negative symptoms for any diagnostic groups (Table 6). In addition, no differences were obtained by dividing the patients at the median VBR and examining the mean difference between the two groups over the three clinical-psychophysiological variables, range of \( t_s(79 \text{ to } 87) = -1.52 \text{ to } 0.83, \text{ all } p_s > .1 \). Quartile splits (equivalent to comparing the group below the 25th with that above the 75th percentile) likewise failed to show significant differences between patients with small and those with large ventricles across premorbid adjustment, negative symptoms, and smooth pursuit eye-movements, range of \( t_s(44) = -0.47 \text{ to } 1.30, \text{ all } p_s > .1 \).

**Third Ventricle.** Table 5 and Figure 3 show that the mean width of the third ventricle in both the schizophrenic and depressed patient groups appears greater than that of the volunteer control group. In addition, the mean ventricle width of the volunteer control group appears greater than the medical control group. In order to determine if these differences are statistically significant, a one-way ANOVA was calculated across groups (schizophrenia, schizophreniform, bipolar, depressed, volunteer control, and medical control). With patients diagnosed according to DSM-III criteria, a
Table 6

<table>
<thead>
<tr>
<th>DSM III Diagnosed Groups</th>
<th>Poor Premorbid</th>
<th>Negative Symptons</th>
<th>Eye Movement Impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia</td>
<td>rho = .11</td>
<td>r = -.15</td>
<td>r = -.02</td>
</tr>
<tr>
<td></td>
<td>(n=28)</td>
<td>(n=31)</td>
<td>(n=30)</td>
</tr>
<tr>
<td>Schizophreniform</td>
<td>rho = -.08</td>
<td>r = -.02</td>
<td>r = -.13</td>
</tr>
<tr>
<td></td>
<td>(n=19)</td>
<td>(n=20)</td>
<td>(n=18)</td>
</tr>
<tr>
<td>Affective (Bipolar and Depressed)</td>
<td>rho = .15</td>
<td>r = -.28</td>
<td>r = .16</td>
</tr>
<tr>
<td></td>
<td>(n=29)</td>
<td>(n=34)</td>
<td>(n=34)</td>
</tr>
<tr>
<td>Total Patients</td>
<td>rho = .06</td>
<td>r = -.15</td>
<td>r = -.18</td>
</tr>
<tr>
<td></td>
<td>(n=81)</td>
<td>(n=89)</td>
<td>(n=88)</td>
</tr>
</tbody>
</table>

Note. No correlation was statistically significant at p<.05 one-tailed.

a Spearman correlations.  
b Pearson correlations.

c The total patient group includes paranoid disorder and schizoaffective disorder patients in addition to the three major diagnostic groups listed in this table.
Figure 3. Distribution of Third Ventricle Width in Each Patient and Control Group.

Note 1. Lines above and below the bars indicate the standard error of measurement.

Note 2. Sz = schizophrenic, Szm = schizophreniform, Dep = depressed, Vol C = volunteer control, Med C = medical control.
significant group effect was obtained over third ventricle width $F(5, 153) = 2.97, p = .014$. In order to maintain an experiment-wise alpha level of .05, the level of significance for each of the three one-way ANOVAs (lateral ventricles, third ventricle and cortex) should be adjusted to $p = .017$. The between groups analysis of third ventricle width achieves this level of significance. However, the Bartlett-Box test indicated that group variances were significantly heterogeneous, $F = 2.88, p = .01$. This violates an assumption of ANOVA and, with unequal numbers of subjects in the groups, can seriously affect the level of alpha that is obtained (Glass, Pedcham, & Sanders, 1974). An examination of the group variances indicated that larger variances tended to be associated with larger groups. A Spearman correlation between group size and variance indicated a moderately strong positive relationship, $\rho = .66$. Under these circumstances, the level of alpha is likely to be underestimated by the ANOVA test (Myers, 1979, p69) and the statistical significance of this ANOVA is therefore accepted.

An hypothesis of the present study, based on previous research findings (see Introduction), predicts that schizophrenic, schizophreniform, bipolar and depressed patients will have larger ventricles than normal individuals. In order to test this hypothesis, planned orthogonal contrasts were computed between the volunteer control group and each of the patient groups in this study. The width of the third ventricle was significantly greater for the
schizophrenic group than for the volunteer control group, $t(73) = 2.12, \ p<.05$ one tailed test. No other patient groups had significant enlargement of the third ventricle. Previous research also suggests that medical patients tend to have smaller ventricles than normal individuals. In order to test this hypothesis, a planned orthogonal contrast was computed between the two control groups. The mean width of the third ventricle in the volunteer control group was significantly greater than that of the medical patients, $t(72) = 1.80, \ p<.05$ one tailed test.

Using an upper limit of 5.75mm as a cut-off (the normal control mean plus two standard deviations), there were three of 31 schizophrenics (10%) with significant enlargement of the third ventricle. No other patients had significant enlargement (Figure 3). There were also three of 44 normal control subjects (7%) with a significantly wide third ventricle. If the medical control group is used as a basis to define normal ventricles, then eight schizophrenics (26%), one schizophreniform (5%), one bipolar (6%), and one depressed patient (6%) have an enlarged third ventricle ($M + 2SD = 4.81mm$). Six normal control subjects (14%) and one medical patient (3%) also have a significantly enlarged third ventricle if the medical control group is used as a standard.

Because premorbid adjustment was measured using an ordinal scale, the relationship between third ventricle width and level of premorbid functioning was assessed using Spearman rank correlations. The relationships between third
ventricle width and both negative symptoms and smooth-pursuit eye movements were assessed using Pearson correlations. The bipolar and depressed patient groups were combined to increase the power of this analysis.

Third ventricle width was not significantly related to premorbid adjustment, smooth-pursuit eye movements (SPEM), or negative symptoms (Table 7). A median split failed to find any differences between patients with large third ventricles and those with small third ventricles on premorbid adjustment, SPEM, or negative symptoms, range of ts(79 to 87) = -1.86 to -0.50, all p>.05. A quartile split also failed to detect any differences, range of ts(44) = 0.16 to 1.50, all p>.1.

Cortical Sulci. Cortical atrophy was rated on a three point ordinal scale. There has been some confusion in the literature regarding whether ANOVA is appropriate for this type of data (Gato, 1980). If the assumptions of normality, independence, and homogeneity of variance are met, ANOVA is an appropriate statistical method regardless of the scale of measurement (Gato, 1980).

A one-way ANOVA across DSM-III diagnosed patient and control groups was significant, F(5, 153) = 2.95, p = .014. The Bartlett-Box test indicated that group variances were homogeneous, F = .925, p = .46. It can be seen from Table 5 and Figure 4 that the mean cortical atrophy ratings are very similar across all groups except for the medical control. Planned orthogonal contrasts were computed between the
Table 7

Correlations Between Third Ventricle Size and Premorbid Adjustment, Negative Symptoms and Smooth-Pursuit Eye Movements

<table>
<thead>
<tr>
<th>DSM III Diagnoses</th>
<th>Premorbid Adjustment</th>
<th>Negative Symptoms</th>
<th>Smooth-Pursuit Eye Movements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia</td>
<td>rho = -.16</td>
<td>r = .23</td>
<td>r = .17</td>
</tr>
<tr>
<td></td>
<td>(n=28)</td>
<td>(n=31)</td>
<td>(n=30)</td>
</tr>
<tr>
<td>Schizophreniform</td>
<td>rho = -.15</td>
<td>r = -.04</td>
<td>r = -.37</td>
</tr>
<tr>
<td></td>
<td>(n=19)</td>
<td>(n=20)</td>
<td>(n=18)</td>
</tr>
<tr>
<td>Affective (Bipolar and Depressed)</td>
<td>r = .10</td>
<td>r = -.01</td>
<td>r = .19</td>
</tr>
<tr>
<td></td>
<td>(n=29)</td>
<td>(n=34)</td>
<td>(n=34)</td>
</tr>
<tr>
<td>Total Patients</td>
<td>rho = .01</td>
<td>r = .14</td>
<td>r = .14</td>
</tr>
<tr>
<td></td>
<td>(n=81)</td>
<td>(n=89)</td>
<td>(n=88)</td>
</tr>
</tbody>
</table>

Note. No correlation was statistically significant at p < .05 one-tailed test.

a  Spearman rank correlations.  b  Pearson correlations.

c  The total patient group includes paranoid disorder and schizoaffective disorder patients in addition to the three major diagnostic groups listed in this table.
Figure 4. Distribution of Cortical Atrophy Ratings in Each Patient and Control Group.

Note 1. The lines above and below the bars denote the standard error of estimate.

Note 2. Sz = schizophrenic, Szm = schizophreniform, Dep = depressed, Vol C = Volunteer control, Med C = medical control.
volunteer control group and each of the patient groups and between the volunteer control group and the medical control group. These analyses indicated that no patient group showed more cortical atrophy than the volunteer control group but that significantly less atrophy was observed in the medical patients than in the volunteer control subjects, $t(72) = 2.35, p<.05$ one tailed.

Cortical atrophy ratings represent an ordinal scale with a high proportion of tied ranks. In this situation, Kendall's tau is an appropriate measure of association and was used in the following analyses. There were no significant relationships between cortical atrophy and level of premorbid adjustment, SPEM integrity, or number of negative symptoms (Table 8). This was also the case when patients were divided into atrophic (ratings of 2 or 3) or nonatrophic (a rating of 1) groups and compared across the three clinical-psychophysiological variables; range of $t$s(79 to 87) = -1.21 to 0.63, all $p$s>.1.

Relationships between Morphological Measures. In order to assess whether lateral and third ventricle size and cortical sulci dilation are interrelated phenomena or whether they are independent morphological characteristics, correlation coefficients were computed between these measures for each group. Pearson correlations were used to measure the association between lateral and third ventricle size, and Kendall's tau to compare the relationship between cortical atrophy and both third and lateral ventricular size. A
Table 8

<table>
<thead>
<tr>
<th>DSM III Diagnosed Groups</th>
<th>Premorbid Adjustment</th>
<th>Negative Symptoms</th>
<th>Smooth-Pursuit Eye Movements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia</td>
<td>$\tau = -0.19$</td>
<td>$\tau = -0.01$</td>
<td>$\tau = 0.01$</td>
</tr>
<tr>
<td></td>
<td>(n=28)</td>
<td>(n=31)</td>
<td>(n=30)</td>
</tr>
<tr>
<td>Schizophreniform</td>
<td>$\tau = -0.11$</td>
<td>$\tau = 0.31$</td>
<td>$\tau = -0.02$</td>
</tr>
<tr>
<td></td>
<td>(n=19)</td>
<td>(n=20)</td>
<td>(n=18)</td>
</tr>
<tr>
<td>Affective (Bipolar and Depressed)</td>
<td>$\tau = 0.15$</td>
<td>$\tau = -0.17$</td>
<td>$\tau = 0.13$</td>
</tr>
<tr>
<td></td>
<td>(n=29)</td>
<td>(n=34)</td>
<td>(n=34)</td>
</tr>
<tr>
<td>Total Patients</td>
<td>$\tau = -0.05$</td>
<td>$\tau = 0.04$</td>
<td>$\tau = 0.07$</td>
</tr>
<tr>
<td></td>
<td>(n=81)</td>
<td>(n=89)</td>
<td>(n=88)</td>
</tr>
</tbody>
</table>

Note. No correlation was statistically significant at $p < 0.05$ one tailed.

