LATERAL VENTRICLE SIZE, SMOOTH PURSUIT EYE TRACKING AND NEUROPSYCHOLOGICAL TEST PERFORMANCE IN CHRONIC SCHIZOPHRENIA

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ABSTRACT

The relationships between lateral ventricle size, smooth pursuit eye tracking, and neuropsychological test performance were investigated using a sample of 30 chronic schizophrenic inpatients. There were no significant correlations between any of the measures. Compared to a control group of normal volunteers, the schizophrenic patients showed abnormally poor eye tracking accuracy but did not show lateral ventricular enlargement. Compared to a group of age matched non-schizophrenic psychiatric patients, the schizophrenic patients were impaired on six out of ten neuropsychological tests. As there was no evidence of lateral ventricle enlargement, it is clear that eye tracking impairment and deficits on neuropsychological tests may occur independently of enlarged lateral ventricles. The absence of relationships between impairments on the neuropsychological tests and poor eye tracking is not thought to be the result of restricted performance ranges for any of the measures. The most parsimonious conclusion is that there is no relationship between eye tracking and the variety of neuropsychological functions assessed in this study. However, an alternative possibility is that the study sample was too homogeneously impaired, and a relationship between eye tracking impairment and neuropsychological deficits might emerge in a more diverse sample representative of the range of individuals currently diagnosed as schizophrenic.

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INTRODUCTION

Over the past decade many researchers have turned their attention to describing physiological and neuroanatomical anomalies which may occur in schizophrenic patients. Viewing schizophrenia as a biologically based disorder has much credibility in light of the clear evidence that many schizophrenics benefit from dopamine antagonistic drugs and repeated demonstrations that there may be a heritable liability or predisposition to schizophrenia. Progressing beyond these observations to the level of describing systematic relationships among critical biological variables has proven to be a very demanding challenge for researchers.

The present study is an investigation of three biological measures, each of which has been associated with schizophrenia. The purpose of the research is to describe the relationship between smooth pursuit eye tracking, neuropsychological test performance, and computed tomography (CT) scan measures of lateral ventricle size. Although there are fairly extensive literatures on each measure in isolation and on ventricle size and cognitive functioning in combination, to date there is only one published study which has simultaneously investigated all three variables in the same sample of subjects (Bartfai, Levander, Nyback, Berggren & Schalling, 1985).

RELEVANT LITERATURE

The following review of the research literature relevant to this study will be organized into five sections. The first three sections will be devoted to reviews of the literature on smooth pursuit eye tracking, CT scan findings of lateral ventricular enlargement, and neuropsychological and cognitive functioning in schizophrenia. The sections on these three measures will be subdivided to discuss i) operational definitions of deviant attainment, ii) the prevalence of deviations in schizophrenic samples, iii) the significance of abnormal attainment on the measure in question, and iv) a summary of findings and methodological issues. The fourth major section of the literature review will summarize research which has investigated relationships among the variables. The fifth section consists of general conclusions and a rationale for the current research project based on the existing literature.

Smooth Pursuit Eye Tracking

Definition

Smooth pursuit eye movements (SPEM) are conjugate following movements utilized in tracking targets in continuous motion at velocities up to 40 degrees/second (Lipton, Levy, & Holzman, & Levin, 1983; Yee, 1983). They are believed to be more or less nonvoluntary in the presence of slow moving targets and to serve the function of maintaining a stable

image on the retina. Beginning with reports by Holzman and associates (Holzman, Proctor, Yasillo, Meltzer, & Hurt, 1974; Holzman, Proctor, & Hughes, 1973) on their investigation of findings that originated in the work of Diefendorf and Dodge in 1908 and Couch and Fox in 1934, numerous studies have found disrupted pursuit eye movements in psychiatric patients and their relatives.

A standard protocol for measuring smooth pursuit eye movements involves placing the subject about 30 cm from a screen on which a small dot or a cursor is driven back and forth at velocities up to 30-40 degrees per second. The movements of the eye may be recorded with a variety of techniques although electrooculography (EOG) and infrared reflectometry (IR) are probably the most common. Both target position and eye position are recorded on a polygraph for visual inspection and may also be stored in some form which allows quantitative analysis by computer. Methods of scoring tracking performance have differed considerably across studies. Tracking performance can be qualitatively evaluated by examining polygraph records and noting the occurrence of obvious deviations in the eye movement channel relative to the target channel, or it may be compared to records of normal subjects. More sophisticated and reliable scoring methods involve quantifying the tracking performance, often through specially designed computer programs that sample the tracking record and compare it to target position.

Each scoring method constitutes an operational definition of the pursuit deficit. Different measurement techniques have focused on qualitatively different aspects of eye tracking performance (Iacono & Koenig, 1983). At present there does not appear to be a consensually agreed-upon definition of the precise nature of the abnormal pursuit pattern. Iacono and Koenig (1983) describe two aspects of the smooth pursuit eye tracking performance of schizophrenic patients which they found differed qualitatively from that of affective-disorder patients and normal individuals. They found that schizophrenic patients tracked with significantly more "phase-lag" (defined as the average number of degrees of visual arc the eyes lag behind the target) and produced saccadic errors of smaller amplitude than those seen in other subjects. Levin, Jones, Stark, Merrin, and Holzman (1982) reported findings on a group of six schizophrenic patients using sophisticated infrared recording instrumentation they believe to be considerably more precise than the measurement techniques used in the other eye movement studies. They describe two types of eye movement irregularities they believe to be the underlying factors in disrupted smooth pursuit eye movements in schizophrenia. They suggest that impaired SPEM is a result of either/both "saccadic intrusions" (defined as pairs of small amplitude saccades, 0.5° to 2.5° in opposite directions to each other and occurring at a rate of 1 to 3 per second) and "saccadic smooth pursuit" tracking (defined as pursuit

tracking accomplished by small saccadic steps of about 1° in amplitude).

Prevalence of SPEM Dysfunction in Schizophrenia

Recent reviews suggest that 50% to 80% of schizophrenics show impaired smooth pursuit eye movement (Holzman, 1983; Latham, Holzman, Manschrech, & Tole, 1981; Spohn, 1983). The findings of the early Holzman studies (Holzman et al., 1974) have essentially stood the test of time and been replicated by Holzman and his group, and confirmed by others (Cegalis & Sweeney, 1979; Levin, Lipton, & Holzman, 1981; Lipton, Levin, & Holzman, 1980; Mialet & Pichot, 1981). In the Holzman et al. (1974) study deviant eye tracking was found in 52% of recently hospitalized schizophrenic patients (n=46); 85% of chronic schizophrenic patients (n=29); 22% of manic depressives (n=9); 21% of non-psychotic psychiatric patients (n=19); 45% of first degree relatives of schizophrenic patients (n=34); 11% of first degree relatives of other psychiatric patients (n=19); and in 8% of normal controls (n=72). Iacono, Tuason, and Johnson (1981) found that the performance of remitted schizophrenics was similar to that found in hospitalized patients indicating the SPEM dysfunction is not simply a state variable occurring during a psychotic episode.

It is frequently acknowledged that SPEM dysfunction is not specific to schizophrenia and occurs in several neurologic

disorders (Leigh, Newman, Folstein, Lasker, & Jensen, 1983; Spohn, 1983; Yee, 1983) and is present in other psychiatric groups such as manic-depressives (Levin, Lipton, Rothenberg & Lipton, 1981; Lipton et al., 1980). Despite the lack of specificity, SPEM dysfunction seems to be more characteristic of schizophrenia than other psychotic groups and also more prevalent in psychotic disorders than in nonpsychotic and normal groups. It also appears that prevalence of disrupted pursuit varies somewhat with the clinical characteristics of the population; a higher prevalence of tracking deficit has been noted in chronic patients (Lipton et al., 1983).

Significance Of SPEM Dysfunction in Schizophrenia

The twin studies and family studies of Holzman and colleagues and the twin studies of Iacono and Lykken lend considerable weight to the proposition that deviant pursuit tracking may serve as a genetic marker for schizophrenia. While this particular aspect of the SPEM literature will not be further pursued at this time it should be noted that a considerable proportion of eye movement research in schizophrenia has been concerned with genetic hypotheses.

Abnormal SPEM have been reported in Parkinson's disease (Leigh et al., 1983) and in Alzheimer's-type dementia (Hutton, Nagel, & Loewenson, 1984; Jones, Friedland, Koss, Stark, & Thompkins-Ober, 1983). Corvera, Torres-Courtney, and Lopez-Rios (1973) reported that 73% of a large group (n=325) of

patients with a variety of neurological disorders showed smooth pursuit abnormalities. As SPEM disruptions are often found to be associated with diffuse neurological disorders it seems possible that ventricular enlargement and poor eye tracking performance might be associated in schizophrenic patients. On the other hand, Levin et al. (1981a) have hypothesized that the tracking impairment of schizophrenic patients is the result of a localized neuropathology in the frontal lobes. They suggest that disorder of a 'saccadic inhibition system' located in the frontal eye fields may be the locus of the smooth pursuit tracking impairment.

To date, two studies have investigated the association between SPEM and lateral ventricle size in schizophrenic patients. Weinberger and Wyatt (1982) report some preliminary results of a comparison of tracking proficiency between 20 schizophrenic patients with normal ventricles and 14 patients with enlarged ventricles. Sixty four percent (9/14) of the patients with large ventricles showed impaired tracking compared with 30% (6/20) of the patients with normal ventricles. Bartfai et al. (1985) rated eye tracking performance of 17 schizophrenics on a 5 point scale. On the basis of their rating system they report that 83% of their sample were impaired on the eye tracking task. Ventricle size was assessed by a linear measure of the frontal horns of the lateral ventricles. Bartfai et al. report that few patiants

had abnormal ventricles. No significant relationship was found between ventricle size and eye tracking.

Summary-SPEM

Smooth pursuit tracking has been found to be abnormal in 50% to 80% of schizophrenics and about 45% of their first degree relatives. Important features of the impairment include the following: 1) it appears to be relatively independent of voluntary attention and is not simply a result of low motivation; 2) it seems to be a trait which is stable over time and independent of the patients' clinical status; 3) it does not appear to be caused or affected by antipsychotic medication; 4) while not specific to schizophrenia it appears more strongly associated with that diagnostic group than any other psychiatric disorders; 5) it has a low base rate in the normal population (about 8%); 6) it shows a high degree of heritability both in normal identical twins and in monozygotic twins discordant for schizophrenia; 7) similar types of impairment are seen in some neurological disorders with known sites of pathology, which may provide some neuroanatomical information useful to understanding schizophrenia. In addition, there is growing understanding and consensus on the methodological issues involved in measurement and scoring of eye movement records. In all likelihood this will lead to a more precise understanding of what is deviant in deviant eye tracking.

CT Scan Findings

Definition

The search for structural abnormalities in the brains of schizophrenics began shortly after Kraepelin described the syndrome of dementia praecox. Post-mortem studies carried out from the 1920s into the 1950s yielded some positive findings, particularly decreased cortical cell and nerve fibre density. However, these deficits were soon recognized as nonspecific to schizophrenia thereby discouraging further effort in this direction (Seidman, 1983).

CT scan studies with schizophrenic patients are a fairly new addition to the literature having first appeared in 1976 (Johnstone, Crow, Frith, Husband, & Kreel, 1976). Several aspects of brain structure have been investigated with the CT scan including lateral ventricle size, third ventricle size, prominence of cortical sulci, cerebellar atrophy, and hemispheric asymmetry. The measure most frequently utilized to date is lateral ventricle size, often expressed as a ratio of ventricle area to total brain area (termed ventricle brain ratio or VBR) on the scan section which shows the lateral ventricles at their largest. There is increased interest in recent studies in sulcal prominence as a measure of cortical atrophy. Unfortunately this aspect of brain structure is difficult to assess from CT scans and is considered by

radiology experts to present more complex measurement problems than ventricular measures (Bird, 1982).

Lateral ventricular enlargement (LVE) is considered to be an index of non-specific alterations in gross brain structure. Weinberger and Wyatt (1982) state "it is a biological marker of a past or present brain disorder, usually one involving either degeneration of brain tissue or obstruction to cerebrospinal fluid circulation" (p.506).

Ventricular enlargement associated with disorders such as dementia is often quite obvious on a CT scan (e.g., VBRs ranging from 16 to 30 in demented patients compared with a mean VBR of 4 in control subjects). Weinberger, Torrey, Neophytides, and Wyatt (1979a) point out that this sort of dramatic structural change is not the sort of ventricular enlargement seen in schizophrenic patients: "Ventricular enlargement seen in schizophrenic patients is modest and may be easily overlooked. In fact, mean ventricular size for these patients falls within the normal range for individuals approximately 70 years old" (p.738).

Defining <u>abnormal</u> LVE in schizophrenic populations has proved difficult. Laboratories differ in the type of scanner used, scanning procedures, scoring methods, cut off score used to define abnormality, and composition of patient and comparison groups (Andreasen, Smith, Jacoby, Dennert, & Olson, 1982; Jernigan, Zatz, Moses, & Berger, 1982a; Maser & Keith, 1983). Recently there is evidence of effort by the major

psychiatric CT laboratories to standardize procedures as much as possible (Maser & Keith, 1983).

Studies by Penn, Belanger, and Yasnoff (1977) and by Jernigan et al. (1982a) have demonstrated that measures of VBR using planimetry or computer derived area on a single cut through the body of the lateral ventricles provides an estimate of ventricular size which correlates highly with more sophisticated computer derived total volume estimates. While VBR obtained by planimetry or computer appears to be a valid measure of ventricular volume and has been demonstrated to have high inter-rater reliability within laboratories, there are differences between research groups, which make it unwise to compare raw values. (Jernigan et al. 1982a) Until objective standardized scoring procedures are available for utilization by groups wishing to compare findings, a short term solution is collection of control group data by each laboratory against which they can compare the data from their clinical populations.

Weinberger and collaborators in the National Institute of Mental Health (NIMH) CT scan group have provided two operational definitions of LVE; 1) a VBR in excess of 2 SD above a control group mean, and 2) VBR greater than 10. While the first definition takes account of different practices in different laboratories, the second definition is based on the findings of Synek and Reuben (1976) and others that VBRs in excess of 10 occur in less than 5% of the normal population.

Both these definitions are widely used, but Andreasen et al. (1982b) have commented that they may be too stringent, particularly in preliminary stages of CT research in schizophrenia.

Prevalence of Lateral Ventricular Enlargement (LVE)

Johnstone et al. (1976) and Weinberger et al. (1979a) were the first research groups to undertake controlled CT scan studies with schizophrenic patients. The Johnstone et al. sample consisted of 17 male chronic patients (mean age 58y) and the Weinberger et al. sample contained 65 patients all under the age of 50; both studies found approx. 50% of the schizophrenic patients evidenced enlarged lateral ventricles relative to controls. Reveley (1985) lists 26 studies conducted between 1976 and 1985 which have reported lateral ventricular enlargement in samples of schizophrenic patients. Many of the studies cited by Reveley did not include normal control groups scanned on the same equipment as the schizophrenic patients and many investigators assessed ventricular enlargement by methods other than VBR.

Boronow, Pickar, Ninan, Roy et al. (1985) reviewed 11 studies which included a normal control group and reported ventricle size in terms of VBR. Nine of these studies reported significantly larger mean VBRs in their schizophrenic samples -- ranging from 35% to 207% -- greater than the mean VBRs for the control groups. The average percentage of

patients with a VBR greater than 2 SDs above the control group mean was 38% (range 6% to 90%). Recent controlled studies have found prevalence rates of significant lateral ventricular enlargement ranging from 15% (Williams, Reveley, Kolakowska, Arlen, & Mandelbrote, 1985) to 7% (Boronow et al., 1985).

In addition to marked variability in prevalence rates for studies with positive findings there are also published studies which failed to find ventricular enlargement (Benes, Pearson, Jones, LeMay, Cohen, & Lipinski, 1982; Gluck, Radu, Mundt, & Gerhardt, 1980; Jernigan et al., 1982; Largen, Smith, Calderon, Baumgartner, Schoolar, & Ravichandran, 1984; Shima, Kanba, Masuda, Tsukumo, Kitamura & Asai, 1985; Trimble, & Kingsley, 1978).

In a paper published shortly after an NIMH sponsored workshop on the CT scan in Psychiatry (see Maser & Keith 1983, for review), Luchins (1982) discusses some sample characteristics which might account for the reported disparities. Comparing research samples with respect to locked-ward vs. open-ward treatment, response to neuroleptic medication, neuropsychological status, levels of social, occupational and self-care functioning, and chronicity suggest that samples comprised of subjects relatively more impaired on these dimensions are the samples most likely to evidence a greater prevalence of ventricular enlargement. A recent paper by Smith & Iacono (1986) suggests that the selection and composition of control groups may be the critical factor in dif-

ferences between studies in prevalence of LVE. In light of the many methodological factors and subject variables which collectively affect estimates of the prevalence of ventricular enlargement, it is apparent that a clear understanding of this parameter will require the further accumulation of evidence from a wide variety of patient samples and measurement techniques.

Significance of Lateral Ventricular Enlargement in Schizophrenia

The brain structure abnormalities observed in CT scan investigations with patients are described by Weinberger and Wyatt (1982) as both subtle and nonspecific. While several investigators report that a proportion of schizophrenics evidence deviantly large lateral ventricles, the significance of LVE remains unclear.

Artifact or coincidence? Research which addresses the possibility that LVE is an artifact, to date, is quite consistent in finding that LVE in schizophrenic patients cannot be accounted for simply on the basis of medication or institutionalization history. LVE occurs in patients who have never been medicated and/or have little or no history of institutionalization. Studies also indicate that there is no significant correlational trend in cross sectional samples between LVE and duration of medication or institutionalization per se, although this possibility cannot be ruled out without

longitudinal data (Johnstone, et al 1976; Nasrallah, 1982; Owens, Johnstone, Crow, Frith, Jagoe & Kreel, 1985; Weinberger, De Lisi, Purman, Targom & Wyatt, 1982).

There is considerable and convincing evidence that LVE is not simply an age dependent anomaly since it has been found to occur in young schizophreniform patients (Schulz, Koller, et al., 1983; Weinberger et al., 1982) and in a number of samples of young chronic patients (Golden, Moses, Zalazowski, et al., 1980; Kling, Kurtz, Tachiki & Orzeck 1982/83; Weinberger et al., 1982).

Addressing the possibility that LVE in schizophrenia may be a coincidental occurrence is made difficult by the lack of independent large scale epidemiological studies of ventricular size (Maser & Keith, 1983). However, there are numerous smaller scale studies in many research areas which are thought to provide fairly reliable and valid estimates of the base rate of LVE in the general population. Based a review of these studies; a) Weinberger, Wagner & Wyatt (1983) conclude that VBR values for normal controls are remarkably consistent and a VBR of 10 probably occurs in less that 5% of normal individuals under 40 years of age (Weinberger et al., 1983 list the mean VBRs for the control groups for 9 studies, total control subject n=329, $\bar{x}$ mean age = 29.8 $\pm$ 8.7 years, $\bar{x}$ mean VBR = 3.9 $\pm$ 0.8); b) Zatz, Jernigan & Ahumanda (1981) suggest that there in general ventricular volume remains constant

until age 60, suggesting that spontaneously occurring marked changes in ventricular size before the 7th decade are unusual.

In summary, the conclusion that LVE is not a simple artifact of age, medication, and institutionalization is well supported and widely accepted.

Clinical correlates of LVE. Considerable research has been concerned with the investigation of factors which might prove to be determining clinical/behavioral correlates of LVE. The work of Crow, Johnstone and collaborators provided a framework for the first series of such studies. Crow (1982) and Crow, Cross, Johnstone, and Owen (1982) proposed that the disorder currently called schizophrenia might actually consist of two overlapping syndromes which differ considerably in presenting symptoms, course, response to treatment, and pathological process. Crow (1982) defined a Type I syndrome as being characterized by positive symptoms (delusions, hallucinations, thought disorder), acute schizophrenia, good response to neuroleptic drugs, reversible outcome, and absence of intellectual impairment. He postulated that the underlying pathological process might be increased dopamine receptors. In contrast, a Type II syndrome was characterized by negative symptoms (flattening of affect, poverty of speech, loss of drive), chronic schizophrenia, poor response to neuroleptics, irreversible outcome, and sometimes, intellectual impairment. The postulated pathological process in Type II schizophrenia was hypothesized to be cell loss and structural changes in the

brain. There are several studies which have investigated these and associated variables using LVE as an independent variable. Andreasen, Olsen, Dennert, and Smith (1982a) found large ventricle patient had a preponderance of negative symptoms while small ventricle patents were characterized by positive symptoms. Weinberger, Cannon-Spoor, Potkin and Wyatt (1980) reported an association between CT scan abnormalities and premorbid ratings. Two studies found ventricular enlargement to be associated with poor response to neuroleptic medication (Luchins, Levine, & Meltzer, 1984; Weinberger, Bigelow, Kleinman, et al., 1980).

Despite these rather promising findings most research which has followed these original reports has failed to replicate their findings.

Owen et al. (1985) found few correlates of ventricular enlargement in a sample of 112 institutionalized chronic schizophrenic patients. Patients with negative symptoms, intellectual impairment, and poor drug-response did not have larger ventricles than a matched group of patients without these features. Williams et al. (1985) were unable to find an association between VBR and symptom type (i.e. positive/ negative), response to neuroleptics, duration of illness, or cognitive impairment in a sample of schizophrenic patients. However, this research group did find that significant ventricular enlargement was most common in the chronic patients in their sample despite the lack of overall

correlation between duration of illness and ventricular enlargement. A recent study by Boronow et al. (1985) investigated the association between drug response, a wide variety of clinical features, and brain morphology in a sample of 30 schizophrenic and schizo-affective patients. They were unable to find any significant correlations between clinical variables or drug response and ventricle size.

In summary, it appears that the early hope that ventricular enlargement might serve as a biological marker for a subtype of schizophrenia characterized by a clinical syndrome of negative symptoms, poor response to medication, and specific to poor outcome has not been supported by the most recent research findings.

Cognitive/neuropsychological function and CT scan abnormalities. In addition to clinical correlates of LVE, many researchers have investigated the possibility that the brain structure abnormalities seen on CT scans of schizophrenics may be associated with intellectual and neuropsychological impairment. The tendency towards increasingly negative findings across time noted in the previous section on clinical correlates of ventricular enlargement also applies to the association between cognitive functioning and lateral ventricular enlargement. Nonetheless CT scan abnormalities in ventricle and sulcal size and cognitive/neuropsychological deficits have frequently been reported to co-occur in schizophrenic patients. Masser and Keith (1983) in their report on

the NIMH CT scan workshop cite Weinberger as stating that he "knew of no published study showing LVE without cognitive impairment" (p.275). While there are good grounds to disagree with this as an entirely factual statement -- indeed Weinberger et al. (1979) failed to find a relationship between VBR and IQ scores -- it does appear that cognitive impairment frequently occurs in samples of patients who also show CT scan abnormalities.

Before presenting the research findings, two measurement/definition issues are worthy of mention. The first relates to the variability in both measures and definition of "cognitive function." While there is undoubtedly overlap between the cognitive functions assessed on a mental status examination, a standard IQ test, and neuropsychological tests, there is considerable research to indicate that these tests are not interchangeable measures of the same functions. Inconsistent findings and loss of useful information may result from treating these different measures as interchangeable indicants of "cognitive" function.

A second measurement/definition problem involves the use of CT measures of either/both ventricular enlargement and sulcal prominence in relation to cognitive function. As will be seen in the studies to follow, both measures of structural abnormality have been found to be associated with impaired cognitive function. Unfortunately their relation to each other is poorly understood and several studies have failed to

find a systematic relationship between lateral ventricle size and sulcal prominence (e.g. Nasrallah, Kuperman, Hamara & McCalley-Whitters, 1983a; Pandurangi, Dewan, Lee, et al., 1984; Weinberger et al. 1979b). On the other hand Kling et al. (1982/83) and Rieder et al. (1983) did find significant covariation between LVE and sulcal prominence.

Weinberger, Torrey, Neophytides, & Wyatt (1979a) have suggested that the two abnormalities may be independent pathological processes. Nasrallah, Kuperman, Jacoby, McCalley-Whitters, & Hamara (1983b) have suggested that the clinical correlates of LVE and sulcal widening may differ, and that sulcal widening may be more strongly associated with intellectual impairment than is LVE. Unfortunately the cortical sulci are not particularly well-visualized by CT procedures, compromising the validity of this index. Some studies (eg. Donnelly, Weinberger, Waldman, & Wyatt, 1980; Weinberger, Torrey, Neophytides, & Wyatt, 1979b) define structural abnormality as a significant difference from the control group on any of a number of CT measures, including LVE and sulcal prominence, and fail to analyse relationships with dependent variables separately for the different forms of structural abnormality. This issue may be found trivial in the long run; however, it is receiving considerable attention in the literature on intellectual changes in aging and dementia as associated with cortical atrophy (sulcal enlargement) and ventricle enlargement. In this area

investigators are also finding that the two measures seem to have different clinical correlates (Bird, 1982; Kaszniak, Garron, Fox, Bergen, & Huckman, 1979).

The original CT scan study carried out by Johnstone et al. (1976) incorporated measures of cognitive functioning similar to a mental status exam (the Withers and Hinton test battery) and found a correlation of -0.70 (n=14) between ventricle size and cognitive function. In the second CT study Weinberger et al. (1979a) completed WAIS testing with 19 individuals in their sample of 73 mixed psychiatric patients (WAIS scores available for 14 chronic schizophrenic patients and 5 "other" psychiatric patients). They found the schizophrenic patients performed significantly worse than the other psychiatric patients on all subtest and IQ measures, but found no significant relationship between ventricle size and any WAIS scores in the chronic schizophrenic group. Similar findings are reported by Kling et al. (1982/1983) who administered a compete "Mental Status in Neurology" examination and found that while schizophrenic patients scored lower than would be expected in a normal population there was no association between mental status scores and VBR. Donnelley et al. (1980) administered the Halstead - Reitan Battery (HRB) and the WAIS to 15 young chronic schizophrenic patients on whom CT scan measures of LVE, width of interhemispheric fissures, width of Sylvian fissures, and width of cortical sulci were available. Test scores on the HRB were combined in

a standardized fashion to form the Average Impairment Rating (AIR) (Russell, Neuringer, & Goldstein, 1970). In the group of 15 patients, 8 had abnormal scans and 7 showed no abnormality -- where CT abnormality was defined as enlargement that exceeded the control range for any of the four measures of brain structure listed above. Utilizing a cutting score on the AIR (5 point scale) of 1.55 (which falls between "average" performance and "mildly impaired" performance) the investigators were able to predict CT status with an overall hit rate of 80% (12/15). They also found significant differences between the normal and abnormal CT scan groups on eight of the eleven subtests of the WAIS (Comprehension, Arithmetic, Similarities, Digit Span, Block Design, Picture Arrangement and Object Assembly), and on all three IQ components. It is unfortunate that they failed to specify the rates of abnormality for each of the four measures of brain structure.

A series of three studies by C.J. Golden and collaborators show impressive classification hit rates and correlations between performance on the Luria Nebraska Neuropsychological Battery (LNNB) and VBR. Golden et al. (1980a) assessed a group of chronic schizophrenia patients (mean age 32.3) with the LNNB. Half of the subjects had been referred because of suspected brain damage. The VBR within the entire group ranged from 1 to 24 (mean 12.0 $\pm$ 5). These ratios are considerably higher than seen in other CT studies and are

believed to reflect a systematic difference in scoring procedures between the Nebraska group and other CT labs (Weinberger, Wagner, & Wyatt, 1983). Unfortunately, Golden et al. (1980a) did not have a control group for this study, making comparison of their VBR scores with other samples unwise. They did, however, state that using a VBR cutoff of >10 as a definition of abnormality - 60% of their sample would be classified as brain damaged. A multiple regression using the eight LNNB scales which had significant correlations with VBR (tactile, expressive, reading, writing, arithmetic, pathognomic, left hemisphere, and right hemisphere) gave a multiple correlation of 0.72. Golden et al. (1980a) investigated the accuracy of a set of interpretive rules applied to LNNB for determining the presence of LVE and sulcal enlargement. Of 42 patients assessed, 26 were diagnosed as normal and 16 as abnormal by the LNNB; 20 were rated as having enlarged ventricles and 22 as having normal ventricles; 16 were rated as showing sulcal prominence and 26 having normal sulci. The overall hit rate for prediction of LVE from LNNB performance was 81%. Overall agreement for sulcal prominence was 90%. Golden, MacInnes, Arial, Ruedrich, Chu, Coffman, Graber, and Block (1982) applied the rules derived in the Golden et al. (1980b) study to a cross-validation sample of 43 chronic schizophrenics. Using the rules to predict LVE they achieve an overall hit rate of 77% with no false negatives and ten false positives. The multiple correlation between the 14

LNNB scales and VBR was 0.76, very similar to that obtained in the Golden et al. (1980a) study. Differences between the Golden et al. (1980a) and the Golden et al. (1982b) studies are found in the specific scales which correlate with VBR and the magnitude of the correlations. Five of the 14 LNNB scales were significantly correlated with VBR in both studies, while non-overlapping sets of three scales were significant in one study but not the other.

The VBR - LNNB correlations reported by Golden's group are impressively high. While the 1980 study had sample characteristics which might be expected to boost the correlation, (half the subjects had been referred for neuropsychological assessment while the other half were believed to be free of brain dysfunction) the 1982 study was not flawed by this sort of sampling procedure and was nonetheless able to replicate the high degree of association found in the earlier study.