- Kendall correlation coefficients were used.
- The total patient group includes paranoid disorder and schizoaffective disorder patients in addition to the three major diagnostic groups listed in this table.
significant positive correlation was found between the size of the lateral ventricles (VBR) and the width of the third ventricle for both the volunteer ($r = .48, p<.01$) and medical ($r = .47, p<.01$) control groups (Table 9). A smaller significant correlation was found for the psychiatric patients ($r = .24, p<.05$). In order to compare the two correlations, each was changed according to Fisher's $Z$ transformations and a $t$-test was computed between the two values. The difference between the total patient and volunteer control group correlations was assessed and found to be nonsignificant, $t(134) = 1.52, p>.05$. The relationship between lateral and third ventricle size was also explored for three DSM-III diagnosed patient groups (schizophrenic, schizophreniform, and combined bipolar and depressed patients). All three groups showed positive nonsignificant correlations that were similar in size to that of the total patient sample (Table 9). These findings suggest that large lateral ventricles tend to be associated with a large third ventricle in normal individuals but this relationship may be weaker in psychotic patients.

The relationship between the size of the lateral ventricles and cortical atrophy was consistently low for all groups (Table 9). Using Kendall correlation coefficients, a low, significantly positive correlation was obtained for the medical subjects and the affective disorder patients. No significant correlations were obtained for the volunteer subjects or schizophrenic or schizophreniform patients.
Table 9

Correlations Between Lateral Ventricle Size (VBR), Third Ventricle Width, and Cortical Atrophy

<table>
<thead>
<tr>
<th>Groups</th>
<th>Lateral by Lateral by Third by Cortex</th>
<th>Cortex</th>
<th>Cortex</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>a b a b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>r = .22</td>
<td>( \gamma = -.23 )</td>
<td>( \gamma = .06 )</td>
</tr>
<tr>
<td>N = 31</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schizophreniform</td>
<td>r = .36</td>
<td>( \gamma = .21 )</td>
<td>( \gamma = .10 )</td>
</tr>
<tr>
<td>N = 20</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Affective</td>
<td>r = .21</td>
<td>( \gamma = .25 ) *</td>
<td>( \gamma = .37 ) **</td>
</tr>
<tr>
<td>N = 34</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Patients</td>
<td>r = .24</td>
<td>( \gamma = .02 ) *</td>
<td>( \gamma = .16 ) *</td>
</tr>
<tr>
<td>N = 91</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volunteer Control</td>
<td>r = .48</td>
<td>( \gamma = .06 ) *</td>
<td>( \gamma = .29 ) *</td>
</tr>
<tr>
<td>N = 44</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical Control</td>
<td>r = .47</td>
<td>( \gamma = .25 ) *</td>
<td>( \gamma = .20 ) *</td>
</tr>
<tr>
<td>N = 30</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Pearson correlations. Kendall correlations

Affective disorder patients include individuals with bipolar disorder or major depression.

The total patient group includes paranoid disorder and schizoaffective disorder patients in addition to the three major diagnostic groups listed in this table.

* \( p < .05 \)

** \( p < .01 \) two tailed.
The relationships between third ventricle width and cortical atrophy were also assessed using Kendall correlation coefficients. Low significantly positive correlations were obtained for the volunteer control group, the affective disorder patients, and the total group of psychiatric patients (Table 9). The correlations between third ventricle width and sulcal dilation that were obtained for the medical control group, the schizophrenic, and schizophreniform groups indicated low nonsignificant correlations.

Summary of Results

The results of this study indicate that all data were reliably collected and no biases due to age or sex were detected. The first research hypothesis was not confirmed. The mean size of the lateral ventricles was not greater in the patient groups than in the volunteer control group. The second hypothesis was confirmed for the schizophrenic patients. There was a significant difference between the schizophrenic patients and the volunteer control subjects over third ventricle width. No other patient groups had significant enlargement of the third ventricle. The third research hypothesis was not confirmed. None of the patient groups had significantly more cortical atrophy than did the volunteer control group. The fourth research hypothesis was not confirmed. Lateral ventricle size, third ventricle width, and atrophy of the cerebral cortex were not significantly related to the level of premorbid adjustment, smooth-pursuit eye movement integrity,
or number of negative symptoms for any patient group. The fifth hypothesis was confirmed over third ventricle width and cortical atrophy. Both the third ventricle and cortical sulci were significantly smaller in the medical patients than in the volunteer control group. The size of the lateral ventricles was positively related to the width of the third ventricle in the total patient sample and in each of the two control groups. Whereas this correlation was significant for the total patient sample, none of the individual patient groups showed a significant relationship between these variables. Consistently low correlations were obtained between cortical atrophy and both lateral and third ventricle size for all patient and control samples.

**Discussion**

The primary purpose of the present study was to test three major research hypotheses. Each of these hypotheses is supported to varying degrees by a large body of research literature. Two additional hypotheses, based on preliminary findings, were also tested. In partial support of one hypothesis, the major significant finding of this study was increased third ventricle width in schizophrenic patients. This result is consistent with eight of ten previous studies that have investigated this phenomenon. The finding of no enlargement of the third ventricle in schizophreniform, bipolar, and depressed patients, because no previous research has addressed this question, represents a preliminary result and requires replication. The two other major hypotheses
(those concerning lateral ventricular enlargement and enlargement of the cortical sulci) were not supported in the present study despite the fact that there was sufficient statistical power. Given the inconsistencies in the literature surrounding these two hypotheses (see Summary of the Literature above), the present finding is not unexpected.

The fourth hypothesis predicted significant relationships between morphological brain anomalies (enlargement of the third ventricle, lateral ventricle, or cortical sulci) and clinical/psychophysiological factors (smooth-pursuit eye movements, premorbid adjustment, and negative symptoms). This hypothesis was not supported in the present study despite the use of a large number of tests with liberal levels of alpha and the inclusion of median and quartile splits. This finding was not unexpected over the lateral ventricles and cortical sulci given the failure to find significant dilation of either of these structures. Also, because no research literature to date has addressed the issue of an association between third ventricular enlargement and SPEM, premorbid adjustment, and negative symptoms, the present finding is not inconsistent with past research.

In partial support of the fifth hypothesis, the mean size of the third ventricle and cortical sulci were found to be smaller in the medical group than in the normal group.

Other statistical tests under the "Subject Characteristics" part of the Results section were designed to provide a clear definition of the sample used in this study.
and do not test hypotheses. Those statistical tests under the section "Relationships between Measures" are also descriptive rather than hypothesis testing. Some exploratory analyses are presented in Appendix H and test the first three hypotheses when RDC diagnoses were used to classify patients.

**Lateral Ventrices.** The schizophrenic group had larger lateral ventricles than did the normal control group but this difference failed to reach statistical significance. Lateral ventricle size was very similar across the remaining patient groups and the normal control group. The finding of no enlargement is contrary to most of the previous reports of lateral ventricle size in psychotic patients. It is noteworthy, however, that the mean VBR for the schizophrenic patients in the present study (6.74) is very similar to that of the patients from the seven previous studies that report no LVE (6.75) and to that of the patients from the 14 studies that found LVE (6.86). This finding suggests that the present group of schizophrenic patients is comparable to those of previous studies regardless of the outcome of these studies. The mean VBR of the control subjects in the present study (6.39), although similar to that of the studies that report no LVE (6.34), is very different from that of the studies that report ventricular enlargement (3.95). This finding supports the results from previous research and suggests that the interpretation of CT results regarding lateral ventricle size depends on the size of the ventricles in the control subjects but not in schizophrenic patients.
The present control group is comprised of 44 healthy volunteers who were screened for chronic illness, alcohol and drug abuse, and for personal or familial psychiatric problems. The large size of this group and the absence of medical or psychiatric problems suggests that these individuals should approximate the distribution of ventricle sizes found in the normal population. In addition, the fact that mean ventricle size in the present normal group is very similar to that of the studies that report no LVE and significantly different from that of the studies reporting LVE (Smith & Iacono, 1986) strongly suggest biases in the control groups of studies that report significant ventricular enlargement.

Even though there is strong evidence to suggest control group bias in some previous research studies, it is possible that failure to obtain a significant effect in the present study could have resulted from type II error or from methodological problems. The power for detecting a significant lateral ventricle effect equivalent to the smallest significant result that has been reported (0.4 SD, Andreasen et al., 1982) is relatively low (50%) in the present study. However, the chances of obtaining a more typical effect size (0.7 SD, Weinberger et al., 1982) is high (95%). Thus, unless there is minimal enlargement, it is unlikely that the present results are attributable to type II error.

It is also unlikely that methodological difficulties are
responsible for the present results. The CT scanning procedure and methods of assessing the ventricles and sulci were standardized for all subjects and were comparable to those used in most previous studies. High interjudge reliability was obtained for all CT measures and these measures corresponded well to global ratings made by a neuroradiologist.

The patient groups comprised a wide cross section of first episode psychotic individuals. Patients were recruited from all hospitals and community agencies as part of an extensive study to determine the incidence of first episode psychosis in the Vancouver area. This sample is as representative as is possible within the limits of informed consent. Nevertheless, a large number of patients who were identified in the epidemiological study did not participate in the CT study. An analysis of nonparticipants failed to detect differential attrition over sex or diagnosis. However, the greater number of males identified initially could reflect a selection bias in the epidemiological study.

Several studies have indicated that the incidence of schizophrenia is the same for both males and females (Flor-Henry, 1985). However, in a review of the literature on sex differences in schizophrenia, Flor-Henry (1985) noted that the sex ratio of males to females for onset under 40 years of age is approximately 2:1. The ratio for onset before 20 years is far greater (4:1) whereas there is an excess of females in those studies that included onset after 45 years
Although an attempt was made to recruit patients of all ages, disproportionately more young people have first break psychosis. Because most of the patients in the present study are young ($M = 23.5$) the ratio of male to female schizophrenics (5:1) is similar to the expected ratio.

The subjects who received a CT scan were significantly younger than the total group of subjects recruited in the epidemiological study. This difference represents a potential bias in the present study. However, previous research indicates that the prognosis for early onset schizophrenia tends to be worse than that for late onset (Neile & Oltmanns, 1981, pp 343-388). Thus if the present sample is biased, it is most likely to be biased towards excluding good prognosis individuals. Because there is some evidence to indicate that LVE is most common in severely impaired patients, and early onset individuals tend to have poor prognosis, then any bias that may have occurred in the present study should exaggerate the size of the lateral ventricles in the population of psychotic patients and would not account for the failure to find LVE. In addition, because patients were recruited from treatment centres, any individuals who were functioning sufficiently well to avoid professional contact would be missed by the present study. This factor would also tend to bias the present sample in the direction of more severe impairment. Thus, the present failure to detect LVE is unlikely to be due to selection bias. Finally, the fact that exploratory analyses indicated that the same results are obtained whether DSM III or RDC diagnoses are used suggests that this result is not due to
the method of diagnosis that was used.

In summary, failure to obtain significant results could result from type II error or from a number of methodological problems. The sample size used in the present study makes type II errors unlikely. Methodological factors that could affect results include the scanning procedure, the methods used in estimating brain characteristics, the selection of a control group, and the selection and definition of a patient sample. All of these factors were rigorously controlled in the present study and are unlikely to account for the negative results.

The present results indicate that large lateral ventricles are neither a marker of vulnerability to psychosis nor the result of an atrophic process that occurs before the onset of illness. In order for a particular characteristic to qualify as a marker of vulnerability, it should be found more in individuals with a particular illness than in the general population (Iacono, 1983). This should be the case regardless of the duration of illness. The present results indicate that no patient group has significantly larger lateral ventricles than the volunteer control group. Likewise, if atrophy occurred before the onset of psychosis in a significant proportion of individuals, some patients should show more ventricular enlargement than the control subjects. This is clearly not the case.

An atrophic process that occurred before the onset of psychosis would also be likely to affect the level of
premorbid functioning. Premorbid functioning should be the worst in those individuals with the largest ventricles; i.e., for those individuals who have suffered the most atrophy. The results of the present study indicate that the size of the lateral ventricles is not significantly related to level of premorbid functioning. Finally, if ventricle size reflects an early atrophic process, then other characteristics that tend to appear more frequently in severely afflicted persons might be expected to be found more in individuals who display the greatest signs of atrophy. The fact that no significant relationships were obtained between lateral ventricle size and either negative symptoms or smooth-pursuit eye movements further supports the contention that the size of the lateral ventricles probably does not reflect the extent of an early atrophic process or that ventricle size does not affect the level of functioning at the time of or before the first psychotic episode.