Recent additions to the literature failed to find enlarged ventricles to be predictive of impaired neuropsychological performance. Williams et al. (1985) studied a group of 40 schizophrenic and schizo-affective patients. The mean VBR of the patient sample was significantly greater than that of the control group and 15% of the patients had ventricles more than 2 s.d. above the control group mean. Of 36 patients given a cognitive assessment, 13 (36%) were classified as impaired. Cognitive impairment was not

associated with ventricular enlargement in these patients. Owens et al. (1985) report findings obtained from a study conducted with a sample of 112 institutionalized chronic schizophrenic patients and 5 comparison groups consisting of 18 out-patient schizophrenics, 8 first-episode schizophrenics, 33 patients with bipolar disorder, and 19 neurotic outpatients. Among the six diagnostic groups the only significant group differences in VBRs were between the chronic schizophrenic inpatients and the neurotic outpatients. Within the inpatient schizophrenic sample, ventricular size and cognitive function were not linearly related. However, Owen et al. found a significant curvilinear relationship between ventricular size and scores on their measure of cognitive function (the Withers and Hinton). There was an excess of patients with impaired cognitive function at both extremes of ventricle size. DeMeyer, Gilmore, DeMeyer, Hendrie, Edwards, and Franco (1984) report significant correlations between VBR and a very extensive battery of neuropsychological tests (a full Halstead-Reitan Battery, Luria-Nebraska Neuropsychological Battery, and Weschler Adult Intelligence Scale) such that individuals with larger VBRs performed significantly better than individuals with small ventricles. The subjects in this study were of mixed psychiatric diagnosis and as such the results are not directly comparable to studies of purely schizophrenic patients.

Summary of CT Scan Findings in Schizophrenia

Many aspects of CT scan investigations with schizophrenic samples have been discussed in this review and may be briefly summarized by the following: 1) Several aspects of brain structure are assessed by CT scan. In schizophrenia the two most frequently investigated variables are lateral ventricular enlargement (LVE) and sulcal widening or prominence. 2) A commonly used index of ventricle size is the ventricle brain ratio (VBR) derived from area measures of the ventricles and the inner table of the skull on the CT slice showing the lateral ventricles at their largest. 3) Ventricular enlargement is usually defined as either a VBR greater than two standard deviations above a control group mean, or in some cases, a VBR>10. 4) LVE is subtle in schizophrenic samples and often would not be classified as abnormal by neuroradiologists although it is believed that a VBR of 10 occurs in less than 5% of a normal population. 5) Prevalence rates vary widely across studies (0% to 60% range). It has been suggested that representative samples of schizophrenic patients may evidence a prevalence rate of 20%. 6) LVE is not specific to schizophrenic patients but is found in other psychiatric populations, particularly manic depressives. 7) LVE is found in young and old patients, chronic and first episode, those with long histories of drug and somatic treatments and hospitalization, and those with no history of such interventions. It is therefore not believed to be a

simple artifact of age, medication, or institutionalization. However, there is reason to expect that LVE may be more prevalent in more seriously-ill patients than in those with milder forms of the disorder. 8) LVE and other structural abnormalities are among the descriptors of the syndrome Crow calls Type II Schizophrenia. Along with structural brain abnormalities, Type II syndrome is postulated to include negative symptoms, chronic irreversible course, intellectual impairment, and poor response to neuroleptic medication. While data are equivocal with respect to clear covariation of this cluster of variables, the Type I / Type II construct has generated a considerable body of biopsychiatric research. 9) Several studies have investigated the association of structural abnormalities and neuropsychological / cognitive impairment and several have demonstrated quite high levels of association, although there are inconsistent and contradictory findings. 10) Some investigators suggest that cortical atrophy as indexed by sulcal widening may occur independently of ventricular enlargement and may have different clinical correlates. Unfortunately sulcal widening is more difficult to assess than is LVE. 11) Speculations based on recent research suggest the possibility that there are at least two neuroanatonically distinct groups of chronic schizophrenics who evidence marked cognitive impairment. Owens et al. (1985) found cognitive impairment was over-represented in portions of their sample which had both the largest and smallest (greater

than 1 s.d. smaller than control group) ventricles. DeMeyer et al. found that smaller ventricles were associated with more marked cognitive impairment than large ones.

Neuropsychological and Cognitive Functioning in Schizophrenia

Definition and Description

Neuropsychological status is inferred from test performance on tasks designed, or believed to measure the behavioral expression of brain function. As Lezak (1981) describes it

> "The distinguishing characteristic of neuropsychological assessment is its emphasis on the identification and measurement of psychological deficits, for it is primarily in deficiencies of intellect, emotionality and control that brain damage is manifested behaviorally" (p.85).

Thus, many neuropsychological instruments were designed by quantifying differences in performance between individuals with known organic syndromes and normal controls, thereby providing measures of a "deficit" presumed to be caused by brain damage.

The majority of neuropsychological research studies with psychiatric populations has been designed to assess the utility of neuropsychological tests in discriminating between patients with 'functional' and 'organic' diagnoses. While some investigators utilize full neuropsychological batteries including intelligence tests, the great majority of studies have used only the popular screening tests (e.g. Memory-for-Designs-Test, the Benton Visual Retention Test (BVRT), the

Trail Making Test, and the Bender Gestalt Test). Often only one of these instruments is used for data collection in a given study (Heaton & Crowley, 1981). Malec (1978) reviewed 31 classification attempts using both single neuropsychological tests and/or the Halstead-Reitan Battery (HRB), and found that in general the HRB failed to demonstrate greater discriminatory power than many of the less time-consuming single measures in differentiating 'functional' and 'organic' patients.

Neuropsychological tests and differential diagnoses of "functional" vs. "organic" conditions. An extensive review by Heaton, Baade, and Johnson (1978) and a subsequent update by Heaton and Crowley (1981) review 118 classification attempts published between 1960-1978. Ninety-nine of the studies utilized group comparisons between organic and psychiatric patients, and eleven compared psychiatric patients to standard scores for impairment. They noted that 90% of the studies had 3 or more methodological flaws, particularly in the areas of sample selection and description. However, despite the weakness of individual studies, Heaton et al. (1978, 1981) provided cumulative estimates of median percent correct classification. These estimates indicated that neuropsychological tests were relatively successful in discriminating functional from organic patients except when the functional sample was composed of chronic/process schizophrenics.

The median percent for correct classification of functional vs. organic was 75% (84 reports) utilizing psychiatric samples ranging from non-psychotic mental disorders to mixed schizophrenic disorders. This is the same median hit rate reported by Spreen and Benton in 1965 for 36 classification attempts they made involving organics and normal controls (Heaton & Crowley, 1981). However the median hit rate for 34 attempts to discriminate chronic/process schizophrenic patients from organic patients was 54%, essentially chance level prediction.

Exceptions to these rather dismal classification rates encountered with chronic schizophrenics are the studies of Golden and collaborators with the HRB (Golden, 1977) and the LNNB (Moses & Golden, 1980; Purisch, Golden, & Hammeke, 1978). In these studies approximately 90% correct classification was achieved. However discussion of these findings by Golden et al. (1980b) and Moses, Cardellino and Thompson (1983) indicate that there may be some question as to the validity of the conclusions reported in these studies. Golden et al. (1982b) state

> "It appears possible that previous studies comparing schizophrenics with brain-injured groups did not necessarily measure what they thought they were measuring. For example, Purisch, Golden and Hammeke (1978) found differences between the schizophrenic and neurological groups. This study established that neurological and schizophrenic patients performed differently on the Luria-Nebraska Battery, not that the schizophrenics were normal, as concluded". (p.84)

Overall the weight of the evidence indicates that when chronic schizophrenic patients are excluded, neuropsychological tests are useful in discriminating emotionally/psychologically disturbed psychiatric patients from individuals with known organic brain dysfunction (Heaton & Crowley, 1981). As Malec (1978) pointed out, these predictions can be no more valid than the diagnostic criteria they predict, hence 75% may be a ceiling imposed by the then current neurodiagnostic techniques.

Heaton et al. (1978) discuss the poor performance on neuropsychological tests of chronic schizophrenic samples with regard to the popular explanation of this group's generalized deficits. It was commonly held that poor performance by chronics on all manner of tests was 'functional' and attributable to motivational deficiencies - often seen as an outcome of long term institutionalization - and thought disorder. While not able to rule out this possibility, Heaton et al. (1978) question it as an adequate explanation. They suggest that "functional problems" are not confined to chronic schizophrenic patients nor do all individuals with thought disorder and motivational deficiencies perform in the impaired range on neuropsychological tests. They discuss the possibility that medication may affect test performance, an issue which will be addressed at a later point in this review. The alternative explanation which is most compelling for Heaton et al. (1978) is that "groups of chronic or process schizo-

phrenics may look organic on neuropsychological tests because a significant proportion of such patients are organic" (p.141).

The Heaton et al. (1978) review signaled a shift in direction for neuropsychological research in schizophrenia. Golden et al. (1982) articulate the change in perspective as follows

> "The CT scan research - as well as the data from many of the studies reviewed by Heaton et al. (1978) ... suggest that there are at least several subgroups of schizophrenia, some of which show brain dysfunction. This conclusion clearly necessitates the adoption of a new research strategy in neuropsychological research with schizophrenia. Rather than compare schizophrenics to neurological patients, our focus should be on identifying those schizophrenics with brain damage and eventually discovering how such patients differ in age of onset, response to treatment, symptoms, likelihood of ending up in chronic institutions or jail or similar settings and other such factors important in understanding these subgroups" (p.89)

<u>Summary of classification studies</u>. With regard to a definition of the form of neuropsychological impairment to be expected in chronic schizophrenic patients, the majority of classification studies are not, in themselves, very useful. Classification studies in which tests are utilized to dichotomize between 'brain damaged' vs. 'non brain damaged' do not provide a great deal of information relevant to defining the nature or extent of the deficits exhibited by schizophrenic patients.

The usefulness of comparison group studies of the sort discussed above has been questioned by many investigators (Golden et al., 1981; Heaton et al., 1978; Satz and Fletcher, 1981). With the growing belief that a sizable proportion of chronic schizophrenic patients are neurologically impaired, difficulty discriminating them from patients with known organic dysfunctions no longer disturbs neuropsychologists.

The classification studies were often carried out with the express aim of separating schizophrenics from organics. In overview, their relatively consistent failure to do so provides us with a few important pieces of descriptive information; a) chronic schizophrenic patients do poorly on a wide range of tests requiring performance in a variety of modalities; b) schizophrenic patients exhibit deficits on a range of tests which are believed to assess the function of various brain regions and do not appear to show clear focal impairment; instead the overall picture is one of diffuse impairment; c) many schizophrenic samples cannot be statistically differentiated from samples of diffusely brain damaged patients (Seidman, 1983).

These conclusions suggest, as does Seidman (1983), that the form of neuropsychological impairment evidenced by chronic schizophrenic patients "appears to be mild to moderate in severity and more likely to be diffuse or bilateral than focal" (p.212)

<u>Selected 'descriptive' studies of neuropsychological impairment in schizophrenia</u>. As stated above, the classification studies designed to validate neuropsychological tests for differential diagnoses were generally conducted with the intention of demonstrating that the tests were differentially sensitive to brain damage. Because of the commonly held a-priori assumption that schizophrenics were 'functional' and not 'organic', investigation and description of "actual" neuropsychological impairment in this group constituted a contradiction in terms and was not extensively pursued. Over the past 6 to 8 years there has been a re-appraisal of the neuropsychological findings in schizophrenia concurrent with a general re-appraisal of the concept of schizophrenia as a unitary disorder. It is now widely believed that a subgroup of schizophrenia patients suffer from a neuropathological disorder. Given this assumption, positive neuropsychological findings in schizophrenic individuals are no longer necessarily seen as a weakness in test sensitivity to functional vs. organic conditions but rather as a potentially valid reflection of brain dysfunction.

Chelune, Heaton, Lehman, and Robinson (1979) carried out an interesting study designed to examine the diagnostic utility of both mean level and pattern of neuropsychological test performance in discriminating a schizophrenic group, n=24, from two groups of diffusely brain damaged patients ('acute brain damage, n=24, and chronic brain damage, n=24).

The schizophrenic group was diagnosed based on Spitzer and Endicott's 1968 Psychiatric Status Schedule. All subjects were voluntary short stay inpatients.

The WAIS and full HRB were given to the schizophrenic group, both neurological groups, and a 150 member normal control sample used to produce a normative profile for pattern and level analysis. On the WAIS, the schizophrenic group performed significantly better than the acute brain damage sample but not differently from the chronic brain damage sample. Acute and chronic brain damage groups did not differ. On the HRB tests the acute and chronic brain damage patients did not differ significantly from each other but did significantly worse than the schizophrenic group. These investigators failed to find differences in pattern of performance between the brain disorder and schizophrenic groups.

Unfortunately, Chelune et al. (1979) present the WAIS and HRB scores only in the form of T-scores with means and standard deviation derived from their control sample hence, it is not possible to compare their samples with those of other studies. However, the study is well-designed to assess the issue of whether patterns of neuropsychological performance differ between schizophrenic patients and brain damaged individuals. This issue has been considered in earlier research (see Heaton & Crowley, 1981, for discussion) with less adequate methodology, and with mixed results. It has been of interest because of the frequent failure of

neuropsychological tests in demonstrating differences between diffusely brain disordered patients and schizophrenic groups in level of performance. According to Chelune et al. (1979), the use of 150 age and education-matched control subjects for derivation of an "ideal" normative test profile allows for more valid pattern analysis of test responses in the patient samples than would be obtained by use of general population norms (which do not control pattern and level differences found to vary with age and education). In light of their efforts at methodological adequacy in pattern analysis, the finding of a high degree of profile similarity between the diffuse brain damaged and schizophrenic samples is interesting.

A pair of studies by Taylor, Redfield, and Abrams (1981), and Taylor and Abrams (1984) provide interesting data on neuropsychological and cognitive impairment in schizophrenic patients, and a discussion of hypotheses related to lateralization of impairment vs. diffuse or bilateral impairment.

Taylor et al. (1981) used a battery of psychological tests which they refer to as "Smith's neuropsychological test battery" comprised of the WAIS, Peabody Picture Vocabulary Test (PPVT), Benton's Sentence Repetition Test, Purdue Pegboard Test, Single and Double Simultaneous Stimulation Test, Hooper Organization Test, Raven's Progressive Matrices, and Benton Visual Retention Test (BVRT). The subjects in this study consisted of 52 patients with affective disorders (both

mania and endogenous depression), 17 schizophrenic patients and 8 patients with "coarse" brain disease (CBD). "Dominant hemisphere function" was assessed from performance on WAIS Verbal IQ, PPVT, Sentence Repetition, right hand Peg Board speed, and right-sided errors on the Double Simultaneous Stimulation Test. "Nondominant hemisphere functioning" was measured by performance on WAIS performance IQ, Hooper, Raven's Matrices, BVRT, left-handed Peg Board speed, and left-sided errors on the Double Simultaneous Stimulation Test. In order to compare diagnostic groups while controlling for the effects of age, sex, handedness, education level, and drug treatment, multiple regression analyses were done with these 5 variables covaried out of the neuropsychological test scores before diagnosis was entered into the equation.

In the hierarchical regression of "dominant hemisphere function", sex, age, handedness, and drug treatment were not found to be significantly related to performance, while education was. After accounting for the variance due to these five variables, diagnosis was still significantly related to test performance and the following pair-wise group differences and similarities were found: schizophrenic subjects were more impaired than manic or depressive subjects, but not different from individuals with CBD; the affective disorder groups did not differ from each other, but did significantly better than the CBD sample.