It is possible that some of the inconsistencies in the CT literature result from an oversimplified view of LVE. The use of cut-offs to distinguish enlarged ventricles from normal sized ventricles is based on the assumption that it is the absolute size rather than the amount of enlargement that has taken place that is the most appropriate measure of LVE. This would be the case if the obtained difference in the size of the ventricles between patients and control subjects was usually great or if normal variability in ventricle size were small.
There is, however, considerable variability in CT research findings concerning the prevalence and magnitude of ventricular dilation in psychotic patients. The median effect size is 1.7 VBR units (approximately 0.7 SD) and there is a large normal range in the size of lateral ventricles within studies (eight to 11 VBR units in the nine studies that report the range). This large normal range and small effect size suggests that, for any individual patient, moderate enlargement of the lateral ventricles would go unnoticed if the ventricles were small before the onset of psychosis. This contention is supported by the findings of three studies in which siblings, discordant for schizophrenia, were investigated (DeLisi et al., 1986; Revelly et al., 1982; Weinberger et al., 1981). In each of these studies, schizophrenic patients tended to have larger ventricles than their siblings but ventricular size in most of these patients was not considered enlarged according to the usual definition of enlargement (i.e., greater than the control mean plus two standard deviations).

Small effect sizes and large normal variability indicate that enlargement would be likely to appear as an overall shift in the distribution of ventricle size rather than a clustering of individuals in the enlarged ventricle range. The present findings provide tentative support for this notion and indicate a shift away from small lateral ventricles in schizophrenic patients. Those studies in which the distribution of VBR values was provided (e.g. Andreasen
et al., 1982b; Schulz et al., 1983; Weinberger et al., 1982) also indicate a relatively small overall shift in the distribution of ventricle sizes.

The present findings of consistently low correlations between any morphological anomaly (third or lateral ventricle size, or sulcal dilation) and premorbid adjustment, negative symptoms or disrupted SPEM is also consistent with this hypothesis. That is to say, a clinical measure associated with neuropathology would be more likely to be related to the amount of ventricular enlargement that has occurred rather than actual ventricle size. This contention was supported in a recent study by Bird, Levy and Jacoby (1986). In this study, a group of 50 normal individuals over the age of 60 received two CT scans over a two year period. A highly significant negative relationship was obtained between level of cognitive functioning and the amount of ventricular enlargement that occurred between the time of the first and second scans.

In summary, the magnitude of ventricular enlargement reported in most previous studies is small. Half of the previous studies report a difference of less than 0.7 SD between the patient and control group. There is also a relatively large range in ventricle size across both patient and control subjects. Because LVE in schizophrenic patients tends to be small and variability in ventricle size is normally large, large samples will be usually needed to obtain significant group differences. Enlargement for any
individual is likely to be in the form of a small shift in ventricle size. Reporting on clusters of patients in the enlarged ventricle range and using absolute ventricle size (VBR) as an index of ventricular enlargement is likely to oversimplify this complex issue.

Third Ventricle

The present results support the findings of eight of the ten previous studies and indicate significant enlargement of the third ventricle in the schizophrenic patient group. Third ventricle size was very similar across the remaining patient groups and the volunteer control group. This result suggests that enlargement of the third ventricle reflects a marker of susceptibility to schizophrenia and/or is associated with etiologically significant factors. The absence of dilation in the other patient groups (schizophreniform, bipolar, depressed) suggests that enlargement of the third ventricle may be specific to schizophrenia in first episode psychotic patients.

It is unlikely that the finding of enlargement in the schizophrenic group is due to a biased patient sample. The fact that no enlargement of the lateral ventricles or cortical sulci was detected in these patients suggests that this group did not have extensive atrophy. In addition, whereas there was a moderately high correlation between third and lateral ventricles for both control groups, this relationship was attenuated in the patient groups. This result suggests that there may be local rather than diffuse
brain changes. Furthermore, a wide range in level of premorbid adjustment, duration of first hospitalization, and age at onset suggests that these patients represent a wide cross section of schizophrenics.

The finding of enlargement of the third ventricle is also probably not due to a spuriously low mean ventricle size in the control sample. The volunteer control group comprised healthy individuals with no indication of psychiatric disturbance, drug/alcohol abuse, or chronic medical problems. The scanning procedures were identical for all participants and all CT measures were taken with the rater blind to the subjects' identity or group membership. Finally, high interrater reliability was obtained for all CT measures.

The studies of Nyback et al. (1982), Smith and Maser (1983), and Boronow et al. (1985) all include chronic patient groups and report effect sizes very similar to that obtained in the present study. In addition, the schizophreniform and bipolar and depressed groups in the present study had similar sized or slightly smaller mean third ventricle widths than the volunteer control group. These findings suggest that the brain changes that result in third ventricular enlargement in schizophrenia occur before the onset of psychotic symptoms. However, it is possible that a rapid change in ventricle size occurs with the onset of schizophrenia or with the administration of neuroleptic medication. Enlargement in other psychotic patient groups, if it occurs, is more likely to result from the illness process or long term treatment
effects. Further research, using repeated CT scans is needed to test these hypotheses. In addition, because no previous study has assessed third ventricle size in first episode psychotic patients, the present findings require replication before any firm conclusions can be drawn.

**Cortical Sulci**

No dilation of the cortical sulci was evident in any patient group relative to the volunteer control group. However, because few medical patients had any visible sulci, the volunteer control group showed sulcal dilation relative to the medical control group. The interpretation of previous reports of cortical atrophy in psychotic patients has been made difficult by a lack of consensus regarding the method of assessing sulcal dilation, and by insufficient procedural information. Within these limitations, most studies (10/13) indicate that cortical atrophy is present in schizophrenic patients. Of the ten studies in which significant findings were reported, eight used medical patients as control subjects. The present findings indicate that these results should be interpreted with caution. Nevertheless, the consistency of reported atrophy and the fact that two investigations in which normal control subjects were used report atrophy, suggests that a proportion of schizophrenic patients have sulcal dilation. The present findings suggest that this atrophy probably occurs after the onset of psychosis.
Control Groups

A review of previous CT studies (see Summary of CT Studies above) indicates that variability in the size of the ventricles in control subjects accounts for many of the inconsistencies in research findings. Some of this inconsistency is accounted for by the fact that medical control groups tend to have smaller ventricles than do groups of normal individuals. The results of the present study support this finding and clearly indicate the mean size of the third ventricle and cortical sulci is less in the medical control group than in the normal control group. If the medical patients are used as a standard of normal morphological brain measures, then the depressed patients, in addition to the schizophrenic individuals would have enlargement of the third ventricle and all patient groups would appear to have cortical atrophy. Whereas there is no significant enlargement of the lateral ventricles in any group relative to the medical patients, the difference between the schizophrenic and medical group approaches significance, \( t(59) = 1.46, .1 > p > .05 \).

There are a number of potential problems with medical control groups. Some medical disorders, including head trauma, hematoma, astrocytomas, and vasospasms, can result in edema and decreased ventricle size (Schneider et al., 1982). The fact that head trauma can result in decreased ventricle size is particularly noteworthy because a number of investigators include accident victims in their medical
control sample (e.g., Schulz et al., 1983; Nasrallah et al., 1982a, 1984).

Biases in medical control groups may also stem from the method of choosing "normal" scans. If scans that are described as showing large ventricles are excluded, an investigator may be rejecting those individuals who have normal but large ventricles. For example, three medical patients in the present study were described as having normal scans but having lateral ventricles that were large for the person's age. Lateral and third ventricle size for these three patients were within the range observed in the volunteer subjects.

It is also noteworthy that the distribution of VBR values in the medical control groups of most previous studies in which the subject distribution was provided are positively skewed. This is notably so in the two studies in which first episode schizophrenic patients were studied (Schulz et al., 1983; Weinberger et al., 1982). The present study and one previous investigation (Pearlson et al., 1984a) used healthy volunteers and found a normal distribution in ventricle size. This finding tentatively suggests that medical patient groups may be biased towards small lateral ventricles.

The practice of using CT scans from regular sized X-ray film when taking planimetry measures can potentially result in measurement error. Planimetry readings are taken from a vernier scale and are read to three decimal places. In the present study the range of area measurements of individual
lateral ventricles from regular (small) sized CT film is 0.001 to 0.019 (These measures are in arbitrary units of area). Normal variability in tracing small figures such as a single lateral ventricle is greater than ventricle size for small ventricles (approximately ± 0.003).

Because of the measurement variability associated with estimating the size of small ventricles from small sized scans, a number of investigators (Andreasen et al., 1982; Targum et al., 1983; Weinberger et al., 1979a, 1982) have classified some small ventricles as too small to measure and ascribed values of zero or 0.5 VBR units to them. However, ascribing low numbers to small ventricles is likely to underestimate the actual size. This could lead to spuriously low estimates of mean ventricle size.

The third ventricle is also susceptible to measurement error. Because the third ventricle is normally small (approximately 1mm to 7.5mm in the present study), and the image on regular sized CT film is reduced by a factor of approximately three, this measure is difficult to take accurately without some magnification. Incomplete reports of methodology in many of the studies of the third ventricle make it difficult to assess the influence of measurement error for this aspect of the brain.

Eight of the ten previous studies of third ventricle size in schizophrenia report significant enlargement. It is noteworthy that seven of the eight used medical patients as control subjects. The one study in which normal individuals
were used as control subjects (Nyback et al., 1982) reported the second largest mean third ventricle width and, when RDC diagnoses were used to define schizophrenic patients, the results were not significant. The present findings also indicate greater mean third ventricle width in the normal control group than those of the controls of eight of the ten previous studies and no enlargement when RDC diagnoses were used. This result, together with the present finding of a significant difference between medical patients and normal control subjects over third ventricle width suggests that the third ventricle in medical control patients may be smaller than those in healthy volunteers. If this is the case, then this factor could systematically bias results in favor of overestimating the prevalence of third ventricular enlargement in psychotic patient groups. Further studies are clearly needed to examine this possibility.

The clearest difference between the medical and normal control groups was obtained over ratings of cortical atrophy. An analysis of the data indicated that the absence of visible sulci in the medical patients was not due to the fact that some of these individuals received an injection of contrast medium before receiving a CT scan. Specified CT procedures (angle and width of CT cut and window and level settings on the CT scanner) were the same for the medical patients as they were for the other subjects in this study. Nevertheless, minor adjustments made to a CT scanner in order to increase the resolution of an area of interest can affect
CT findings with medical patients (Boronow et al., 1985). The cortical sulci, because they are small, are more likely to be obscured by variable scanning procedures than are larger brain structures. In addition, the fact that the volunteer control group does not show a similar pattern of ratings suggests that the findings from the medical control group do not accurately reflect the usual distribution of sulcal dilation in the normal population. It is, however, unclear what accounts for the dearth of visible sulci in the medical patients used in this study.

In summary, the present results indicate that medical control groups are potentially biased towards a small mean size of the third ventricle and fewer visible sulci. An analysis of previous studies of the lateral ventricles together with the present findings also suggests that lateral ventricle size may be smaller in medical control groups than in normal individuals. Possible causes of small ventricles in medical patients are pathologically small ventricles, subject selection biases, measurement error associated with estimating small structures, and differences in CT scanning procedures between research subjects and medical patients. Together the present results and the findings of previous investigations suggest that the prevalence of ventricle and sulcal enlargement in psychotic patients is exaggerated by abnormally small ventricles and sulci in medical control patients. There are no clear standards of normal ventricular and sulcal size at the present time (Maser & Keith, 1983).
Until normal variability is defined, researchers must be cognizant of the problems associated with using medical patients.