In the regression analysis of "nondominant hemisphere function" it was found that age, education level, drug treatment and diagnosis were all significantly related to performance. Education level and increasing age were inversely related to neuropsychological performance, serum lithium level was associated with less impairment, whereas neuroleptic exposure was associated with greater impairment. After accounting for variance due to those variables Taylor et al. found that schizophrenic patients did not differ from the manic or depressed groups or from the CBD sample. The manics and depressives were not different from each other but did perform significantly better than CBD subjects.

Interestingly in stepwise discriminent function analysis using both dominant and nondominant hemisphere tests, the variables which significantly discriminated between groups were the WAIS Information, Comprehension, and Object Assembly subtests and the Hooper Visual Organization Test. Using these variables Taylor et al. obtained an overall hit rate of 84% (they comment that the discriminatory power of these four tasks is probably statistically inflated!). In summary, the authors report that the outcome of the analyses shows different patterns of hemispheric dysfunction among patient groups. The schizophrenic sample showed bilateral dysfunction and performed less well than manics on dominant but not nondominant hemispheric tasks. Affective disorder patients were impaired on tasks of nondominant hemisphere function.

In another study, Taylor and Abrams (1984) compared cognitive functioning of 62 schizophrenic subjects and 42 normals, using a variety of 'neuropsychological tasks' that included assessment of soft neurological signs, an aphasia screening test, tachistoscope stimulation, auditory threshold determinations, and items from the Mini-Mental State, Halstead-Reitan, and Luria-Nebraska batteries. Each participant's protocol was rated blindly for impairment of each hemispheric region, for laterality of impairment, and for global impairment on 5-point scales.

Using statistical procedures similar to those described in the Taylor et al. (1981) study, to control for variance attributable to age, sex, handedness, and drug administration, the investigators found that three quarters of their schizophrenic subjects showed marked to severe 'cognitive' impairment, while none of their controls did. They state that their schizophrenic subjects exhibited bilateral diffuse cognitive impairment which was more pronounced in the fronto-temporal regions. In discussing this study, the authors address conflicts in the literature with respect to the hypothesis that schizophrenia is exclusively a left-hemisphere disorder. They suggest that even the studies which were originally cited as evidence for left hemisphere dysfunction in schizophrenia (e.g. Flor-Henry's 1969 studies) actually show only a correlation between bilateral foci and schizophrenic symptoms. They conclude that their own data,

and those from studies using a variety of test strategies, can be most parsimoniously interpreted to reflect bilateral diffuse cognitive impairment in schizophrenia. However, they add that their studies and those by other investigators often find that the impairment is most pronounced in the dominant fronto-temporal regions. They make the following interesting speculation,

> "This pattern of bilateral cortical dysfunction with dominant fronto-temporal accentuation in schizophrenia may reflect selection for specific psychopathological features. Studies using diagnostic criteria for schizophrenia that rely heavily on the presence of formal thought disorder, the first-rank symptoms of Schneider, and emotional blunting and then find the pattern of dysfunction noted above raise the possibility that these phenomena are associated with dominant-hemisphere (particularly fronto-temporal) dysfunction. The cognitive pattern that we and others have observed in schizophrenics may thus reflect the choice of diagnostic criteria, and one might logically predict that patients with formal thought disorder, first-rank symptoms, and emotional blunting should demonstrate dominant fronto-temporal impairment." (p. 200)

They conclude their report with the following,

> "... lateralized dominant fronto-temporal dysfunction may give the schizophrenic syndrome its characteristic stamp, but the diffuse bilateral impairment may ultimately lead nosologists to return schizophrenia to its original classification as a dementia." (p. 200)

Finally, a study by Kolb and Whishaw (1983) shows some interesting parallels to and differences from the Taylor et al studies (1981, 1984). Kolb and Whishaw utilized an extensive battery of psychological tests to assess general intelligence and left and right frontal, temporal, and parietal lobe function in 30 carefully diagnosed DSM-III schizophrenic patients and 30 age-matched controls. The tests used in this study have been validated on patients with static atrophic lesions from the Montreal Neurological Hospital. They found that relative to the control group, schizophrenic subjects showed marked impairment on tests sensitive to right and left temporal lobe functioning (e.g. on tests of Verbal and non Verbal memory such as recall of Weschler stories and figures), on tests sensitive to right and left frontal lobe functioning (eg. Chicago Word Fluency, Gotman Design Fluency, Wisconsin Card Sorting Test). In contrast to poor performance on tests of temporal and frontal lobe function, the schizophrenic patients performed within normal limits on tests sensitive to parietal lobe function (eg. Rey Complex Figures, Corsi Block Span, Digits Forward and Backward, Right-Left Differentiation). The schizophrenic sample had a mean Full-Scale WAIS IQ 15 points lower than the control group, their Performance IQ was 19 points lower than the control group, and their verbal IQ 6 points lower.

The authors conclude that the data suggest that schizophrenia is accompanied by a selective bilateral dysfunction of

the frontal and temporal lobes in the presence of relatively normal functioning of the parietal lobes. They discuss an alternative possibility, suggesting that if parietal lobe tests are less sensitive to diffuse disorders than the other tests used, then rather than having a specific deficit of frontal and temporal lobe functioning, schizophrenics might be better described as exhibiting diffuse impairment. They argue against this interpretation on grounds that: a) tests such as digit span and Right/Left Differentiation have been shown to be very sensitive to diffuse left hemisphere abnormality; b) glucose metabolism and cerebral blood flow studies indicate abnormal function in frontal lobes of schizophrenic individuals; c) and absence of reported evidence of structural abnormality within the parietal cortex of schizophrenics.

Summary of descriptive studies. Chelune et al. (1979) found that their schizophrenic sample performed at a significantly higher level on the HRB than both the acute and chronic diffusely brain damaged patients. On the WAIS schizophrenic patients did not differ from chronic brain damaged patients but did better than acute brain damaged patients. When level of performances differences were removed, profiles of tests performance were very similar among the groups. On the basis of their data the authors conclude that when carefully screened groups of noninstitutionalized schizophrenics and brain damaged individuals are compared, differences in mean level of performance will be found, but schizophrenic subjects

would be expected to show a pattern of test battery scores on the HRB that is indistinguishable from that of diffusely brain damaged patients.

Taylor et al. (1981, 1983) found global deficits indicative of diffuse impairment in their two samples of schizophrenic patients. Taylor et al. (1981) were unable to distinguish schizophrenic patients from individuals with coarse brain damage on tests intended to assess dominant and nondominant hemisphere function. In addition to global impairment, Taylor and Abrams (1984) found an accentuation of deficit performance on tests intended to measure dominant frontal lobe function in their schizophrenic sample. Kolb and Whishaw (1983) found marked performance deficits on tests sensitive to frontal and temporal lobe function, with normal performance on tests sensitive to parietal lobe lesions.

Thus the literature reviewed presents some consistencies and a few apparently contradictory findings. Results such as those reported by Chelune et al. (1979) might be expected in light of a) the 'subgroup hypothesis', under which we would expect only a certain proportion, probably considerable less than one half of a representative sample of schizophrenics, to be members of a subgroup with identifiable neurologic dysfunction, and b) the findings of the numerous classification studies which indicate that 'chronicity' or severity of illness is a significant factor in determining the likelihood that a neuropsychological deficit will be found.

The Chelune et al. (1979) schizophrenic sample were a) "rigorously screened" to rule out neurologic disease, b) voluntary patients in a short stay treatment facility and c) were diagnosed by DSM-II criteria, potentially contributing to a more heterogeneous sample than in other studies. Given these sample characteristics this study may resemble those reported by Heaton et al. (1978) under the headings of classification studies with "acute or reactive schizophrenia". The median hit rates for distinguishing between psychiatric and organic groups for studies using these populations were 77% and 69% respectively.

The Taylor et al. (1981) and Taylor and Abrams (1984) studies are consistent in demonstrating a high prevalence of global impairment in neuropsychological functioning. The Kolb and Whishaw (1983) study reports marked impairment on frontal- and temporal lobe-sensitive tests which is consistent with Taylor and Abrams (1984); however these studies differ in that Taylor and Abrams also report impaired performance on parietal lobe tests. These investigators used different tests to assess parietal function and unfortunately Taylor and Abrams (1984) do not specify which tasks in their battery were considered parietal lobe tests. In any case, although these studies do not show consensus on the issue of diffuse vs. localized dysfunction, the Taylor et al. (1981), Taylor and Abrams (1984), and Kolb and Whishaw (1983) studies are

concordant with respect to observing bilateral deficits on tests believed sensitive to temporal and frontal function.

Concluding comments on definition and description of neuropsychological and cognitive functioning in schizophrenia. As one proceeds through the topics discussed in this review (i.e. eye tracking deficits, CT scan abnormalities and finally neuropsychological and cognitive dysfunction) there appears to be an exponential increase in the number of ways abnormalities might be and have been defined. The terms 'neuropsychological' and/or 'cognitive' function - also impairment, deficit, and dysfunction - have a wide variety of specific and general referents. For the purposes of this review, little would be gained from what would necessarily be an inadequate attempt to enumerate the many different senses in which these terms might apply (or be inappropriate) in schizophrenia. Even the potentially important distinction between measures of 'intelligence' as distinct from 'neuropsychological function' will not be attempted. For present purposes it will be asserted that neuropsychological function may be operationally defined as scores on a variety of tests, including intelligence tests, conventionally thought of as neuropsychological measures.

It is apparent from the literature reviewed that some schizophrenics, and particularly chronic schizophrenic patients, perform in a manner statistically indistinguishable from brain damaged comparison groups. Deficits are found in

such a wide variety of tests that many investigators conclude there is a subgroup of schizophrenic patients who are globally impaired and who probably suffer from a diffuse brain disorder. Despite repeated findings of this sort, there are a sufficient number of inconsistencies and outright contradictions in the literature to preclude specifying any set of tests, or any measurement paradigm, as the most appropriate or sensitive measure of 'the schizophrenic deficit', if indeed such a thing exists.

Prevalence of Neuropsychological Impairment

Information on this parameter is rather scarce, and necessarily confounded with diagnostic and sampling procedures applied by individual investigators, as well as the fact that 'impairment' is relativistic, not absolute. To date there are no published reports of attempts to systematically collect neuropsychological data from a large representative sample of individuals who would be currently diagnosed as schizophrenic.

Some of the studies reviewed do provide estimates of the rates of impairment in their samples that are based on cutting scores derived from neurologic populations. Donnelley et al. (1980) and Reider et al. (1979) used the Average Impairment Rating method to assess degree of impairment on the HRB. Donnelley et al. (1980) classified 9/15 (60%) of their sample of young chronic schizophrenics as impaired and Reider et al.

(1979) found 5/8 (62%) of a similarly diagnosed sample were impaired.

Taylor and Abrams (1984) and Kolb and Whishaw (1983) compared their samples to normal control groups. Taylor and Abrams found that approximately 75% of the 62 schizophrenic subjects exhibited moderate to severe dysfunction relative to normals. Kolb and Whishaw (1983) report that only 5 of their 30 schizophrenic subjects performed in the normal range for the whole battery of tests which assessed frontal and temporal lobe function; however, it does not necessarily follow that the remaining 25 would be classified as "impaired". While the authors report that mean level of impairment was greater in the schizophrenic group they do not attempt to distinguish or enumerate "impaired" vs "nonimpaired" individual subjects so as to provide rates.

The above "prevalence rates" are actually arbitrary and sample specific definitions of impairment, except for the 3 studies which used standard impairment indexes with the HRB. A more satisfactory approach might be the development and application of test norms derived from psychiatric populations, such that one could compare test scores to standard performance of other similarly diagnosed patients and determine the extent of "impairment" in a given individual. Obviously an even more ideal situation would be the development of tests, for psychiatric disorder patients, with known neurologic criterion validity. At present, however,

impairment must in general be defined relative to a specific control sample or to cut off scores developed in neurologic patient samples, and prevalence rates will be therefore be a function of these definitions.

Medication and neuropsychological performance. Given the powerful effect neuroleptic drugs have on the psychotic behavior of schizophrenic patients, the possibility that neuropsychological performance deficits are the result of medication must be seriously considered. Ethical considerations preclude full experimental investigation of this issue over a time span sufficient to address the effect of chronic neuroleptic use. Heaton and Crowley (1981) selectively reviewed the literature on the effects of neuroleptic drugs on neuropsychological performance. They indicated that much of the research to date is flawed by the failure of researchers to distinguish the effects of drug classes, failure to use diagnostically homogeneous groups of patients, inattention to the complex relationships of dose and blood levels of medication, and failure to control for other concomitant treatments. In addition, some studies fail to consider drug tolerance and test learning as possible factors in re-test performance changes.

The majority of studies of acute or short-term administration of neuroleptics typically have utilized normal subjects such as college students. These studies measure side effects of acute administration of neuroleptics at various

doses. Heaton and Crowley (1981) report that acute administration in higher doses of the neuroleptics with significant anticholinergic properties (eg. chlorpromazine and thioridazine) impair performance on a variety of motor and cognitive tests. The neuroleptics in the piperazines group (eg. trifluoperazine) and haloperidol have little anticholinergic effect and do not seem to impair cognitive function or motor speed, but are more likely to produce acute extrapyramidal side effects which impair performance on some motor coordination tasks. The studies suggest that early in the course of neuroleptic drug administration, or shortly after marked increases in dosage, there may be significant drug-induced abnormalities in neuropsychological performance which will vary with the type and dose of neuroleptic, and of the ability being tested (Heaton and Crowley 1981).

In long tern administration of neuroleptics the early side effects diminish as tolerance develops and there is frequently a clinical improvement in psychiatric symptoms. A paradigm for assessing drug effects on neuropsychological performance in patients treated with long-term courses of neuroleptics involves a drug washout period of at least one month followed by random assignment to drug and placebo conditions. Heaton and Crowley (1981) cite 4 studies of this sort. The findings suggest that relative to the placebo condition there was a favorable effect of neuroleptic drugs on

attention and simple information processing but not a measurable effect on more complex cognitive processes.

Subject characteristics; effect of age, education and ethnicity on neuropsychological performance. Age has repeatedly been shown to interact with performance on neuropsychological tests (Bak and Greene, 1980; Karzmark, Heaton, Grant, & Matthews, 1984). Although this is an issue to be considered when research is conducted with samples composed of subjects varying widely in age, marked effects of age on test performance are most usually noted in subjects entering their 70s and 80s.

Education level has been found to have a significant effect on the accuracy of test-derived classifications of 'normal' vs. 'brain damaged' status. Non-brain damaged individuals who are younger, more intelligent, and well educated tend to be correctly classified whereas less well educated individuals are more likely to be misclassified as brain damaged. The converse is true for brain damaged individuals (Adam, Boake, & Crain, 1982; Anthony, Heaton, & Lehman, 1980; Finlayson, Johnson, & Reitan, 1977).

Karzmark et al. (1984), using 491 neurologically normal persons, developed and cross-validated an equation that uses demographic variables to predict the Average Impairment Ratings on the HRB. They found that in this sample of normals, AIR correlated significantly with age ($r=0.66$), race ($r=0.23$), education ($r=-0.54$), and occupation ($r=-0.43$). In a

regression analysis using these variables, 65% of the variance in AIR scores for the derivation sample was accounted for and 59% in a cross validation sample.