Conclusion

The present failure to detect lateral ventricular enlargement in psychotic patients is in conflict with the majority of previous results. Because measures in the present study were obtained from a unique patient sample (a representative cross section of first episode patients) and two independent control groups were used, it provides strong evidence that a significant proportion of patients do not have enlargement of the lateral ventricles at the onset of psychosis. In addition, the present result is in agreement with a number of recent studies in which no lateral ventricular enlargement was found. Together these negative findings emphasize a need for caution in drawing conclusions in this research area and strongly suggest that it is premature to conclude that a significant proportion of all schizophrenic patients have LVE. The present results also suggest that any changes in lateral ventricle size that do occur may follow rather than precede the onset of psychosis.

The finding of significant enlargement of the third ventricle in the present study provides strong evidence for brain anomalies at the onset of psychosis in a significant proportion of all schizophrenic patients. Because this finding was obtained in first episode patients, these results suggest that changes in the area of the third ventricle may
be a marker of susceptibility to schizophrenia, have etiological significance, or that changes occur rapidly with the onset of psychosis. No morphological anomalies in nonschizophrenic psychotic patients, on the other hand, suggest that previously reported brain anomalies in chronic nonschizophrenic patients may result from the illness process or from long term treatment. The fact that this finding was obtained whether a normal or medical control group was used, adds confidence to the assertion that brain changes occur in some schizophrenic patients before the onset of psychotic symptoms.

The suggestion of atrophy in the diencephalic region of the brain is intriguing because the surrounding structures are central to prevailing theories of neural functioning in schizophrenia (Neale & Oltmanns, 1981, pp 217-252). The present findings support the contention that structural brain changes in the midbrain are central to the schizophrenic deficit. However, in order to verify this hypothesis, it will be necessary to estimate the amount of ventricular enlargement that has occurred rather than use a measure of actual ventricle size. If this can be achieved, then research into the correlates of brain anomalies is likely to advance our knowledge about schizophrenia substantially.

The present study clearly indicates that no patient group has significant cortical atrophy. Methodological problems and insufficient procedural descriptions associated with previous studies make it difficult to compare findings.
However, the present results suggest that the sulcal dilation that was obtained in other studies may have resulted from the illness process or treatment effects or may result from biased control samples.

An important finding of the present study together with an analysis of past studies indicate that control groups chosen from radiology records may be biased towards small lateral and third ventricles and fewer visible sulci. If this is the case, many previous CT studies have overestimated the prevalence of morphological brain anomalies in psychotic patients. The present results clearly indicate that there is an immediate need for research into this problem.

The present findings bring into sharp focus both the exciting possibilities that this line of research holds and a clear warning that caution is needed in drawing conclusions at the present time. The complexity of research findings indicate a need for consensus on the methodology that is used and for more detailed subject and procedural information. As Boronow et al. (1985) noted, there is a growing need for a collaborative effort in the CT research of schizophrenia. In order to resolve some of the contradictions in the present literature, a co-operative effort is needed to conduct longitudinal research, involving repeated CT scans, a number of different patient groups, and careful monitoring of clinical status. This research must include normal individuals for comparison with the psychiatric patients and comparisons between medical and normal control groups.
References


psychological test performance, and computed tomography in schizophrenia. Psychiatry Research, 15, 49-62.


Archives of General Psychiatry, 33, 508-516.


Famuyiwa, O. O., Eccleston, D., Donaldson, A. A., & Garside,


Johnstone, E. C., Crow, T. J., Frith, C. D., Husband, J., &


Largen, J. W., Smith, R. C., Calderon, M., Baumgartner, R.,
Abnormalities of brain structure and density in
schizophrenia. Biological Psychiatry, 19, 991-1013.

Reversible cerebral atrophy caused by corticotrophin.
Lancet, 1, 1246.

hemispheres on computed tomograms. Journal of Computer
Assisted Tomography, 2, 471-476.

pursuit eye movements, schizophrenia and distraction.
Perceptual and Motor Skills, 50, 159-167.

Luchins, D. J. (1982). Computed tomography in schizophrenia:
Disparities in the prevalence of abnormalities. Archives
of General Psychiatry, 39, 859-860.

Lateral ventricular size psychopathology and medication
response in the psychoses. Biological Psychiatry, 19,
29-44.

findings in acute and chronic ward schizophrenics. Psychiatry Research, 17, 7-14.

development of schizophrenia. In L. C. Wynne, R. L.
Cromwell & S. Matthysse (Eds.), The nature of schizophrenia,
(401-429).


subtypes of chronic schizophrenia. Archives of General Psychiatry, 39, 774-777.


Pass, H. L., Salzman, L. F., Klorman, R., Kaskey, G. B., &


Shima, S., Kanba, S., Masuda, Y., Tsukumo, T., Kitamura, T.,


York State Psychiatric Institute.


Weinberger, D. R., Bigelow, L. B., & Kleinman, J. E.


Appendix A

Linear Measures of the Lateral Ventricles

1. Evan's Ratio is the width of the greatest span of the frontal horns divided by the greatest width of the internal diameter of the skull (AB/KL).

2. Cella Media Ratio is the narrowest width of the bodies of the lateral ventricles divided by the greatest internal diameter of the skull (IJ/KL).

3. Bicaudate Ratio is the width of the ventricles lying between the caudate nuclei divided by the internal diameter of the skull at the same level (GH/EE).

4. Frontal Horn Ratio is the width of the frontal horns divided by the internal diameter of the skull at the same level (AB/CD).

Horizontal sections of the brain at the level of the third (left) and lateral (right) ventricles. Arrows indicate linear measurements as described above.
APPENDIX B

Premorbid Status Interview and Scales

Interview

1. Did you belong to any groups, clubs, organizations, or athletic teams, including school organizations, while you were a teenager?
   Yes ___ (ask i)
   No ___ (ask iv)

   (i) What type of organization or group did you belong to?

   ____________________________________________
   How long were you a member? ______
   Did you hold an office or position of leadership in (any of) the group(s)?
   Yes ___ (ask ii)
   No ___ (ask iii)

   (ii) What position(s) did you hold? ________________
   How long did you hold this (these) position(s)?____

   (iii) Would you describe yourself as an active and interested member or were you not very active in this (any of these) organization(s)?
   Active/interested ___
   Not active___

   (iv) While you were a teenager, did you belong to a group of friends who did things together?
   Yes ___ (ask v)
   No ___ (ask vi)
(v) Would you describe yourself as an active and interested member?
Yes____
No____

(vi) Did you have any friends while you were a teenager?
(ALLOW SUBJECTS TO USE THEIR OWN DEFINITION OF FRIEND)
Yes____ (ask vii)
No____ (ask viii)

(vii) When you were a teenager, how many friends did you have? ________
How many of these people were close friends you could really trust or count on? ________

(viii) Would you describe yourself as generally prefering to be by yourself during your teenage years or did you prefer to be with other people?
With others____
Alone____

(ix) Did you prefer to be alone in the years before your teens?
Yes____
No____

2. Are you presently married or are you widowed, separated, divorced, or have you never been married?
married____ (ASK A & B)
widowed____ (ASK A) When did your husband/wife die?____
separated____ (ASK A) When did you and your husband/wife
divorced ____ (ASK A) When did you and your husband/wife separate? ____
never married ____ (SKIP TO 5)
A. When were you married? ____
B. Are you presently living with your husband/wife? ____
3. How many times have you been legally married? ____
   (IF MORE THAN ONCE ASK A)
   A. How long were you married the first (second) time? ____
4. (So you've never been/How many times have you been)
   Divorced? ____
5. Have you ever lived with someone for at least a year as though you were married? ____
6. Did you date as a teenager?
   Yes ____ (ASK A)
   No ____ (ASK B)
7. How many times did you date in an average month between the ages of 16 and ____ ? ____
8. Did you ever get engaged to be married when you were a teenager? ____
9. What is the longest period of time you have been in one relationship since you were a teenager? ____
   A. How old were you then? ____
   B. How often did you see this person in an average month? ____
10. Have you ever been engaged to be married since you were a teenager? ____
11. Have you ever had sexual relations with a man/woman (SAME
SEX AS EXAMINEE)?
Yes__ (ASK A)
No ___
A. Would you say you have had sexual relations more with
men or more with women? ____

12. Have you been sexually attracted to both men and women,
or only men or only women?
Not attracted to either__
Opposite sex only__
Both sexes__
Same sex only__

13. (IF NOT MARRIED) Are you living with someone now as
though you were married?
Yes__ For how long? ____
No___
Abbreviated Form of Phillips Premorbid Adjustment Scale
(Harris, 1975).

1. Premorbid Social-Personal Adjustment

61-70 A leader or officer in formally designated groups, clubs, or athletic teams in senior high school, vocational school, college, or in young adulthood.

51-60 An active and interested participant, but did not play a leading role in groups of friends, clubs, organizations, or athletic teams in senior high school, vocational school, college or in young adulthood.

41-50 A nominal member, but had no involvement in, or commitment to, groups of friends, clubs, organizations, or athletic teams in senior high school, vocational school, college or in young adulthood.

31-40 From adolescence through early adulthood, had only a few casual or close friends.

21-30 From adolescence through early adulthood, had no real friends, only a few superficial relationships or attachments to others.

11-20 From adolescence through early adulthood, quiet, seclusive, preferred to be by self; minimal efforts to maintain any contact at all with others.

1-10 No desire to be with playmates, peers, or others, from early childhood. Either asocial or antisocial.
2. Premorbid Sexual Adjustment

A. Married Presently or Formally

61-70 Married, only one marriage (or remarried only once as a consequence of death of spouse), living as a unit.

51-60 Married more than one time, maintained a home in one marriage for at least five years.

41-50 Married and apparently permanently separated or divorced without remarriage but maintained a home in one marriage for at least five years.

31-40 Same as (41-50) but maintained a home in one marriage for less than five years.

B. Single (30 years or over)

41-50 Has been engaged one or more times or has had a long term relationship (at least 2 years) involving heterosexual relations or apparent evidence for a "love affair" with one person, but unable to achieve marriage.

31-40 Brief or short-term heterosexual or social dating experiences with one or more partners, but no long lasting sexual experiences with a single partner.

21-30 Sexual and/or social relationships primarily with the same sex, but may have had occasional heterosexual contacts or dating experiences.

11-21 Minimal sexual or social interest in either men or women.
C. Single (under 30 years)

61-70 Has had at least one long-term "love affair" (minimum of six months to one year) or engagement, even though religious or other prohibitions or inhibitions may have prevented actual sexual union.

51-60 Brief or short-term heterosexual or dating experiences, "love affairs", with one or more partners, but no long lasting sexual experiences with a single partner.

41-50 Casual sexual or social relationships with persons of either sex, with no deep emotional meaning.

31-40 Sexual and/or social relationships primarily with the same sex, with no deep emotional meaning.

21-30 Minimal sexual or social interest in either men or women.
Question 7 from Gittleman-Klein Ratings of Premorbid Asociality (Gittleman-Klein & Klein, 1969)

Sociosexual Adjustment from 16 to 20 Years of Age.

61-70 Healthy interest in girls/boys; steady close relationship with sexual intercourse or sexual play. Went out with girls/boys regularly; steady close relationship with little or no sexual play.

51-60 Went out with girls/boys regularly; steady casual relationship with or without sexual play or intercourse.

41-50 Went out with girls/boys regularly; passing casual relationship with or without sexual intercourse.

31-40 Casual occasional contact with girls/boys with or without sexual intercourse or sexual play.

21-30 Interested in girls/boys, but never went out on dates.

11-20 Homosexual involvement only.