Clearly, demographic variables cannot be ignored in research utilizing neuropsychological tests. Small sample studies typically attempt to obtain fairly homogeneous groups or alternately use statistical techniques such as those applied by Taylor et al. (1981, 1984) to control for variance attributable to differences in subject status on demographic variables.

Significance on Neuropsychological Deficits in Schizophrenia

The importance of reported neuropsychological impairment in schizophrenic patients is critically related to two issues. First, it must be determined whether deviant performance on neuropsychological tests is indeed a valid indication of brain dysfunction and not simply an artifact of clinical, demographic, or treatment factors. Further, if there are grounds for reasonable confidence that neuropsychological deficits are not simply secondary phenomena, then there remains the task of determining the clinical significance of these deficits in schizophrenic patients - ie. are neuropsychological deficits systematically associated with important etiological or prognostic factors?

The occurrence of cognitive impairment in some schizophrenic patients and its association with poor prognosis are

observations as old as the diagnosis itself. Neuropsychological literature is quite consistent in demonstrating that impairment is most common and severe in chronically ill patients. Further research must address the antecedents of this correlation, as it is still not clear whether neuropsychological impairment is causally implicated in the development of severe and chronic psychopathology or is a by-product of that clinical syndrome.

Despite the present ambiguities in the interpretation of neuropsychological findings in schizophrenia, some recent studies provide valuable descriptive information and contribute to the emergence of a broadly based 'new look' at the schizophrenia syndrome.

Summary of Neuropsychological Findings in Schizophrenia

Several aspects of the neuropsychological literature have been discussed in this review and may be summarized as follows: 1) Overall, the classification or differential diagnosis studies show that chronic schizophrenic patients are very difficult to distinguish from individuals with diffuse brain dysfunction. When popular neuropsychological screening tests and full neuropsychological batteries are applied to groups with prior diagnoses of brain damage and chronic schizophrenia, investigators report essentially chance level of classification accuracy. In contrast, the median level of correct classification between brain damaged patients and less

disturbed schizophrenics or other types of psychiatric patients is approximately 75%. 2) The majority of descriptive studies of the nature of the neuropsychological impairment occurring in schizophrenics, suggest that the pattern of impairment involves generalized deficits on most common neuropsychological tests. However research is not unanimous on this matter. Some investigators report that impairment is most marked on tests sensitive to frontal and temporal lobe function, and Kolb and Whishaw (1983) report normal attainment on parietal lobe tests. 3) Difficulties associated with the definition of neuropsychological impairment, and the choice of appropriate comparison groups for schizophrenic patients, make it difficult to assess the prevalence of neuropsychological dysfunction in samples of schizophrenic patients. Four studies discussed earlier in this review report the proportion of patients who perform in an impaired range relative to either standard impairment cutting scores or normal control groups. The Average Impairment Rating (AIR) is a commonly used scale for reporting the severity of impairment on the HRB. Donnelley et al. (1980) and Reider et al. (1979) classified as impaired 60% and 62% respectively of their samples of chronic schizophrenics. Relative to normal controls, Taylor and Abrams described 75% of their sample of schizophrenics as exhibiting moderate to severe impairment. 4) Because diagnostic practices have changed over time, and research reports vary considerably in

the extent to which the sample is described on factors such as chronicity and severity of illness, it is not possible to derive cumulative rates of neuropsychological impairment in chronic, vs. acute schizophrenic patients. Nonetheless there is considerable converging evidence that impairment is most frequent in chronic severely-ill patients, and occurs at a lower rate in groups of acute/reactive schizophrenic patients despite the presence of clear psychotic symptoms. 5) The relationship of neuroleptic medication to neuropsychological performance is not well understood. Available research suggests that the most marked detrimental effects of neuroleptics may be early in the course of administration or shortly after marked increases in dosage (ie. during times when the side effects of the medications are typically most pronounced). There is evidence that antipsychotic medication may have a positive effect on neuropsychological functioning; patients who are stabilized on medication exhibit increased ability on tests of attention and simple information processing relative to their performance in an unmedicated state. 6) Age, IQ, education level and ethnicity have all been associated with attainment on neuropsychological tests. Demographic variables must be considered in research utilizing neuropsychological tests. 7) The significance of findings of neuropsychological impairment in schizophrenia awaits further research. There remains the possibility that neuropsychological performance deficits are not valid

indicants of brain dysfunction in psychiatric patients. It may be more realistic to attribute impaired scores to generalized behavioral disorder associated with psychiatric disturbance. Testing the correctness of this interpretation will require considerable further research. Particularly useful would be assessment in high risk samples and longitudinal investigations of patients who evidence remissions. However, as neuropsychological impairment appears to be most common in severely ill, unremitting patients, decoupling severe behavioral disturbance from impairment on neuropsychological tests is often not possible. 8) Research most likely to establish the significance of neuropsychological deficits will be in the area of documenting relationships between neuropsychological performance and other variables of clinical, biological, etiological, and prognostic significance.

Summary of Relationships Among Measures of Smooth Pursuit Eye Movements (SPEM), Lateral Ventricle Enlargement (LVE), and Neuropsychological Test Performance (NTP) in Schizophrenia

This final section of the literature review will be a brief summary of several studies cited in the previous three sections. The purpose of this section is to highlight research which has examined associations between various

combinations of measures of smooth pursuit eye movements (SPEM), lateral ventricle enlargement (LVE), and neuropsychological test performance (NTP).

SPEM and LVE

Weinberger and Wyatt (1982) assessed the association between tracking proficiency of 20 patients with normal ventricles, and 14 patients with enlarged ventricles. Sixty four percent of the large ventricle subjects showed impaired tracking compared with thirty percent of the small ventricle subjects. This work by Weinberger and Wyatt was investigatory in nature. The eye movements were generated by a swinging pendulum and rated qualitatively. Nonetheless it does suggest that enlarged ventricles may be associated with impaired SPEM. The other investigation which assessed the association between SPEM and LVE was carried out by Bartfai et al. (1985) (see the following section on SPEM, LVE and NTP, for a full description of this study). They found that few patients in their sample had evidence of morphological changes in anterior horn size (a linear measure of lateral ventricle size), but they noted a tendency for the most impaired eye trackers to have a larger anterior horn index than patients with good or slightly impaired eye movements.

SPEM and NTP

Holzman (1974) and Cegalis and Sweeny (1979, 1982) addressed associations between Wechsler scale IQs, educational attainment, and tracking performance. These investigators failed to find correlations between partial or full scale IQ or educational attainment and tracking proficiency. See following section on SPEM, LVE and NTP for discussion of the Bartfai et al. study.

LVE and NTP

There are several studies which have addressed this relationship as indicated in a previous section of this review (see 'Cognitive/neuropsychological function and CT scan abnormalities'). It was pointed out that a sizable proportion of the literature on cognitive impairment and brain morphology has included measures other than lateral ventricle size; most frequently assessments of sulcal prominence. Several investigators have reported a relationship between marked sulcal prominence and deficits in cognitive functioning. Unfortunately there is no consensus in the literature with respect to assessing this aspect of brain structure from CT scans; there is evidence that the level of the upper most CT scan cut has considerable influence on ratings of sulcal prominence and is not standardized across studies. In addition to studies which have focused on the relationship between sulcal prominence and cognitive functioning in schizophrenia there are

other investigations which assess the relationship between "structural abnormality" (on several CT scan visualized aspects of brain structure) and cognitive impairment. Thus while Donnelly, Weinberger, Waldman, and Wyatt (1980), and Weinberger et al. (1979b) found associations between structural abnormality and impaired cognitive functioning, they do not report the extent of the relationship between LVE and impaired intellectual performance. In overview, it appears that many of the strongest claims for an association between brain structure and level of cognitive functioning derive from investigations involving measures of the sulci and combinations of several morphological measures.

There are reports of a significant relationship between LVE and cognitive impairment. Johnstone et al (1976) reported a correlation of -.70 between Withers-Hinton scores and VBR; Golden et al. (1980a) reported a multiple correlation coefficient of 0.72 between eight Luria Nebraska Battery scales and VBR. Golden et al. (1982) found a multiple correlation of 0.76 between 14 Luria Nebraska scales and VBR.

Some studies assessing the relationship between lateral ventricle size and neuropsychological/intellectual function have failed to find significant correlations despite reasonable ranges in levels of cognitive performance and a reasonable proportion of individuals evidencing LVE (Nasrallah et al., 1983a & 1983b; Weinberger et al., 1979; Williams et al., 1985).

Two recent additions to the literature have reported novel relationships between measures of cognitive functioning and lateral ventricle size. DeMeyer et al. (1984) found significant VBR/neuropsychological test correlations in the direction opposite to that normally predicted for total summary scores and individual subtests on the Luria Nebraska Battery, the Halstead-Reitan Battery, and the Wechsler Adult Intelligence Scale. The correlation of VBR with the Halstead Impairment Index was -.77, VBR correlated .79 with WAIS verbal IQ, .59 with performance IQ, and .73 with full scale IQ. These correlations were obtained using the scores of a sample of 13 treatment-resistant psychiatric patients of mixed diagnoses (half were schizophrenic). In this sample, the nonschizophrenic patients tended to have larger VBR's and had a slightly higher mean IQ. Overall, the DeMeyer et al. study is not specific to schizophrenia. Rather it assesses the relationship between VBR and neuropsychological performance in a sample of psychiatric patients selected by chronicity and poor response to treatment rather than diagnosis. Finally, Owens et al. (1985) reported a significant curvilinear relationship between VBR and scores on the Withers and Hinton test in a sample of 110 institutionalized schizophrenic patients. This unexpected finding of an excess of patients with low Withers and Hinton scores at both extremes of ventricle size suggested to Owens et al. that there may be two groups of cognitively impaired schizophrenic patients. One group would

be expected to exhibit ventricular enlargement, while another group of cognitively impaired patients may have ventricles which are small compared to the normal control mean.

SPEM, LVE and NTP

The study by Bartfai et al. (1985) is of particular interest as they examined the same set of variables as those used in the present research study. Bartfai et al. report that most of their sample of 18 schizophrenic patients exhibited some degree of eye tracking impairment. They found that SPEM impairment was related to worse performance on the three neuropsychological measures administered. Eye movement records were visually rated for deviance from the stimulus pattern on a 5-point scale. The eye tracking ratings obtained by subjects were then correlated with their scores on the Finger-Tapping Test, Trail-Making Test, and reversals of a Necker cube. They found the following correlations between smooth pursuit tracking proficiency of a sinusoidal target and the neuropsychological tests: $r = -.45$ ($p<0.10$) for finger-tapping left hand; $r = -.49$ ($p<0.05$) for finger-tapping right hand; $r = .56$ ($p<0.01$) for Trail-Making Test A; $r = .37$ (NS) for Trail-Making Test B; and $r = -.53$ ($p<.05$) for the number of Necker Cube reversals. Bartfai et al. failed to find a significance difference in anterior horn index between groups of subjects created on the basis of eye tracking proficiency. However, they suggest that subjects who tracked more poorly

tended to have wider lateral ventricles than subjects with good or slightly impaired eye tracking. The authors do not report findings relating the neuropsychological tests to the measure of lateral ventricle width.

Despite apparent similarities, the present study and the Bartfai et al. (1985) report differ in several significant ways. The Bartfai et al. sample was a heterogeneous group of schizophrenic patients consisting of 18 subjects (11 males, 7 females) ranging in age from 23 to 42 years. Two thirds of the sample were outpatients, one half of the subjects had only one hospitalization, and one third were classified as chronic. In contrast, the 30 subjects participating in this study were considerably more homogeneous. All were male DSM-III chronic schizophrenics who were inpatients at the time of testing. There are advantages and drawbacks implicit to both types of samples. While the Bartfai et al. sample is more likely to be representative of schizophrenics in general, the heterogeneity in sex, age, duration of illness and hospitalization status may introduce numerous confounds which obscure the relationships between variables. In addition, the present study differs considerably from that of Bartfai et al. with respect to measurement and quantification techniques for smooth pursuit eye tracking, lateral ventricle size, and in terms of the extensiveness of the neuropsychological battery. The following report discusses the results of a research project involving 1) sophisticated measurement and computerized

scoring of smooth pursuit eye tracking performance; 2) an extensive neuropsychological battery including a full Weschler Intelligence scale (WAIS-R) and 3) a measure of lateral ventricle size estimated by mechanical planimetry in conjunction with a large series of scans that include a volunteer normal control group. The above methodological refinements stand somewhat in contrast to the measurement techniques of Bartfai et al. These investigators assessed smooth pursuit tracking performance using visual ratings of tracking deviance. Lateral ventricle size was estimated by a linear width measurement of the anterior horns of the lateral ventricles. This method has consistently been found to have the lowest inter-rater reliability, and the lowest correlation with criterion measures of ventricular volume of any of the commonly used indexes of lateral ventricle size (Reveley, 1985). The neuropsychological tests were administered on a computer in a session lasting 10 minutes. While two of the tests are routinely administered, the computerized presentation is not standard and the results may not be comparable to other studies. Finally, Bartfai et al. did not include control groups for any of their measures; it is not possible to determine if their sample were actually deviant on any of the variables, hence the significance of their findings is unknown. Overall, despite the similarity of purposes between this study and the Bartfai et al. study, there are considerable differences in subject characteristics, measure-

ment techniques, and the use of control groups. These differences make the present study and the report of Bartfai et al., two distinct approaches to the investigation of the relationships between smooth pursuit eye tracking, lateral ventricle size, and neuropsychological performance.

Conclusions From Literature Review

The preceding review has dealt with progress to date in matters of definition/description, prevalence rates and clinical/theoretical significance of smooth pursuit eye tracking dysfunction, CT scan abnormality, and neuropsychological performance deficits in schizophrenia. Repeatedly the research has demonstrated that some, but not all, schizophrenic patients are deviant relative to the normal range on these variables. This is consistent with the contemporary view of schizophrenia as a heterogeneous disorder which is probably composed of a number of more homogeneous subgroups. It is clear that for each of the three variables discussed, deviant standing would not be predicted for all individuals currently diagnosed as schizophrenic. However, it is equally apparent that the majority of studies were not specifically designed to address this issue. The following discussion of the subgroup issue is offered as an attempt at synthesis of the research findings and as a rationale for the present study.

Attempts to delineate and describe subgroups within the diagnostic classification 'schizophrenia' have a long history. A typical research approach to the subgroup issue is to find or posit a variable or dimension on which groups of schizophrenics may be differentiated. Subgroups which differ with respect to this classification variable are then investigated to determine the ways in which they differ for other clinically significant aspects of the disorder. Historically subgroups have been formed on the basis of clinical or phenomenological dichotomies such as paranoid vs. non-paranoid, or good premorbid vs. poor premorbid status (Wyatt, Potkin, Kleinman, Weinberger, Luchins, & Jeste, 1981). As pointed out in the introductory statement of this review, current research in schizophrenia is increasingly turning to biological variables in attempts to understand the causes of schizophrenia, and when characterizing the underlying dimensions which may delineate subgroups within the diagnostic category.