1-10 No sexual interest in either sex.
Appendix C
Symptom Checklists

Schizophrenia Inclusion Criteria

A. Phenomenology

DSM-III: At least one of 1 to 6.
RDC: A least 1 of 1 to 8 for probable, 2 for definite.

a. Somatic, grandiose, religious, nihilistic or other delusions without persecutory or jealous content.

b. Auditory hallucinations, running comment- any on patient or 2 or more voices conversing with each other.

c. Auditory hallucinations with no apparent relation to depression or elation.

DSM-III: More than 1 time & more than 1 or 2 words.

RDC: Spoken to the patient.

d. Incoherence, loose associations, illogical thinking or marked poverty of content of speech with blunted or inappropriate affect

delusions or hallucinations (or)
grossly disorganized/catatonic behavior

e. Delusion if accompanied by hallucinations

DSM-III: Delusions must have persecutory or jealous content.

RDC: Delusions of any type for at least one week.

f. Thought insertion, blocking or withdrawal
<table>
<thead>
<tr>
<th>g. Bizarre delusions, or delusions of control or influence, or other multiple delusions.</th>
<th>Yes</th>
<th>No</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>h. Hallucinations of any type throughout the day for several days or intermittent for one month</td>
<td>6b</td>
<td>7</td>
<td>8</td>
<td></td>
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</tbody>
</table>

B. Duration: ___ weeks

DSM-III: Prodromal + active phase + residual is at least 2 weeks.

RDC: Active phase is at least 2 weeks.

C. Deterioration from previous level of functioning in work, social relations or self-care.

D. Check YES if full (probable for RDC) depressive or manic syndrome is either NOT present or, for DSM-III, developed after any psychotic symptoms, or was brief in duration relative to the duration of psychotic symptoms.

E. Onset (prodromal or active) before age 45.

F. Not due to OBD or MR

Prodromal/Residual Symptoms (DSM-III)  

<p>| a. Social isolation or withdrawal | ___ | ___ |
| b. Marked impairment of role functioning | ___ | ___ |
| c. Markedly peculiar behavior | ___ | ___ |
| d. Marked impairment of personal hygiene | ___ | ___ |
| e. Blunted, flat or inappropriate affect | ___ | ___ |
| f. Digressive, vague, overelaborate, circums- stantial, or metaphorical speech | ___ | ___ |
| g. Odd or bizarre ideation, magical thinking | ___ | ___ |</p>
<table>
<thead>
<tr>
<th>Schizophrenia Subtypes</th>
<th>DSM-III</th>
<th>RDC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes No</td>
<td>Yes No</td>
</tr>
</tbody>
</table>

1. Paranoid: Persistence or preoccupation with one or more of
   a. Persecutory delusions
   b. Grandiose delusions
   c. Delusions of jealousy
   d. Hallucinations with persecutory or grandiose content

2. Disorganized (Hebephrenic)
   RDC: a., b. or c., and d. are required.
   a. RDC: Marked formal thought disorder
      (incoherence, loose association, illogical thinking, poverty of content of speech, neologisms)
      DSM-III: Frequent incoherence
   b. RDC: Affect that is shallow, silly or incongruous
      DSM-III: Blunted, inappropriate or silly affect
   c. Fragmentary delusions or hallucinations with content not organized into a coherent theme
   d. Not associated with marked emotional turmoil except during exacerbation

3. Catatonic: Clinical picture is dominated by any of
   a. Catatonic stupor
   b. Catatonic negativism
   c. Catatonic rigidity
   d. Waxy flexibility
   e. Catatonic excitement
4. Undifferentiated (or Mixed): Illness meet\textsuperscript{+}\textsubscript{+} the criteria for more than one subtype or for none

Yes No Yes No

5. Residual
Schizoaffective Disorder: RDC

This category includes forms in which the schizophrenic symptoms are brief in duration compared to the affective symptoms or the converse.

1. Diagnostic Criteria

A. a) Subject must fulfill the criteria for probable or definite manic or depressive syndrome (symptoms A, B, and C from the respective checklists)

b) Signs of illness must last at least one week from the onset of a noticeable change in the patient's usual condition

c) Affective symptoms overlap temporarily to some degree with the active period of schizophrenic-like symptoms (delusions, hallucinations, thought disorder, bizarre behavior).

B. At least one of the following symptoms suggestive of schizophrenia is present during the active phase of illness.

a) Delusions of control or influence, or thought broadcasting, insertion, or withdrawal.

b) Nonaffective hallucinations of any type throughout the day for several days or intermittently throughout a one week period.

c) Auditory hallucinations in which either a voice keeps up a running commentary on the subject's behavior or thoughts, or two or more voices converse with each other.

d) At sometime during the period of illness, more than one week with no prominent depressive or manic symptoms but had delusions or hallucinations (typical depressive delusions such as delusions of guilt, sin, poverty, nihilism, self-depreciation or hallucinations of similar content are not included).

e) Several definite instances of marked formal thought disorder accompanied by either blunted or inappropriate affect, delusions or hallucinations of any type, or grossly disorganized behavior. For mania only, this must occur during a one week interval when no prominent
f) Preoccupation with a delusion or hallucination to the relative exclusion of other symptoms or concerns (other than typical depressive delusions and hallucinations.)

2. **Mainly Schizophrenic if either A or B.**

   A. Core schizophrenic symptoms listed under 1.B. above were present for at least one week in the absence of manic or depressive features.

   B. Prior to the onset of depressive features, the patient exhibited the following features which are often associated with schizophrenia: Social withdrawal, impairment of occupational functioning, eccentric behavior, emotional blunting, or unusual thoughts or perceptual experiences.

3. **Mainly affective if both A and B.**

   A. Schizophrenic-like symptoms listed under 1.B. above followed manic or depressive symptoms and were never present for at least one week in the absence of manic or depressive symptoms.

   B. Good premorbid social and occupational functioning

4. **Other, does not clearly fit 2 or 3.**
<table>
<thead>
<tr>
<th>Manic Episode Inclusion</th>
<th>DSM-III YES NO</th>
<th>RDC YES NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Elevated, expansive or irritable mood that is prominent and persistent.</td>
<td></td>
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<tr>
<td>B. Duration: ___ weeks, YES = 1 week or more.</td>
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<td></td>
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<tr>
<td>C. DSM-III and RDC: 3/7 symptoms needed if mood is expansive 4/7 if irritable.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Increased social or sexual activity or restlessness.</td>
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<tr>
<td>2. Increased talkativeness or pressure to talk.</td>
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<tr>
<td>3. Flight of ideas or racing thoughts.</td>
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<tr>
<td>4. Inflated self-esteem.</td>
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<td>5. Decreased need for sleep.</td>
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<tr>
<td>6. Distractible.</td>
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<td>7. Excessive involvement in activities without recognizing the high potential for painful consequences.</td>
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<td></td>
</tr>
<tr>
<td>D. DSM-III: Check YES if before the episode developed or after it remitted there were NO mood incongruent delusions or hallucinations or bizarre behavior. RDC: Check YES if criteria for schizoaffective disorder are NOT met.</td>
<td></td>
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<tr>
<td>E. Check YES if disorder is NOT superimposed on schizophrenia, paranoid disorder, or organic mental disorder.</td>
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</table>
Mania with Psychotic Features: DSM-III

1. **Mood Congruent**

   a. Delusions or hallucinations whose content is entirely consistent with themes of inflated worth, power, knowledge, identity or special relationship to a deity or famous person.

   YES NO

   b. Flight of ideas without apparent awareness by the individual that the speech is not understandable.

   YES NO

2. **Mood Incongruent** (either a or b below)

   a. Delusion or hallucinations whose content does not involve themes of either inflated worth, power, knowledge, identity, or special relationship to a deity or famous person. Included are persecutory delusions, thought insertion, and delusions of control, whose content has no apparent relationship to the themes noted above.

   YES NO

   b. Any of the following catatonic symptoms: stupor, mutism, negativism, posturing.

   YES NO
<table>
<thead>
<tr>
<th>Major Depressive Episode Inclusion Criteria</th>
<th>DSM-III YES NO</th>
<th>RDC YES NO</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Prominent persistent dysphoric mood or</strong>&lt;br&gt;<strong>loss of interest or pleasure.</strong></td>
<td>__ __</td>
<td>__ __</td>
</tr>
<tr>
<td><strong>B. Duration ____ weeks.</strong></td>
<td>___ ___</td>
<td>___ ___</td>
</tr>
<tr>
<td>DSM-III: 2 weeks or more.</td>
<td>___ ___</td>
<td>___ ___</td>
</tr>
<tr>
<td>RDC: 2 weeks or more for definite, 1 week for probable.</td>
<td>___ ___</td>
<td>___ ___</td>
</tr>
<tr>
<td><strong>C. DSM-III: 4/8 symptoms needed.</strong>&lt;br&gt;RDC: 5/8 symptoms for definite, 4/8 for probable.</td>
<td>___ ___</td>
<td>___ ___</td>
</tr>
<tr>
<td>1. Poor/increased appetite with weight loss or gain (1lb per week or 10lb in a year)</td>
<td>___ ___</td>
<td>___ ___</td>
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<tr>
<td>2. Insomnia or hypersomnia</td>
<td>___ ___</td>
<td>___ ___</td>
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<tr>
<td>3. Loss of energy or fatigue.</td>
<td>___ ___</td>
<td>___ ___</td>
</tr>
<tr>
<td>4. Loss of interest, pleasure or sex drive.</td>
<td>___ ___</td>
<td>___ ___</td>
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<tr>
<td>5. Feelings of worthlessness, guilt or self reproachful.</td>
<td>___ ___</td>
<td>___ ___</td>
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<tr>
<td>6. Diminished ability to think, concentrate or indecisiveness.</td>
<td>___ ___</td>
<td>___ ___</td>
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<tr>
<td>7. Recurrent thoughts of death, suicide or suicidal behavior.</td>
<td>___ ___</td>
<td>___ ___</td>
</tr>
<tr>
<td>8. Agitation or retardation.</td>
<td>___ ___</td>
<td>___ ___</td>
</tr>
<tr>
<td><strong>D. DSM-III: Check YES if before the episode developed or after it remitted there were NO mood incongruent delusions or hallucinations or bizarre behavior.</strong></td>
<td>___ ___</td>
<td>___ ___</td>
</tr>
<tr>
<td>RDC: Check YES if criteria for schizoaffective disorder is NOT met.</td>
<td>___ ___</td>
<td>___ ___</td>
</tr>
<tr>
<td><strong>F. Check YES if the disorder is NOT superimposed on schizophrenia paranoid disorder, OBD, or uncomplicated bereavement.</strong></td>
<td>___ ___</td>
<td>___ ___</td>
</tr>
<tr>
<td><strong>G. Patients sought help; took medications or was dysfunctional during episode.</strong></td>
<td>___ ___</td>
<td>___ ___</td>
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</table>
Subclassification of Major Depressive Episode

1. Psychotic DSM-III  
   Gross impairment in reality testing (e.g. delusions or hallucinations) or
   
   Depressive stupor (mute or unresponsive)

   a. Mood congruent psychotic features: 
      Delusions or hallucinations whose content is entirely consistent with themes of personal inadequacy, guilt, disease, death, nihilism, or deserved punishment.
   
   b. Mood incongruent psychotic features: 
      Delusions or hallucinations with themes other than the above (e.g. persecutory delusions, thought insertion, thought broadcasting, and delusions of control).

2. Psychotic RDC
   
   a. Criteria for schizoaffective disorder are not met.
   
   b. One of the following: 
      Delusions 
      Hallucinations 
      Depressive stupor (mute or unresponsive)

3. Melancholic DSM-III
   
   Loss of pleasure in almost all activities
   
   Lack of reactivity to usually pleasurable activities.
   