CT scans and eye movement measures are examples of what Wyatt et al. (1981) call "biological tools for subclassification". They point out that to date researchers have been unable to divide schizophrenia into biological subtypes. In part they attribute this to a long held bias toward a unitary disease model. However, they add that even when the concept of subgroups is subscribed to, the success of the endeavor is compromised by "enormously high variance in almost all current

measures on schizophrenic patients". (Wyatt et al., 1981, p.100). At present it appears that single biological measures are insufficient in providing a basis for valid identification of homogeneous subgroups. An alternative approach might be the use of combinations of measures which are believed to tap a similar underlying dimension. Use of a combination of measures also aids in describing the characteristics of the putative subgroup in a more adequate fashion than would result from single measures. However, it clearly requires a multi-stage research strategy to validate the use of a combination of measures as a more adequate basis of classification. A preliminary stage in this endeavor involves simultaneous measurement of the variables of interest in a single sample of subjects in order to demonstrate an association.

As indicated repeatedly in this review, many investigators speculate that there is a subgroup of schizophrenic patients who suffer from a brain disorder which might be characterized as a form of dementia (Crow, Cross, Johnstone, & Owen, 1982; Taylor & Abrams, 1984). It is speculated that smooth pursuit eye tracking dysfunction, lateral ventricular enlargement, and deficits in neuropsychological performance are all potential indicants of putative brain disorder. Further, it is assumed that each measure has weaknesses in sensitivity and specificity for detecting this disorder. The current project is an investigation of the covariation of these measures in a population expected to have a moderately

high prevalence of these dysfunctions. Clearly the major issue of whether a brain dysfunction does or does not exist cannot be determined in this manner. What can be assessed is the extent of relationship between these variables. This should allow an estimate of the likelihood that they might form a useful combination for defining a subgroup which might then be investigated with respect to meaningful psychosocial and clinical parameters.

RESEARCH OBJECTIVES

The primary purpose of this study is the investigation of the relationship between lateral ventricle size, smooth pursuit eye tracking, and neuropsychological test performance in a sample of carefully diagnosed chronic schizophrenic patients. The relationships among these measures is of interest because each of them is considered to be either a sign of, or sensitive to, brain dysfunction. If deviations on these measures is indeed a feature of a subtype of schizophrenia involving significant neuropathology, one might expect this subgroup to be most highly represented among seriously ill institutionalized patients of the sort assessed in this study.

In order to relate the results of this study to others in the literature it is necessary to assess the extent to which the present sample exhibits deviant status on the measures of interest. To address this issue, two control groups are included in the design. A group of normal volunteer controls serve as comparisons for VBR and eye tracking. The neuropsychological performance of the schizophrenic group is compared to that of a group of non-schizophrenic psychiatric patients and to norms obtained from test manuals. The issues involved in selection of an appropriate comparison group for neuropsychological tests used with schizophrenics are not simple. The advantage of using non-schizophrenic psychiatric

patients is that this group provides some measure of control for psychiatric status per se, and is a more conservative comparison than would be obtained by using test norms derived from normal samples. The obvious drawback is that non-schizophrenic psychiatric patients may exhibit peculiar patterns of strengths and deficits which make interpretation of group differences difficult.

In addition, relationships among the neuropsychological tests in the schizophrenic sample will be examined. The small sample size precludes sophisticated multivariate and factor analytic analyses. Nonetheless, examination of intercorrelations is a means of linking this study to theoretical and empirical statements in the literature.

Hypotheses

Group Differences

It is predicted that the sample of schizophrenic subjects will differ significantly from the control groups, in the direction of greater impairment, on the measures of 1) VBR, 2) smooth pursuit eye tracking, and 3) neuropsychological test performance.

Correlations Among VBR, Smooth Pursuit Eye Tracking and Neuropsychological Performance

It is predicted that there will be the following relationships among the principal measures:

i) Ventricle brain ratio and smooth pursuit eye tracking performance will be correlated such that individuals with larger ventricles will be found to have more impaired eye tracking.

ii) Ventricle brain ratio and neuropsychological performance will be correlated such that individuals with larger ventricles will be more impaired on the neuropsychological tests than those with smaller ("normal") ventricles.

iii) Smooth pursuit eye movements (SPEM) and neuropsychological performance will be correlated such that individuals with more impaired eye tracking will be more impaired on the neuropsychological tests. The relationship between SPEM and neuropsychological performance could be of two sorts: a) if SPEM impairment is associated with a diffuse brain disorder then one might expect SPEM impairment to be related to global impairment on the neuropsychological tests. b) if SPEM impairment is a result of a marked, or specific frontal lobe dysfunction, it might be expected that impaired eye tracking would be most strongly associated with tests considered sensitive to frontal function (six of ten in battery).

Correlations Within Battery

Although not central to the major hypotheses of the study, there are certain correlations which might be predicted within the neuropsychological test battery on the basis of the literature.

i) WAIS-R Verbal and Performance IQ's are predicted to be correlated the other measures of neuropsychological performance.

ii) The neuropsychological test battery includes the Category Test, Finger Tapping Test, Trial Making Test, Word Fluency Test, and the Wisconsin Card Sort Test. These tests are believed sensitive to frontal lobe functioning and would be expected to be correlated in the sample of schizophrenic patients.

METHOD

Subjects

Chronic schizophrenic patients. Thirty male chronic schizophrenic patients, recruited form a large provincial mental hospital (Riverview Hospital), served as subjects. Recruitment procedures were carefully designed and executed to insure that the obtained sample was composed of consenting consecutive admissions, who satisfied the inclusion and exclusion selection criteria for the study. Individuals were included in the project if they, i) satisfied Diagnostic and Statistical Manual III (DSM III; American Psychiatric Association, 1980) criteria for diagnosis of chronic schizophrenia, ii) were male and under 35 years of age, iii) were sufficiently verbal and cooperative to participate in the diagnostic interview and give written consent, iv) were without documented neurological conditions and, v) had not been treated for substance dependence.

Initial screening of the hospital population was done from a computerized data-bank which provided demographic information and principal and secondary psychiatric and medical diagnoses, using the International Classification of Diseases System (ninth edition). From the computer data base an initial subject pool of males under age 35 with diagnoses of schizophrenia was identified. The hospital records of these individuals were examined to determine duration of illness, presence of neurological diagnoses, history of

treatment for substance dependence, number of previous hospitalizations, and to record information which would assist in the diagnostic interview that was conducted as part of the selection procedures. If, on the basis of charted information there were no clear grounds to exclude the individual, his psychiatrist was contacted and permission to discuss the project with the patient was requested.

Using the subject selection procedure outlined above, 103 consecutive admissions were identified as potential subjects over the period of recruitment and testing (5 months). Due to a several week lag time in processing of patient discharges through the hospital computer data base, 25 patients in the initial group of 103 had been discharged before it was possible to contact them about the study. From a pool of 78 inpatients, 35 were interviewed and met the selection criteria for this study. Five of these patients could not be included in the study; one refused to continue after the selection interview, one refused to do the neuropsychological testing, two were too seriously disturbed to be taken from the hospital to the CT scanner location and one was extremely hostile and expressed paranoid concerns about the experimenters during the diagnostic interview. Of the remaining 43 individuals, 20 refused to participate, 8 patients were interviewed but did not meet the diagnostic criteria for the study, and 15 were felt to be unsuitable by their physicians. In this latter group unsuitability was determined by a number of factors

including; i) the patient was considered an extreme elopement risk or had recently been violent, ii) the patient was grossly disorganized or inaccessible, iii) the patient was to be discharged before a selection interview could be arranged or, (iv) the patient had recently been rediagnosed, often as having a neurological disorder.

Comparisons between subjects who refused to participate (n=20) and those who took part in the study could be done using information available from the Riverview Hospital data bank. Subjects who refused had a mean age of 27.9 (SD 4.27) and an average number of admissions to Riverview Hospital of 2.6 (SD 2.1) whereas those who participated had a mean age of 28.2 (SD 3.71) and had an average number of admissions to Riverview Hospital of 1.9 (SD 2.3) admissions. The groups do not differ significantly on either of these variables.

The thirty schizophrenic patients who participated in the study were given a structured diagnostic interview using the Present State Examination (PSE) (Wing, Cooper, & Sartorius, 1974) as a routine part of the selection procedure. This interview was conducted by one of two Ph.D. psychologists with extensive experience with the PSE and the diagnostic issues relevant to selecting schizophrenic patients for research. Symptom checklists for DSM-III diagnostic criteria were completed for each patient based on the PSE, and supplemented by chart information relevant to duration of illness, previous diagnoses and decline in level of functioning. The diagnosis

of DSM-III chronic schizophrenia and the schizophrenic subtype (see Table 5) were determined on the basis of consensus on the above issues by the two diagnosticians. Thus each patient included in the project had an ICD-9 diagnosis of schizophrenia according to hospital records and was also independently diagnosed for the study using DSM-III criteria for chronic schizophrenia based on an extensive diagnostic interview supplemented by chart information. It should be noted that despite the care taken in diagnosis, some patients were found to be poor historians who presented contradictory information, inconsistencies in patient reports were often recorded in their charts as well.

Tables 1 and 2 present age and educational levels for all groups involved in the study. Tables 3 and 4 present a summary of the number of hospitalizations and total accumulated length of institutionalization for the chronic schizophrenic patients. Seventy six percent (23) of the schizophrenic patients did not finish high school, one patient completed one year of a community college. The range for number of hospitalizations was from 1 to 12, with 80% of the patients having 5 to 8 admissions. The range of accumulated duration of hospitalization spans several years (from 10 years to 2 months); 20% of the sample had spent more than four and one half years in mental institutions, 50% had spent between two and four and one half years in hospital, and 30% had spent less than two years in hospital. It is interesting to note

Table 1

Age of Participants

	Groups		
	Schizophrenics (n=30)	Normal Controls (n=29)	Psychiatric controls (n=21)
Mean	28.2	24.2	25.4
SD	3.71	5.74	5.5
Range	22-34	16-42	17-34

Table 2

Educational Attainment of Participants

	Groups		
	Schizophrenics (n=30)	Normal Controls (n=29)	Psychiatric controls (n=21)
Educational Level	number (%)	number (%)	number (%)
Grade 9 or less	9 (30%)	-	1 (5%)
Grade 10 to 12	19 (63%)	7 (24%)	15 (70%)
Post secondary training	1 (3%)	14 (48%)	2 (10%)
BA/BSc	-	5 (17%)	2 (10%)
Post Graduate	-	1 (3.3%)	1 (5%)
Not Known	1 (3%)	2 (6.8%)	-

Table 3

Number of Psychiatric Hospitalizations for Chronic Schizophrenic Patients[a]

Number of Hospitalizations	Number of Patients	Mean Age of Group
1-3 hospitalizations	1	33.0
4-6 hospitalizations	15	28.5
7-9 hospitalizations	10	27.2
10-12 hospitalizations	4	30.3

Note. There are no significant differences in age between the groups

[a]Average number of admissions for entire sample is 6.7 (SD 2.6)

Table 4

Accumulated Duration of Institutionalization (in months) for Chronic Schizophrenic Patients[a]

Duration	Number of Patients	Mean Duration for Group	Mean Age of Group
2 m. to 23 m.	11	10.3 m.	28.3
24 m. to 47 m.	12	33.2 m.	27.7
48 m. to 83 m.	5	60.4 m.	27.8
84 m. to 113 m.	2	92.2 m.	32.0

Note. There are no significant differences in age between the groups

[a]Average accumulated duration of hospitalizations for entire sample is 33.6 months (SD 25.69)

Table 5

DSM III Subtypes of Schizophrenia in Chronic Schizophrenic Sample

	Groups		
Measure	Paranoid Subtype	Disorganized Subtype	Undifferentiated Subtype
Number of Patients	21	4	5
Mean age (SD)	28.3 (3.72)	28.2 (3.30)	28.0 (4.47)
Mean Cumulative Duration of Hospitalizations (SD)	32.5 (27.4)	44.2 (36.29)	29.0 (20.24)

that there are no significant age differences between subjects grouped on the basis of number or duration of hospitalizations. Five patients in the study were on an extended care locked ward, 12 were on wards designated for long term patients, and 13 patients were on wards intended for admissions of less than six months.

The exclusion criteria for this study included history of treatment for substance dependence. While no subjects had specifically been treated for substance dependence, several subjects had histories of extensive substance abuse and/or dependence involving alcohol, marijuana, LSD, and a variety of illicit street drugs. Each subject was interviewed using the drug and alcohol portions of the NIMH Diagnostic Interview Schedule (DIS-III: Robins, Helzer, Croughan, Williams, & Spitzer, 1981). The accuracy of several patient reports is questionable, particularly as the DIS requires specific information about the duration of daily use, number of times various drugs were used, and the effect of drug and alcohol use on social, familial, and work functioning. Some individuals appeared to exaggerate their drug use histories (e.g., one individual claimed to be using vast quantities of street drugs and drinking large amounts daily during several months within he was in hospital; hospital staff denied that this occurred), while several patients were believed to minimize the extent of their past drug use. Based on material recorded in patients' charts and information obtained from the

DIS it it estimated that 11 of the subjects had histories of extensive alcohol or illicit drug abuse (e.g. daily use of marijuana over periods of several months, frequent glue sniffing, extended periods of alcohol use on a daily basis, etc.); 11 subjects had experimented with illicit drugs and alcohol but had not used them frequently or on a daily basis; two patients had tried marijuana once; five said they had never used illicit drugs and had rarely used alcohol; and one patient refused to answer the questionnaire although it was noted in his chart that he had used marijuana on several occasions.

All subjects in this study were taking antipsychotic drugs; the majority were on several medications simultaneously. Calculation of daily medication dosage in chlorpromazine (CPZ) equivalents was not attempted; many patients were given 2 to 3 different oral antipsychotics on a daily basis as well as a monthly depot injection of fluphenazine and also had standing orders for PRN administration of haloperidol and CPZ for agitation. Although medication levels were generally high, most patients who participated in the study had been medicated for an extended period and did not exhibit the marked side effects often seen when medication is first initiated. None of the participants was thought to be showing signs of tardive dyskinesia, although mild parkinsonian movements and akathisia were not

uncommon. Twenty six of the subjects were right handed and four were left handed.

Normal Control Group. A group of 29 male volunteers recruited from family practice clinics, employment centers, community centers, and community colleges served as a control group of the CT scan and smooth pursuit eye tracking measures. All the control subjects were given a psychiatric screening interview to insure that there was no history of treatment for psychiatric problems or alcohol or drug abuse for either the participant or any of his first degree relatives. Ages and educational levels of the volunteer control sample are listed in Tables 1 and 2. The volunteer control group is significantly younger than the chronic schizophrenic patients ($t(57)=3.17$ $p<.01$) and is better educated. Procedures for CT scanning, measurement of VBR, and recording and scoring eye tracking are identical for the schizophrenic and volunteer control patients. Both of these subject groups are part of a large scale study of schizophrenia which has developed highly standardized and very reliable measurement and quantification procedures for ventricle brain ratio and smooth pursuit eye tracking.