   Three of the following:
   
   a. Depressed mood distinctly different from that associated with the death of a loved one.
   
   b. Depression worse in the morning.
   
   c. Early morning wakening (2 hours early)
   
   d. Marked psychomotor retardation or agitation.
   
   e. Significant anorexia or weight loss.
4. Endogenous RDC

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>One symptom from a. plus four symptoms from a. and b. for probable, six for definite.</td>
<td></td>
</tr>
<tr>
<td>a. Depressed mood distinctly different from that associated with the death of a loved one.</td>
<td></td>
</tr>
<tr>
<td>Lack of reactivity to environmental changes.</td>
<td></td>
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<tr>
<td>Mood worse in the morning.</td>
<td></td>
</tr>
<tr>
<td>Pervasive loss of interest or pleasure.</td>
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</tr>
<tr>
<td>b. Self reproach or excessive/inappropriate guilt.</td>
<td></td>
</tr>
<tr>
<td>Early morning wakening or middle insomnia.</td>
<td></td>
</tr>
<tr>
<td>Psychomotor retardation or agitation.</td>
<td></td>
</tr>
<tr>
<td>Poor appetite.</td>
<td></td>
</tr>
<tr>
<td>Weight loss (2lb/week for several weeks or 20lb year when not dieting)</td>
<td></td>
</tr>
<tr>
<td>Loss of interest/pleasure or decreased sex drive.</td>
<td></td>
</tr>
</tbody>
</table>

5. Primary RDC

| Episode NOT preceded by other nonaffective psychiatric disorder, serious physical illness or physical illness often associated with psychological symptoms. | |

6. Secondary RDC

| Episode preceded by one of the above. | |

7. Incapacitating RDC

| One of the following; a. Unable to function at work or school, or to take care of the house for at least one week (or, if was hospitalized, was so impaired that obviously could not work). | |
| b. Unable to feed or clothe himself or maintain minimal personal hygiene without help. | |
8. Agitated RDC

Two of the following symptoms are present for at least several days;

- a. Pacing
- b. Handwringing
- c. Unable to sit still
- d. Pulling or rubbing on hair, skin, clothing, or other objects
- e. Outbursts of complaining or shouting
- f. Talks on and on or cannot seem to stop talking

9. Retarded RDC

Two of the following symptoms are present for at least one week;

- a. Slowed speech
- b. Increased pauses before answering
- c. Low or monotonous speech
- d. Mute or markedly decreased amount of speech
- e. Slowed body movements

10. Situational RDC

An event or situation seems likely to have contributed to the depressive episode.

11. Simple RDC

No significant signs of psychiatric disturbance in the previous year, other than those associated with the affective illness.

Often begins with phobias, panic attacks, or excessive somatic concern.
DSM-III Diagnosis

**Axis I. Clinical syndromes:**


**Axis II. Personality disorders:**

**Axis III. Physical disorders:**

**Axis IV. Severity of psychosocial stressors:**

This rating should be based on the clinician’s assessment of the stress an average person in similar circumstances with similar sociocultural values would experience from the particular psychosocial stressors. Consider

a. the amount of change in the individual’s life caused by the stressor.

b. the degree to which the event is desired.

c. the degree to which the event is under the individual’s control.

d. the number of stressors.

The rating should not be based on the individual’s vulnerability to the particular stressor. In most cases the stressor will have occurred within the year prior to the onset of the current episode. In some instances it could be the anticipation of a future event, e.g., retirement.

<table>
<thead>
<tr>
<th>Code</th>
<th>Term</th>
<th>Adult Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>No apparent stressor</td>
</tr>
<tr>
<td>2</td>
<td>Minimal</td>
<td>Minor violations of the law; small bank loan</td>
</tr>
<tr>
<td>3</td>
<td>Mild</td>
<td>Argument with neighbor, change in work hours</td>
</tr>
<tr>
<td>4</td>
<td>Moderate</td>
<td>New career, death of a close friend, pregnancy</td>
</tr>
<tr>
<td>5</td>
<td>Severe</td>
<td>Serious illness in self or family, major financial loss, marital separation, birth of a child</td>
</tr>
<tr>
<td>6</td>
<td>Extreme</td>
<td>Death of a close relative, divorce</td>
</tr>
<tr>
<td>7</td>
<td>Catastrophic</td>
<td>Concentration camp experience, devastating natural disaster</td>
</tr>
<tr>
<td>8</td>
<td>Unspecified</td>
<td>No information or not applicable</td>
</tr>
</tbody>
</table>
**Axis V. Highest level of adaptive functioning in the past year**

Adaptive functioning is a composite of three major areas: social relations, occupational functioning, and use of leisure time. In making the rating, special attention should be paid to social relations.

<table>
<thead>
<tr>
<th>Code</th>
<th>Term</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Superior</td>
<td>Unusually effective functioning in all three areas</td>
</tr>
<tr>
<td>2</td>
<td>Very good</td>
<td>Better than average functioning in all three areas</td>
</tr>
<tr>
<td>3</td>
<td>Good</td>
<td>No more than slight impairment in either social or occupational functioning</td>
</tr>
<tr>
<td>4</td>
<td>Fair</td>
<td>Moderate impairment in either social or occupational functioning, or some impairment in both</td>
</tr>
<tr>
<td>5</td>
<td>Poor</td>
<td>Marked impairment in either social relations or occupational functioning, or moderate impairment in both</td>
</tr>
<tr>
<td>6</td>
<td>Very poor</td>
<td>Marked impairment in both social relations and occupational functioning</td>
</tr>
<tr>
<td>7</td>
<td>Grossly impaired</td>
<td>Gross impairment in virtually all areas of functioning</td>
</tr>
<tr>
<td>8</td>
<td>No information</td>
<td></td>
</tr>
</tbody>
</table>

**RDC Diagnosis**

RDC diagnosis

---

**Notes:** Use the space below for any qualifying information or important details.
Possible Diagnoses

DSM-III

Schizophrenia: Paranoid, Disorganized, Catatonic, Undifferentiated, Residual, Atypical, Schizophreniform.

Brief reactive psychosis.

Bipolar disorder: Manic, Depressed, Mixed, Atypical.

Major depressive disorder, Atypical depression.

Paranoia: Shared paranoid disorder, Acute paranoid disorder, RDC (Note: Diagnoses can be probable or definite.)

Schizophrenia: Paranoid, Disorganized, Catatonic, Undifferentiated, Residual.

Schizoaffective Disorder: Manic, Depressed.

Depressive syndrome superimposed on residual schizophrenia.

Manic Disorder.

Major Depressive Disorder: Primary, Secondary, Recurrent unipolar, Psychotic, Incapacitating, Endogenous, Agitated, Retarded, Situational, Simple.

Unspecified Functional Disorder.
Appendix D

Consent Forms

Consent Form 1

Name__________________________

I agree to participate in this study of health and social problems. I understand that my involvement will include interviews, the completion of questionnaires, and the review of my health records. I also understand that I may be asked to participate again in this study in 9 months and in 18 months and that I may be invited to participate in another part of this study in which my physical reactions to simple tones and lights will be measured. This separate section of the study, dealing with physical reactions, will be explained in more detail later and I can decide at that time whether or not I wish to take part in it. I understand that information that will be helpful to my care or treatment will be conveyed to my (patient's name:____________________) therapist. I understand that publications that are the products of this study will contain reports about groups of persons and that no individual will be identifiable. Finally, I understand that I am (or [patient's name]____________________ is) free to withdraw from this project at any time; this will in no way affect any health or social services that I am (or [patient's name]____________________ is) receiving.

Signature: (Parent or guardian must sign if individual is under 16 or if unable to give valid consent)____________________
Consent Form 2 (Psychophysiological Testing)

I have been asked to participate in a study in which my body's responses will be recorded while I perform several simple tasks. These tasks include comfortably relaxing while listening to brief tones, watching brief flashes of light, and watching a spot of light move back and forth on a screen and attempting to produce similar movements by turning a knob back and forth. The responses of my body that will be recorded include my eye movements, heart beat, brain waves, and the activity of my sweat glands. To make these recordings, sensors will be attached to my arms, legs and head, but no danger or discomfort to myself is involved. In another part of this study, a drop of oil, similar to cooking oil, will be placed on my skin near each of my fingernails and a photograph of my skin will be made. I understand that these tests will not influence my medical care or treatment, and that all the information obtained in this project will be kept confidential and used only for the purposes of this study. By signing this form, I agree to participate, although I realize that I am free to withdraw from this study at any time without prejudice to current and future care and treatment.

Signature ____________________  Witness ____________________

Print name ____________________

Date ________________

I.D. number __________
Consent Form 3a (CAT Scan; Patient)

You have been asked to participate in a study in which pictures of your head will be made with a machine called a CAT scanner or body image scanner. A CAT scan is very much like an X-ray and makes it possible to look at the structure or organs inside a person's body. Having a CAT scan made is a routine hospital procedure that takes about 20 minutes. There is nothing unpleasant about a CAT scan; all you have to do is lie still on a bed while the machine takes the picture. Like an X-ray, a CAT scan involves exposure to some radiation. The purpose of our study is to determine if there are features of the brain that are related to the kinds of problems that you have been having or that are related to the measures of eye-movement, sweat gland, and brain wave activity that we have recorded from you earlier in the MAP study. Information that will be helpful to your care or treatment may be conveyed to your therapist (or to ________). Otherwise, all the information obtained in this project will be kept confidential and used only for the purposes of this study. You are free to ask questions about the procedure at any time. By signing this form, you agree to participate, although you are free to withdraw from this study at any time without prejudice to current and future care and treatment.

Witness____________________ Signature____________________
Date______________ ID Number____________________
Consent Form 3b (CAT Scan; Control)

You have been asked to participate in a study in which pictures of your head will be made with a machine called a CAT scanner or body image scanner. A CAT scan is very much like an X-ray and makes it possible to look at the structure or organs inside a person's body. Having a CAT scan made is a routine hospital procedure that takes about 20 minutes. There is nothing unpleasant about a CAT scan; all you have to do is lie still on a bed while the machine takes the picture. Like an X-ray, a CAT scan involves exposure to some radiation. The purpose of our study is to determine if there are features of the brain structure that are related to different kinds of psychiatric disorder and to the findings from the eye-movement, sweat gland, and brain wave tasks you completed earlier in the study. Of course, we need people who do not have psychiatric disorders, such as yourself, in our study for comparison with those who do. Information that may be helpful to your health may be conveyed to your personal physician ________________, (or to __________________). Otherwise, all the information obtained in this project will be kept confidential and used only for the purposes of this study. You are free to ask questions about the procedure at any time. You have the right to refuse to participate or withdraw from the study at any time.

Witness_________________ Signature____________________
Date_________________ ID Number____________________
Appendix E

Screening Schedule for Patients

WHO collaborative study on determinants of outcome of severe mental disorder.

Name of Facility: ____________________________

Person who made this assessment:

Name: ____________________________

Position: ____________________________

Patient's research number (to be completed by research team): ___/___/___

Date when this form was filled in: ___/___/___

Sex of patient (1 = male, 2 = female): ___

A. 1) Is this patient's age below 15 or above 54? Yes No

2) Does this patient at present live outside the catchment area defined for this study? Yes No

B. Is there evidence that this patient has any of the following problems? (see guidelines)

1) Clinically manifest organic cerebral disorder (e.g., infectious, parasitic, cerebrovascular, toxic, epilepsy, brain injury, etc.) Yes No

2) Severe mental retardation (i.e., IQ less than 50, or clinically manifest as such) Yes No

3) Severe alcohol dependence manifest in:
   Presence of marked withdrawal symptoms Yes No
   Presence of alcohol encephalopathy or Korsakov's psychosis Yes No
   History of acute alcohol psychosis (delirium tremens or hallucinosis) within the last year Yes No

4) Demonstrable dependence on either:
   i) Opium or derivatives or Yes No
   ii) Barbiturates


C. During the past one year has the patient presented any of the following?

1) Hallucinations or pseudohallucinations in any modality. Yes No

2) Delusions. Yes No

3) Marked thought and speech disorder (e.g., incoherence, irrelevance, thought blocking, neologisms, incomprehensibility of speech) other than simple retardation or acceleration. Yes No

4) Marked psychomotor disorder (e.g., negativism mutism or stupor; catatonic excitement; constrained attitudes or unnatural postures maintained for long periods) other than simple retardation or acceleration. Yes No

5) Emergence or marked exacerbation of bizarre and grossly inappropriate behavior (e.g., talking or giggling to self, acts incomprehensible to others, loss of social constraints, etc.) Yes No

D. During the past one year, has the patient presented a definite change of personality and behavior manifested in any of the following?

1) Marked reduction or loss of interests, initiative and drive, leading to serious deterioration of the performance usual activities and tasks. Yes No

2) Emergence of or marked exacerbation of social withdrawal (active avoidance of communication with other people). Yes No

3) Severe excitement, purposless destructiveness or aggression. Yes No

4) Episodic or persistent states of overwhelming fear or severe anxiety. Yes No

5) Gross and persistent self neglect. Yes No

E. Has the patient been admitted to any hospital, or otherwise diagnosed or treated for a psychotic disorder, similar to or continuous with the present illness, at any time before the current contact or spell of treatment for psychiatric disorder? (Do not consider contacts for minor problems long ago, like attendance to a child guidance clinic for conduct or emotional disorders disorder, etc.) Yes No
F. Diagnosis of the patient made at the facility:

__________________________________________________________________________  __/__/__/__/__
__________________________________________________________________________  __/__/__/__/__

G. Conditions for inclusion in the study:

1) All replies to questions in section A, B1, B2, and E must be "No" and there should be at least one "Yes" in section C or two "Yes"s in section D.

OR

2) If the patient does not meet the criteria specified in 1) the patient may still be included if the rater has other reasons to believe that he/she may be suffering from a schizophrenic disorder. Such reasons should be specified below:

Other reasons for inclusion____________________________________

______________________________________________________________

TO BE COMPLETED BY RESEARCH TEAM:

CONCLUSION: This patient is INCLUDED (ring as appropriate) EXCLUDED
Guidelines for Use of the Screening Schedule

General

The screening schedule should be filled in by a psychiatrist or by another investigator with relevant experience qualifying him to apply reliably the screening criteria. Any user of the schedule, whether a member of the project team or not, should be given brief but adequate training in the use of the instrument. The chief investigator should check the adequacy of such training by discussion and by a joint screening exercise on a few cases.

The screening schedule will be filled in on the basis of information from: (i) a brief interview with the patient, (ii) a brief interview with the informant, (iii) admission or outpatient notes, (iv) any combination of these. Considering the limited access to some kinds of information at the screening stage, the investigator should preferably err on the overinclusive side and not exclude cases which raise doubts or cannot be adequately assessed with the screening criteria. Such patients can be excluded, if necessary, after a more detailed assessment with the PSE and the Psychiatric History Schedule.

Organic cerebral disorder is considered to be present if there is clear evidence at the time of examination or in the last three months of any of the following: (i) marked disturbance of memory, (ii) episodes of clouding of consciousness or confusion manifested in impaired orientation in place and/or time, (iii) focal symptoms like aphasia.
Organic cerebral disorder is also considered present if in the last one year there was: (i) a history of head injury followed by coma lasting for eight hours or more, or by post-traumatic amnesia lasting for 72 hours or more, (ii) two or more epileptic fits, or evidence that the patient has been on anti-convulsant medication for more than six months.

Severe alcohol dependence is presumed to be present if with regard to the last 12 months there is evidence of excessive alcohol intake and any of the following: (i) withdrawal symptoms (tremor, sweating, palpitations, insomnia, irritability) on cessation of drinking, (ii) history of alcohol psychosis in the past year, (iii) symptoms of alcohol encephalopathy or polyneuritis. Caution should be exercised in cases of suspected alcohol hallucinosis accompanied by clear consciousness: such patients should be provisionally included.

The diagnosis to be entered is the one made at the facility prior to the assessment of the patient by the project team. The project diagnosis made after the assessment should be recorded on the Present State Exam (PSE).
Appendix F

Screening Schedule for Volunteer Control Subjects

1. Have you ever received treatment for emotional or psychiatric illness?
   
   No__
   
   Yes Nature of problem__________________________
   What kind of treatment (inc. meds or hosp)__________________________

2. Have your mother, father, brothers, sisters, or children ever received treatment for emotional or psychiatric illness?
   
   No__
   
   Yes Nature of relative's problem__________________________
   Relative_______________
   Treatment_______________

3. Have you ever had a drinking problem or has anyone ever suggested that you had a drinking problem?
   
   No__
   
   Yes Treatment__________________________

4. Have your mother, father, brothers, sisters, or children ever had a drinking problem?
   
   No__
   
   Yes Who__________________________
   Extent__________________________
   Treatment__________________________

5. Do you have any disorder affecting your brain or spinal cord, long term pain disorder, or long term physical disorder (e.g., epilepsy, chronic back pain, arthritis, diabetes, hypertension, multiple sclerosis, stroke, etc)

   No__
   
   Yes Specify__________________________
Guidelines for Use of the Screening Schedule

A. Exclusion Criteria

1. Patients who have received medication (other than minor tranquilizers for psychiatric problems) or who have been hospitalized because of an emotional or psychiatric illness.

2. Patients who are alcoholics or are recovered alcoholics.

3. Patients whose parents, siblings, or children have received medication or been hospitalized because of emotional or psychiatric illness, are alcoholics or recovered alcoholics, or are perceived as being in need of treatment for alcoholism.

4. Patients with neurological disorders such as epilepsy, multiple sclerosis, stroke, vestibular disorders (including nystagmus), or dementia.

5. Patients whose vision cannot be normalized with corrective lenses; e.g., patients with cataracts, glaucoma, or detached retinas.

6. Patients who would have difficulty participating in the study because of chronic pain; e.g., patients with chronic back pain, cancer, or arthritis.

7. Patients who are receiving treatment for pregnancy or postpartum care.

8. Patients with chronic physical illness such as diabetes, Crohn's disease, chronic obstructive lung disease, hypertension, etc.

B. Inclusion Criteria

1. Age: 15 to 40 years of age.

2. Persons are permanent or temporary residents of the cities of Richmond or Vancouver (minimum of six months residency).

3. People who have sought treatment for preventative services such as immunizations; well baby check-up; annual pap smear; physical examination; family planning; and diet counselling; or for medical management of a short episode of illness or any acute condition such as flu.

4. Parents of children brought into treatment either for
Appendix G

Negative Symptom Ratings


36. Anergia
Do you seem to be slowed down in your movements, or have too little energy recently? How much has it affected you? (Do things seem to be moving too fast for you?)

RATE SUBJECTIVE ANERGIA AND RETARDATION
0 = Symptom not present to a significant degree.
1 = Marked subjective listlessness and lack of energy.
2 = Marked retardation and underactivity (Irrespective of time during month)

54. Lost Emotions
Do you feel you have lost your emotions in some way? (That you are empty of all feelings, incapable of reacting emotionally?) (Is this a definite change, or have you always been like that?) (How do you explain it?)

RATE LOST EMOTIONS: Rate only subjective loss of affect, i.e., subject can remember being able to react emotionally, though this might have been months or even years ago.
0 = Symptom not present to a significant degree.
1 = Symptom definitely present during the past month but less than 50% of the time.
2 = Symptom present more than 50% during the past month.

58. Thought Block
Do you ever experience your thoughts stopping quite unexpectedly so that there are none left in your mind, even when your thoughts were flowing freely before? (What is that like?) (How often does that occur? What is it due to?) Do your thoughts ever seem to be taken out of your head, as though some external person or force was removing them? (Can you give an example?) (How do you explain it?)
RATE THOUGHT BLOCK OR WITHDRAWAL.

1 = Thought block. Do not include if due to anxiety or lack of concentration; only if it occurs totally unexpectedly when thoughts are flowing freely. One single occasion is not sufficient for a rating. Be very critical in rating this symptom.

2 = Delusional explanation that thoughts are withdrawn.

107. Social Impairment

Of all the problems that you have told me about, which one affects you the most? How much does it interfere with your work or your relationships with other people? (Have you actually been out of work, or been unable to do the housework, or go shopping, travelling, etc., during the past month?) (Have the symptoms impaired your efficiency in any other way?)

RATE SOCIAL IMPAIRMENT DUE TO PSYCHOTIC CONDITION.

0 = No neurotic or psychotic symptoms present.

1 = Psychotic symptoms present but little diminution of subject's efficiency or interference with everyday activities.

2 = Psychotic symptoms interfere with subject's efficiency to a moderate extent but are not incapacitating, e.g., subject neglects housework or can't enjoy leisure activities or social relationships, or finds work-efficiency reduced. Subject does not, however, stop work altogether or completely neglect the household.

3 = Subject severely incapacitated by psychotic symptoms: had to have at least a week off work during the past month; was housebound for a week or more; was actively withdrawn from all social relationships, etc. The subject does not have to be totally incapacitated for the whole month for this rating to be made, but impairment has to be very severe.

108. Self Neglect. (during the interview)
Cleanliness, shaven, make-up, state of hair and clothes.

RATE SELF NEGLECT.

0 = Normal
1 = Fairly severe.
2 = Very severe.
110. Slowness and Underactivity (during the interview)  
Sits abnormally still, walks abnormally slowly, delay in performing movements.

RATE SLOWNESS.  
0 = Symptom absent  
1 = Present in fairly severe degree, or very severe but intermittent during the interview.  
2 = Present in very severe degree and almost continuous during the interview.

119. Catatotonic Movements (during the interview)  
Negativism: does the opposite of what is asked.  
Ambitendence: begins to take proffered hand, then withdraws etc.  
Echopraxia: imitates examiner's movement.  
Flexibilitas cerea: arm remains where it is put for at least 15 seconds.  
Mitgehen: excessive cooperation in passive movement.  
Echolalia: imitates words and phrases with the same intonation and inflection of voice.)

0 = Symptom absent.  
1 = Present in fairly severe degree, or very severe but intermittent during interview.  
2 = Present in very severe degree and almost continuous during the interview.

128. Blunted Affect (during interview)  
Expressionless face and voice, uniform blunting whatever the topic of conversation, indifference to distressing topics, whether delusional or normal.

0 = Symptom absent.  
1 = Blunting not uniform, e.g., at times responds affectively but at other times is markedly flat; or responds with some evidence of affect, but definitely less than expected.  
2 = Severe and uniform blunting.

129. Incongruity of Affect (during the interview)  
Incongruity of affect (emotion is shown, but not congruent with topic).

0 = Symptom absent.  
1 = Present in fairly severe degree, or very severe but intermittent during the interview.  
2 = Present in very severe degree and almost continuous during the interview.
130. **Slow Speech**

Slow speech (long pauses before answering, long pauses between words).

0 = Symptom absent.
1 = Present in fairly severe degree, or very severe but intermittent during the interview.
2 = Present in very severe degree and almost continuous during the interview.

133. **Muteness**

0 = Normal speech.
1 = Almost mute.
2 = Totally mute.

134. **Restricted Quantity of Speech**

Subject frequently fails to answer, questions have to be repeated, restricted to minimum necessary, no extra sentences, no additional comments.

0 = Symptom absent.
1 = Present in fairly severe degree, or very severe but intermittent during the interview.
2 = Present in very severe degree and almost continuous during the interview.

138. **Poverty of Content of Speech**

The subject talks freely but so vaguely that little information is given in spite of the number of words used: rambles on without coming to a point; may wander far from original theme. Exclude incoherence or flight of ideas. Rate only if severe and always give written example.