Psychiatric Control Group. Control group scores for all neuropsychological tests administered in this study were obtained for a sample of nonschizophrenic psychiatric patients. From a computerized data bank at the U.B.C. Health Sciences Center Psychiatric Care Unit (H.S.C.-P.C.U.) a group

of 21 males under the age of 35 were selected who, as inpatients at the hospital, had been referred for neuropsychological testing. This group was composed of 7 individuals diagnosed as depressed, 5 diagnosed as substance abusers, 2 as having anxiety disorders, 2 as personality disordered and 4 with other unspecified but nonschizophrenic psychiatric diagnosis. Test administration procedures for the psychiatric controls and the chronic schizophrenic patients were well standardized across settings as the examiner for this study had received extensive training at the H.S.C.-P.C.U. and had in fact worked as a testing technician at this hospital. For three of the nine measures administered there were fewer than 21 patients with control scores available. In the psychiatric control sample, 75% of subjects had grade 9 to 12 education whereas 93% of the chronic schizophrenics were in this category. Only 1 subject in the schizophrenic sample had any post secondary education whereas 5 of the control subjects did. The two groups do not differ significantly in age.

Measures

Smooth pursuit eye movement recording. Smooth pursuit eye movements were recorded in a psychophysiological laboratory at U.B.C. H.S.C-P.C.U. using a well standardized procedure. With head stabilized in a chin and forehead rest subjects observed a 5 mm luminous spot, driven by a sine wave generator at a frequency of .4 hz for 20 cycles of target

oscillation, displayed on an oscilloscope screen positioned 30 cm from the subject's eyes. Eye movement were recorded by electro-oculographic (EOG) techniques using silver/silver chloride electrodes placed at the outer canthi of each eye. Electrodes placed at the superior and inferior orbital rims of the left eye allowed blink artifacts to be monitored. Eye movements and target position were recorded on a Beckman type R-612 Dynograph and a Vetter model FM recorder for computerized analysis.

Accuracy of eye tracking was analysed by a computer-based scoring program which generates a value equal to the root-mean-squared (RMS) deviation of the eye movement wave form from the target waveform for the 16 best cycles of tracking. The RMS deviation is obtained by utilizing a computer program which aligns the target and eye tracking channels, adjusts for amplitude differences and then computes the difference between the target signal and the subject's eye movements in standard deviation units. The distribution of RMS scores is typically positively skewed making the logarithmic transformation of RMS scores a more appropriate expression of tracking accuracy for use in testing group differences.

Lateral ventricle sizes. Subjects were scanned on a third generation, high resolution, total body scanner (Siemens Somatom DR2) located at the U.B.C. Health Sciences Acute Care Hospital. Scanning of all patients and volunteer controls was done without injecting an enhancement contrast medium and with

a scanner window width setting of 80 at a level of 27; this setting allows perfectly adequate visualization of the lateral ventricles while minimizing the radiation dose. Subjects were scanned parallel to the cantho-meatal line for 13 to 16 successive axial sections of 8 mm thickness. The CT scan section which showed the lateral ventricles at their largest was selected for each subject and enlarged on film to a 23.5 cm by 17.5 cm format for use in measurement of VBR.

Measurement of VBR ventricle size. The enlarged film of the scan section showing the lateral ventricles at their largest, was attached to a light box, and a Sokkish 19908 compensating polar planimeter was used to measure the area of the lateral ventricles and the area of the brain in order to calculate the ventricle brain ratio. The area of each lateral ventricle was measured three times, averaged, and then summed across the two ventricles to give ventricular size. The brain area was measured six times and averaged to provide the denominator for the ratio. The ratio of ventricle to brain was multiplied by 100 to form the VBR as it is reported in most published studies.

Neuropsychological assessment. The neuropsychological assessment was carried out at Riverview Hospital using interview rooms on the various wards. Testing took approximately three hours and was usually completed in one day comprised of two sessions organized around a lunch break for the patient. The following tests were administered following

standardized procedures outlined in the test manuals; Weschler Adult Intelligence Scale - Revised (WAIS-R - approximately 1.5 hours administration time), Benton Visual Retention Test, Form D, with Background Interference Procedure (BVRT- approximately 10 min administration time), Categories Test- Victoria Revision (CAT - approximately 15 min administration time), Trail Making Test A and B (TMT - approximately 10 min administration time), Right and Left Hand Finger Tapping Test (TAPR & TAPL - approximately 10 min administration time), Word Fluency Test (WF - approximately 5 min administration time), Rey Auditory Verbal Learning Test (RAVLT - approximately 10 min administration time), and the Wisconsin Card Sorting Test (WCST - approximately 20 min administration time).

Scoring neuropsychological tests. Tests were scored according to standard procedures described in the test manuals. For a number of the neuropsychological tests several different but related measures of performance are often obtained from the same test. For this study the following scores were used: BVRT = total number of errors on the Benton Visual Retention test, Form D with Background Interference Procedure; CAT = total number of errors on the Categories Test - Victoria Revision; TMT = total number of seconds taken to complete parts A and B of the Trail Making Test; TAPR = average number of right hand index finger taps over five, 10 second trials; TAPL = average number of left hand index finger taps over five, 10 second trials; WF = the total number of

words generated in response to three different letters of the alphabet with one minute allowed per letter; RAVLT = total recall on five immediate and 1 delayed recall trial for the 16 item list used in the Rey Auditory Verbal Recall Test; WCST = the total number of errors which occurred during presentation of the 128 cards used in the Wisconsin Card Sorting Test.

Procedure

Schizophrenic patients identified as potential subjects by the procedures outlined earlier, and for whom the recruiter had been given permission to discuss the study, were approached on the ward and requested to accompany the recruiter to an interview room to discuss the research project. The study was described as consisting of four major portions. The first stage involved a 2 hour selection interview to which the subject gave written consent; at the conclusion of this interview all individuals were paid $5 whether or not they were selected for the rest of the study. If individuals met the diagnostic criteria and if they wished to continue, a second consent form was utilized which provided a detailed description of the remaining three stages of the project; (i) a 2.5 hour neuropsychological test battery, ii) a CT scan and iii) a two hour battery of psychophysiological tests. Subjects were informed that they were free to terminate testing at any time. Upon completion of the research protocol the subjects were paid $35.

Neuropsychological testing was done at Riverview Hospital by a single examiner, usually within a week of the diagnostic interview. Within the next two weeks the subject was driven to the University of British Columbia by the Riverview transport service where psychophysiological testing and the CT scan were done. CT scans were done using highly standardized procedures by hospital radiologists. With few exceptions the time span from recruitment to completion of testing was less than three weeks.

For the normal controls, all psychophysiological testing procedures and CT scanning procedures were identical to those used with the patients. The psychiatric control group consisted of inpatients referred for neuropsychological testing. These individuals were tested by one of two neuropsychological testing technicians working under the supervision of Dr. D. Crockett. The patients in this group were typically tested over a three hour span (with a lunch break) using the same tests and test materials as those used with the schizophrenic patients. Both groups of subjects were given the WAIS-R first, usually followed by a break and then administration of the rest of the neuropsychological battery.

RESULTS

The results of this study are presented in five sections. The first section reports reliability for the measurement of ventricle brain ratio. The second section is concerned with the relationship of age, duration of hospitalization, and substance abuse to the principal measures in the study. It is important to assess the effect of these subject variables on the principal measures as they might affect interpretation of data pertinent to the major hypotheses. The third section assesses group differences for comparisons between the chronic schizophrenic sample and the control groups on the measures of lateral ventricle size, smooth pursuit eye tracking and neuropsychological test performance. As the schizophrenic group was predicted to be more impaired than controls on all measures, 1-tailed t-tests are utilized. Bonferroni corrected probability values were used to assess mean differences between the psychiatric controls and the schizophrenic patients on the neuropsychological tests. The fourth section reports relationships among the measures of VBR, log root mean square (LRMS) deviation in eye tracking, and neuropsychological test performance in the schizophrenic sample. Correlations presented in this section are tested with one tailed, or directional tests, in accord with the hypothesized relationships between VBR, smooth pursuit eye tracking and neuropsychological test performance. Because

there were no specific a priori hypotheses about the relationship between any individual neuropsychological test result and the measures of VBR and LRMS, an overall Bonferroni adjustment was made by dividing the p-value of .05 by the number of relationships examined for each variable. Because there were 10 neuropsychological tests, the Bonferroni corrected p-value = .005. Finally, a fifth section presents findings related to the relationships between tests within the neuropsychological battery for the schizophrenic sample.

Means, standard deviations, and t-values for the measures of ventricle size and eye tracking accuracy are displayed in Table 7. Means and standard deviations for the neuropsychological tests are displayed in Table 8. Note that WAIS-R Full Scale IQ is reported in Table 8 but not used in further analyses as it is redundant with the WAIS-R Verbal and Performance IQs.

Reliability of VBR measure

The reliability of the VBR measurement was assessed during measurement of over 200 CT scans including the 30 chronic schizophrenics and 29 normal controls who participated in this study. Interjudge reliability was obtained by comparing the planimetry measures of VBR for two independent raters for 25 CT scans. A Pearson correlation of .93 was obtained indicating a high level of reliability. In addition 20 randomly selected CT scans were rank ordered by a

neuroradiologist according to lateral ventricle size; the Spearman rank order correlation between the neuroradiologists ranking and the planimetry measure of VBR was high (r=.80) providing an indication of the validity of planimetry obtained VBR as a measure of ventricle size.

Relationships Between Duration of Hospitalization, Age and Substance Abuse and the Principal Measures

Despite considerable range in total duration of hospitalization across the sample of schizophrenic patients (range 2 months to 113 months), this variable was not significantly correlated with any of the principal measures used in this study. Duration of hospitalization was correlated r = .02 with VBR, and r = .30 with LRMS tracking deviation. Table 10 displays the correlations between duration of hospitalization and the tests in the neuropsychological battery.

The correlation between age and WAIS-R Full Scale IQ was r=.40, indicating that in this sample some of the older individuals tended to have higher IQs. Age was not significantly correlated with any other principal measure. The correlation between age and LRMS was r = .01; between age and VBR was r = .08; and between age and duration of hospitalization was r = .20. The correlation coefficients between age and the 10 neuropsychological tests ranged from -.33 to .24.

In order to address the important possibility that substance abuse might have a significant effect on VBR, eye tracking or neuropsychological test performance, t-tests were computed to compare the group of patients with notable history of substance abuse, to those patients who had little or no history of substance use. As mentioned in the method section, patient reports and chart information on alcohol and drug use were difficult to evaluate. This was particularly the case with respect to documenting specific quantities and actual duration of use for each of many illicit drugs covered in the DIS sections for assessing drug and alcohol use. However, it is less difficult to divide the patient sample into two groups, one with ample evidence (both by self report and charted information)of substantial substance abuse, and another group which, according to patient report and chart information, consists of individuals with minimal or no exposure to illicit drugs or alcohol. Individuals in this sample who were classified as substance abusers or substance dependent often had histories of daily use of marijuana over periods of several months; there were two individuals who had been glue shiffers on a daily basis for more than two weeks, several had used alcohol to the point of intoxication on a daily basis for periods of weeks to months, and many were poly-drug abusers. Among the group classified as having minimal, or no drug and alcohol use, there were five who had never used any illicit drugs; two who had used marijuana, but

not more than five times; and three who had used marijuana more than five times but never on a daily basis or regularly over a period of weeks or months. Two individuals in this group had never been drunk; two had been drunk only once; three had been drunk occasionally but did not use alcohol regularly; one individual had drunk two beers a week during a period of six months but had stopped drinking altogether several years before; and two had at some points drunk as much as seven drinks at least one evening a week but never for a period greater than two months. Table 6 presents the results of comparisons between 11 subjects with extensive histories of substance abuse and/or dependence (as recorded in their charts and confirmed by interview), and 10 subjects whose denial of more than very minimal use of drugs or alcohol was not contradicted by chart information. There were no significant differences between these groups for VBR, eye tracking, or WAIS-R Full Scale IQ.

Group Differences

The schizophrenic patients and normal control group did not differ significantly with respect to VBR, $t(57)=.39$ $p>.1$, (see Table 7 for means and SD's). None of the schizophrenics, and one of the control group subjects had a VBR $\geq$ 2 SD above the control group mean (control group $\bar{x}$ + 2SD is a VBR of 11.57). Three of the schizophrenic patients and four of the control group subjects had VBRs which were between 1 and 2 SD

Table 6

Means, Standard Deviations and t-test Values for VBR, LRMS Deviation in Eye Tracking and WAIS-R Full Scale IQ for Schizophrenic Patients with Histories of Alcohol and/or Illicit Drug Abuse (n=11) Compared with Schizophrenic Patients with Little or No Use of Illicit Drugs and Alcohol (n=10)

	Groups[a]		
	Drug and/or Alcohol (n=11)	Little or No Drug and/or Alcohol use (n=10)	
Measure	Mean (SD)	Mean (SD)	t-value
VBR	6.99 (2.24)	6.83 (.57)	.228
LRMS deviation in eye tracking	2.33 (.26)	2.22 (.21)	.095
WAIS-R Full Scale IQ	84.18 (9.44)	82.10 (8.68)	.053

Note: There are no significant differences between groups on any of the principle measures, all ps>.1, two tailed.

[a] Groups were formed on the basis of information obtained from patient's charts and interview on the drug and alcohol portions of the Diagnostic Interview Schedule.

Table 7

Means, Standard Deviations and t Values for VBR and Eye Tracking Accuracy for Schizophrenic Patients and Normal Controls

	Groups				
	Schizophrenics (M=30)		Control (n=29)		
Measure	Mean	SD	Mean	SD	t-value
Ventricle Brain Ratio	6.75	1.70	6.53	2.52	.39
Log Root Mean Square Error (LRMS) in Eye Tracking	2.23	.25	2.04	.14	3.62*

* $p < 0.005$, one tailed t test, df 57

above the control group mean (control group $\bar{x}$ + 1SD is a VBR of 9.05). Figure 1 is a graphic display of the distributions of ventricle brain ratios for the schizophrenics and control subjects. It is clear from this figure that the means, ranges and standard error of measurement for the two groups are very similar.

The situation is quite different in the case of eye tracking. The schizophrenic group evidenced significantly less accurate eye tracking than the normal control group (see Table 7). Figure 2 is a graphic representation of the LRMS deviation scores for the schizophrenics and controls.