0 = Symptom absent.
1 = Present in fairly severe degree, or very severe but intermittent during the interview.
2 = Present in very severe degree and almost continuous during the interview.
### Appendix H

#### Correlations between Age and Each CT Measure

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>#</th>
<th>Lateral Vent</th>
<th>Third Vent</th>
<th>Cortex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia</td>
<td>31</td>
<td>$r = -.14$</td>
<td>$r = .03$</td>
<td>$= .28$</td>
</tr>
<tr>
<td>Schizophreniform</td>
<td>20</td>
<td>$r = .50$</td>
<td>$r = .55$</td>
<td>$= .48$</td>
</tr>
<tr>
<td>Bipolar and Dep</td>
<td>34</td>
<td>$r = .16$</td>
<td>$r = -.13$</td>
<td>$= .14$</td>
</tr>
<tr>
<td>Total</td>
<td>91</td>
<td>$r = .14$</td>
<td>$r = -.13$</td>
<td>$= .08$</td>
</tr>
<tr>
<td>Vol Control</td>
<td>44</td>
<td>$r = .18$</td>
<td>$r = .22$</td>
<td>$= .16$</td>
</tr>
<tr>
<td>Med Control</td>
<td>30</td>
<td>$r = -.09$</td>
<td>$r = .04$</td>
<td>$= .14$</td>
</tr>
</tbody>
</table>

All correlations for schizophreniform patients were influenced by one subject outlier (age 33). With this individual removed from the calculations, the age correlations for the schizophreniform patients were $r = .26$ over the lateral ventricles, $r = .35$ over the third ventricle, and $= .37$ over the cortical sulci. None of these correlations was statistically significant at $p < .05$. 
APPENDIX I

The Effects of Using RDC Diagnoses on the Results

Most researchers use either RDC or DSM-III diagnostic criteria. There are a number of basic differences between these systems that could influence research results; e.g., schizophreniform disorder and schizoaffective disorder are not used or are not used in the same way in both systems. As with the majority of previous studies, the hypotheses in the present study were tested with patients diagnosed according to DSM-III criteria. The following exploratory analyses will address the research hypotheses with the patients diagnosed according to RDC specifications. The hypotheses of the present study predict that the psychotic patients have enlarged 1. lateral ventricles, 2. third ventricle, and 3. cortical sulci. A fourth hypothesis predicts that medical patients selected from radiology records have smaller ventricles and sulci than do healthy individuals. Table 1 shows the number and age of subjects in each RDC defined patient group and each control group.

Results

There were no significant group differences in lateral ventricle size when RDC diagnoses were used to classify patients, \( F(5, 155) = 1.04, p = .40 \), Table 2. This is the same result that was obtained when DSM-III diagnoses were used. Five patients with VBR values greater than ten were diagnosed schizophrenic and one was diagnosed unspecified functional psychosis. This compares to four schizophrenic, one
Table II
Demographic Characteristics of Subjects

<table>
<thead>
<tr>
<th>RDC Diagnosed Groups</th>
<th>Number of Subjects</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>34</td>
<td>5</td>
</tr>
<tr>
<td>Schizoaffective</td>
<td>17</td>
<td>11</td>
</tr>
<tr>
<td>Mania</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Depression</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Unspecified Func. Psychosis</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

Total Patients             | 67     | 24     | 91    | 23.5| 6.5  | 16-47 |
Volunteer Control           | 29     | 15     | 44    | 23.2| 5.6  | 15-42 |
Medical Control             | 13     | 17     | 30    | 23.2| 4.4  | 15-32 |

...schizophreniform and one paranoid disorder when patients were classified according to DSM-III criteria. As was the case when DSM-III criteria were used, there were no significant relationships between lateral ventricle size and premorbid adjustment, smooth-pursuit eye movements, or negative symptoms for any RDC defined diagnostic group.

No significant group differences were obtained over the width of the third ventricle when Research Diagnostic Criteria were used to classify patients, $F(5, 155) = 1.69, p = .14$. No significant relationships were obtained between third ventricle size and level of premorbid adjustment, negative symptoms, or smooth-pursuit eye movements. This finding differs from that obtained when DSM-III diagnoses...
**Table I2**

Mean Values for Ventricle and Cortex for Each Group with Patients Diagnosed According to Research Diagnostic Criteria

<table>
<thead>
<tr>
<th>Groups</th>
<th>Lateral Vent (VBR)</th>
<th>Third Vent (mm)</th>
<th>Cortex (Rating)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia</td>
<td>6.45</td>
<td>3.73</td>
<td>1.95</td>
</tr>
<tr>
<td>N = 39</td>
<td>SD 2.76</td>
<td>1.42</td>
<td>0.79</td>
</tr>
<tr>
<td>Schizoaffective</td>
<td>6.10</td>
<td>3.40</td>
<td>2.07</td>
</tr>
<tr>
<td>N = 28</td>
<td>SD 2.29</td>
<td>0.83</td>
<td>0.86</td>
</tr>
<tr>
<td>Manic</td>
<td>5.75</td>
<td>3.57</td>
<td>2.00</td>
</tr>
<tr>
<td>N = 10</td>
<td>SD 1.65</td>
<td>1.13</td>
<td>0.94</td>
</tr>
<tr>
<td>Depression</td>
<td>7.82</td>
<td>3.77</td>
<td>2.10</td>
</tr>
<tr>
<td>N = 10</td>
<td>SD 2.11</td>
<td>0.92</td>
<td>0.88</td>
</tr>
<tr>
<td>Total Patients</td>
<td>6.45</td>
<td>3.62</td>
<td>2.05</td>
</tr>
<tr>
<td>N = 91</td>
<td>SD 2.51</td>
<td>1.18</td>
<td>0.83</td>
</tr>
<tr>
<td>Volunteer Control</td>
<td>6.39</td>
<td>3.49</td>
<td>1.82</td>
</tr>
<tr>
<td>N = 44</td>
<td>SD 2.76</td>
<td>1.13</td>
<td>0.76</td>
</tr>
<tr>
<td>Medical Control</td>
<td>5.77</td>
<td>3.01</td>
<td>1.39</td>
</tr>
<tr>
<td>N = 30</td>
<td>SD 2.55</td>
<td>0.90</td>
<td>0.61</td>
</tr>
</tbody>
</table>

A rating of 1 = no atrophy, 2 = moderate atrophy, and 3 = severe atrophy.
were used.

As was the case when patients were classified according to DSM-III criteria, significant differences were obtained between RDC diagnosed groups over the level of cortical atrophy, $F(5, 155) = 3.15$, $p < .01$. Planned orthogonal contrasts indicated that RDC diagnosed schizophrenic, schizoaffective, and affective disorder patients did not show significantly more cortical atrophy than the volunteer control subjects. However, like the DSM-III findings, the volunteer control group had more sulcal dilation than the medical control group, $t(72) = 2.58$, $p < .01$, one-tailed. No significant relationships were obtained between cortical atrophy and level of premorbid adjustment, negative symptoms or smooth-pursuit eye movements. These findings are essentially the same whether patients were classified according to RDC or DSM-III criteria.

In summary, the results that were obtained when RDC criteria were used to classify patients are essentially the same as when DSM-III criteria were used over lateral ventricle size and cortical atrophy. There is, however, a discrepancy between the two diagnostic systems over the width of the third ventricle. The findings from the present study suggest that significant group differences in the size of the third ventricle are more likely to be obtained if DSM-III criteria are used to diagnose patients.
Discussion

The present study suggests that the method of diagnosis may influence the results that are obtained. Whereas clear dilation of the third ventricle was obtained in the schizophrenic patients when DSM-III diagnoses were used, no effect was found when RDC diagnoses were employed. The results over lateral ventricle size and sulcal dilation were the same whether patients were diagnosed according to RDC or DSM-III criteria.

The results of previous investigations suggest that the method of diagnosis that is used does not affect the significance of obtained results. Of the 28 studies of lateral ventricle size in which patients were diagnosed according to either RDC or DSM-III criteria, 16 used DSM-III and 12 used RDC diagnoses. Positive results were obtained in 81% (13/16) of DSM-III and 75% (9/12) of RDC diagnosed patients. This difference is not significant, \( x^2 (1, N = 28) = .12, p > .1 \). The number of investigations that obtained enlargement of the third ventricle was the same whether patients were diagnosed according to RDC (3/4) or DSM-III (3/4) criteria.

A major difference between RDC and DSM-III diagnoses of schizophrenia is the minimum duration of illness that is required. For a diagnosis of schizophrenia using DSM-III criteria, an individual must exhibit some symptoms for at least six months. This can include prodromal, active, and residual symptoms. Because patients in the present study
were recruited within three months of their first psychotic illness, they must have had prodromal symptoms for a minimum of three months in order to receive a diagnosis of schizophrenia. Patients who had a rapid onset of psychotic symptoms will have received a DSM-III diagnosis of schizophreniform disorder in the present study. However, because an RDC diagnosis of schizophrenia requires only two weeks of active psychotic symptoms, this method of classifying patients does not discriminate on the basis of rapid or insidious onset in the present study.

Because of the differences between DSM-III and RDC systems, it is possible that the use of DSM-III criteria has segregated patients with schizophrenic-like symptoms into rapid onset (schizophreniform) versus insidious onset (schizophrenia). This distinction is suggestive of the process-reactive dichotomy (Neale & Oltmanns, 1980) and may reflect good versus poor prognosis in these patients. An inspection of the level of premorbid adjustment in schizophrenic and schizophreniform patient groups fails to support this hypothesis. There were similar levels and ranges of adjustment in both groups (schizophrenic median = 106, range = 44 to 140, schizophreniform median = 103, range = 46 to 140; n.b. premorbid adjustment was measured on a scale of two to 140). This result suggests that there are no differences between these groups over level of adjustment during several years before the onset of psychosis. In order to resolve this issue, a follow-up study including recent
onset patients needs to be conducted. If it were the case that the DSM-III diagnosed schizophrenic patients in the present study had a poor prognosis, then this would suggest that brain changes may be associated with illness severity.
Appendix J

Mean Values for Scores of Premorbid Status, Negative Symptoms and Smooth-Pursuit Eye Movements

<table>
<thead>
<tr>
<th>Group</th>
<th>Premorbid Status</th>
<th>Negative Symptoms</th>
<th>SPEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia</td>
<td>M 99.54</td>
<td>2.58</td>
<td>246.70</td>
</tr>
<tr>
<td>SD 26.32</td>
<td>1.43</td>
<td>24.66</td>
<td></td>
</tr>
<tr>
<td>Range 44-140</td>
<td>1-6</td>
<td>207-296</td>
<td></td>
</tr>
<tr>
<td>n 28</td>
<td>31</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Schizophreniform</td>
<td>M 101.74</td>
<td>2.55</td>
<td>234.33</td>
</tr>
<tr>
<td>SD 22.18</td>
<td>1.50</td>
<td>21.56</td>
<td></td>
</tr>
<tr>
<td>Range 46-140</td>
<td>0-6</td>
<td>194-263</td>
<td></td>
</tr>
<tr>
<td>n 19</td>
<td>20</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Bipolar</td>
<td>M 107.80</td>
<td>1.29</td>
<td>245.94</td>
</tr>
<tr>
<td>SD 21.67</td>
<td>0.85</td>
<td>21.62</td>
<td></td>
</tr>
<tr>
<td>Range 69-140</td>
<td>0-3</td>
<td>215-281</td>
<td></td>
</tr>
<tr>
<td>n 15</td>
<td>17</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Depressed</td>
<td>M 109.14</td>
<td>1.93</td>
<td>230.25</td>
</tr>
<tr>
<td>SD 16.15</td>
<td>1.28</td>
<td>23.89</td>
<td></td>
</tr>
<tr>
<td>Range 77-128</td>
<td>1-5</td>
<td>205-286</td>
<td></td>
</tr>
<tr>
<td>n 14</td>
<td>15</td>
<td>16</td>
<td></td>
</tr>
</tbody>
</table>