Neuropsychological performance of the schizophrenic sample was compared to that of the psychiatric control group. Table 9 presents the results of t-test comparisons between the means of the schizophrenic sample and the psychiatric control group. Six of the 11 comparisons were significant with Bonferroni correction for multiple t-tests. The chronic schizophrenic group did significantly less well than the psychiatric controls for WAIS-R Performance IQ, the Categories Test, the Wisconsin Card Sorting Test, the Trail Making Test, the Benton Visual Retention Test, and the Rey Auditory Verbal Learning Test. On 4 of the tests there were no significant differences between groups; schizophrenic patients and psychiatric controls did not differ for WAIS-R Verbal IQ, right and left Finger Tapping, and Word Fluency. Table 8

Table 8

Means, Standard Deviations and Ranges (where available) for Neuropsychological Tests for Schizophrenic Patients, Psychiatric Controls and Normative Groups Reported in the Literature

	Groups						
	Schizoprenics[a]			Controls			Norms Reported in Literature
Neuropsychological Tests	Mean	(SD)	Range	Mean	(SD)	Range	Mean (SD)
WAIS-R Verbal IQ	87.13	(12.9)	132-70	91.95[b]	(14.8)	128-71	100 (15)[f]
WAIS-R Performance IQ	80.37	(9.2)	101-63	90.67[b]	(15.4)	118-69	100 (15)[f]
WAIS-R Full Scale IQ	82.13	(8.5)	102-66	90.76[b]	(14.6)	126-72	100 (15)[f]
Categories Test (errors)	43.27	(13.4)	63-8	28.00[c]	(16.0)	57-1	20.24 (9.5)[g]
Finger Tapping - Right	45.67	(6.9)	59-29	45.95[b]	(7.3)	61-32	46.7 (5.3)[h]
Finger Tapping - Left	41.73	(6.9)	51-20	40.37[b]	(5.5)	53-30	43.2 (5.3)[h]
Word Fluency Test	32.23	(13.1)	58-6	33.81[b]	(12.9)	67-9	33 (50% percentile)
Wisconsin Card Sorting Test (errors)	49.17	(16.8)	87-14	30.18[d]	(20.9)	71-8	24.9 (19.4)[j]
Trail Making Test - total time for A and B (seconds)	191.07	(93.7)	562-85	129.24[b]	(53.1)	284-61	86.3[k]
Benton Visual Retention Test with background interference procedure (errors)	9.90	(4.4)	18-1	4.36[b]	(2.8)	10-1	Not available
Rey Auditory Verbal Learning Test - total recall over 6 trails	33.70	(12.5)	54-6	51.83	(10.1)	61-38	69.3[l]

[a] n=30, [b] n=21, [c] n=20, [d] n=11, [e] n=6,

[f] Weschler Adult Intelligence Scale-Revised Manual (1981)

[g] Norms for Victoria Revision of the Halstead Categories. Labreche (1982). N = 50, mean age 37.2 years, mean Full scale I.Q. 116.

[h] Norms for Finger Tapping Test from control study by Lorne Yeudall (1978), n=46, ages 26-30.

[i] Taken from Spreen and Benton (1968), Neurosensory Center Comprehensive Examination for Aphasia, Edition A, Profile Form A (Normal Adults). Scores are listed on a percentile basis within the profile, a score of 33 falls at the 50th percentile while a score of 22 falls at the 10th and a score of 49 at the 90th percentile.

[j] From Manual for Wisconsin Card Sorting Test, Heaton (1981) n=150.

k Norm for Trail Making Test taken from Yeudall (1978) n=46, age 26-30. For comparison to the schizophrenic sample and psychiatric controls, times for the A form and B forms have been added together.

[l] From Lezak (1983). The value reported is the sum of the means for the six separate trials as reported by Lezak.

Table 9

T-tests Between Schizophrenic Patients and Psychiatric Controls for the Neuropsychological Tests

Neuropsychological Test	t-value	Degrees of Freedom	Probability[a]
WAIS-R Verbal IQ	1.20	49	$p > 0.1$
WAIS-R Performance IQ	2.74	49	$p < 0.005$*
Categories Test (errors)	3.57	48	$p < 0.0005$*
Finger Tapping - Right	.14	49	$p > 0.1$
Finger Tapping - Left	.77	49	$p > 0.1$
Word Fluency Test	.42	49	$P > 0.1$
Wisconsin Card Sorting Test (errors)	2.71	39	$P < 0.005$*
Trail Making Test - total time for A and B	2.99	49	$P < 0.0025$*
Benton Visual Retention Test with background interference procedure (errors)	4.75	39	$P < 0.0005$*
Rey Auditory Verbal Learning Test - total recall over 6 trials	3.84	34	$P < 0.0005$*

* Starred entries are significant with one tailed probabilities as listed in table.

[a] The t-tests are one tailed with Bonferroni adjustment for multiple comparisons. Bonferroni adjustment was made by dividing the p-value of 0.05 by the number of comparisons computed. Because there 10 neuropsychological tests, the Bonferroni corrected p-value = 0.005.

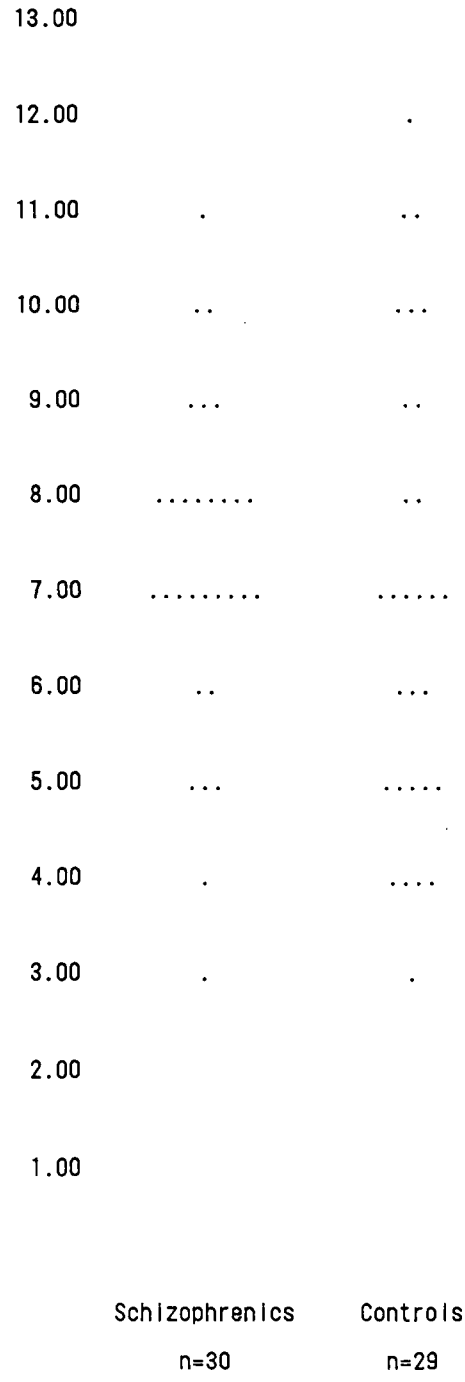

Figure 1. Distribution of Ventricle Brain Ratios for Schizophrenic Patients and Volunteer Controls.

Note 1. The horizontal bars denote the mean VBR for each group while the lines above and below the bar indicate the standard error of measurement. Mean for schizophrenia is 6.75, standard error is .305. Mean for controls is 6.53, standard error is .460 units.

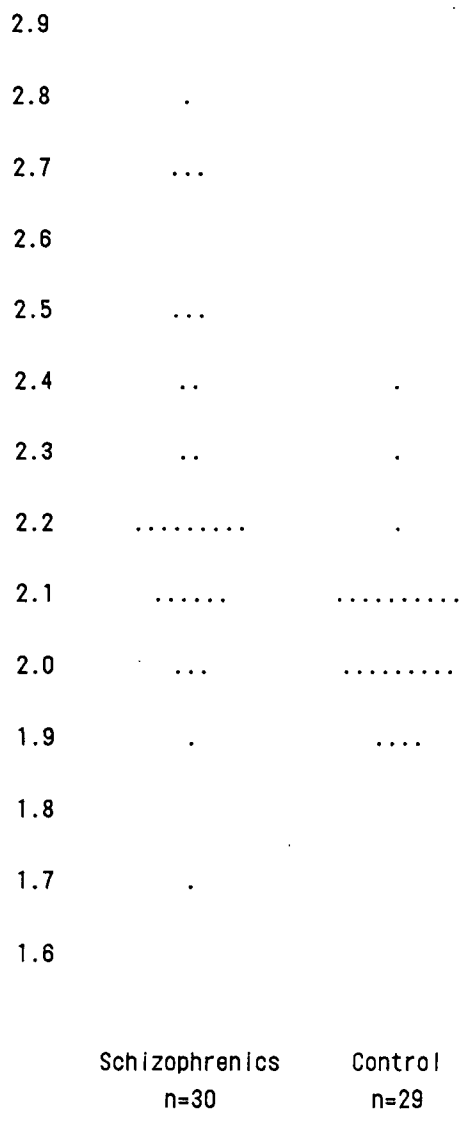

Figure 2. Distribution of LRMS eye tracking accuracy scores for Schizophrenic Patients and Volunteer Controls.

Note 1. The horizontal bars denote then mean LRMS for each group while the lines above and below the bar indicate the standard error of measurement. Mean for schizophrenics is 2.23, standard error of measurement is .25. Mean for control group is 2.04, standard error of measurement is .14.

presents the means, standard deviations, and ranges of scores for the neuropsychological tests for the schizophrenic and control group; means and standard deviations for normative groups have been included for comparison.

Relationships Among VBR, LRMS Deviation in Eye Tracking and Neuropsychological Test Performance

Analyses in this section pertain to the central hypotheses of this study.

VBR and eye tracking. The prediction that ventricle size and eye tracking would be related, such that individuals with larger ventricles would exhibit less accurate eye tracking, was not confirmed. The correlation between VBR and LRMS in the schizophrenic sample was less than zero ($r = -.34$) and indicates that larger lateral ventricle size tended to be associated with better eye tracking performance. The correlation between VBR and LRMS in the volunteer control group was also not significant ($r = .18$).

VBR and Neuropsychological Test Performance. None of the hypothesized relationships between lateral ventricle size and neuropsychological performance were supported by the data. Table 10 shows the correlation coefficients between the 10 neuropsychological tests and VBR. None of these correlations is statistically significant. The two largest coefficients are the correlations between VBR and WAIS-R Verbal IQ, and VBR and the Word Fluency Test. These correlations are in a

Table 10

Correlations Between VBR, LRMS Tracking Error, Duration of Hospitalization and the Neuropsychological Tests for the Chronic Schizophrenic Sample (n=30)

Neuropsychological Test	VBR	LRMS[a]	Institutionalization[b]
WAIS-R Verbal IQ	.40	-.17	.08
WAIS-R Performance IQ	-.24	-.33	-.14
Categories Test (errors)	-.14	.37	.06
Finger Tapping - Right	-.22	-.02	.08
Finger Tapping - Left	.00	.12	-.11
Word Fluency Test	.32	-.28	.09
Wisconsin Card Sorting Test (errors)	.00	.19	.16
Trail Making Test - total time for A and B	-.03	.22	-.08
Benton Visual Retention Test with background interference procedure (errors)	-.02	.09	-.18
Rey Auditory Verbal Learning Test - total recall over 6 trials	-.06	-.05	-.01

Note 1: No significant relationship were found between VBR, LRMS deviation or Institutionalization and any Neuropsychological Tests. Tests of the significance of correlations between the neuropsychological test battery and VBR, LRMS tracking deviation and institutionalization are directional one tailed tests as stated in hypotheses. Bonferroni correlated p-value = .005

[a] LRMS is the log root mean square eye tracking error

[b] Institutionalization was determined from the hospital records by adding the time spent in hospital for all recorded hospitalizations. The final figure was calculated to the nearest month.

direction opposite to that predicted, in that individuals with larger ventricles tended to have higher scores on the Verbal IQ scale and to perform better on the Word Fluency Test.

Eye Tracking and Neuropsychological Test Performance. None of the hypothesized relationships between eye tracking and neuropsychological performance was supported by the data. Table 12 shows the correlation coefficients between LRMS tracking deviation and the 10 tests which make up the neuropsychological battery.

Correlations within the Neuropsychological Test Battery

A ten by ten correlation matrix containing 45 non-redundant Pearson coefficient is shown in Table 11. With such a large number of correlations it is important to consider Type I error as contributing to the number of significant coefficients obtained. Steiger (1980) provides a method to test the null hypothesis that all correlations in a matrix are equal to zero. This test, which is a special case of statistic X^2 is described by Steiger (1980) as a means of obtaining experiment wise error rate protection (see Appendix A for procedure). In the case of a matrix with 45 non-redundant correlations, a X^2 value of 61.65 (df=45) ($p<.05$) would be required in order to reject the null hypothesis that the matrix is an identity matrix, or all correlations are equal to zero. For the matrix displayed in Table 13 the X^2 value obtained equals 100.7 ($p<.05$), allowing rejection of the null hypothesis.

Table 11

Correlation Matrix of Neuropsychological Tests for Schizophrenic Sample (n=30)

	1 VIQ	2 PIQ	3 BVRT	4 RAVLT	5 TAPR	6 TAPL	7 TMT	8 WCST	9 CAT	10 WF
1) VIQ	----									
2) PIQ	.25	----								
3) BVRT	-.17	-.46**	----							
4) RAVLT	.24	.09	-.15	----						
5) TAPR	.05	.16	-.16	.33*	----					
6) TAPL	.07	.02	-.011	.38*	.63**	----				
7) TMT	-.28	-.36*	.55**	-.24	-.15	-.17	----			
8) WCST	-.33*	-.47**	.08	-.25	-.12	-.19	.08	----		
9) CAT	-.40*	-.23	.33*	-.23	-.07	-.19	.24	.42*	----	
10) WF	.43**	.25	.00	.15	.21	-.08	-.33*	.00	.08	----

Note. Abbreviations stand for the following tests ordered from 1 to 10. VIQ = WAIS-R Verbal IQ; PIQ = WAIS-R Performance IQ; BVRT = Benton Visual Retention Test, Form D, with Background Interference Procedure (errors); RAVLT = Rey Auditory Verbal Learning Test - total recall over six trials; TAPR = Finger Tapping Right; TAPL = Finger Tapping Left; TMT = Trial Making Test total time for A and B (seconds); WCST = Wisconsin Card Sorting Test (errors); CAT = Categories Test (errors); WF = Word Fluency Test.

* $p > 0.05$ one-tailed, df = 28

** $p > 0.01$ one-tailed, df = 28

Within the matrix of 45 correlations, 13 coefficients are significant at a probability of .05 or less, one tailed. All significant correlations are directionally consistent; relationships between two tests which are both scored for attainment or both scored for errors show positive coefficients, pairs of tests in which one is an attainment score and the other an error score show negative coefficients.

The prediction of significant relationships between WAIS-R Verbal and Performance IQs and the remaining neuropsychological tests is supported by the data. Although Right and Left Finger Tapping and the Rey Auditory Verbal Learning Test are not correlated with either IQ Scale, the remaining five neuropsychological tests are. Verbal IQ correlates with the Wisconsin Card Sorting Test, the Categories Test and the Word Fluency Test. Performance IQ correlates with the Trail Making Test, the Benton Visual Retention Test and the Wisconsin Card Sorting Test.

Amoung the group of six neuropsychological tests thought to be sensitive to frontal lobe functioning (Finger Tapping Right, Finger Tapping Left, Trail Making Test, Wisconsin Card Sorting Test, Categories Test, and Word Fluency Test) there are three correlations significant at a probability of .05 or less. When the X^2 test of the null hypothesis that the entire matrix of correlations equals zero is applied to the 15 non-redundant correlations amoung these tests, the obtained X^2 value of 31.4 is compared with a tabled X^2 ($p>.05$) of 24.99

allowing rejection of the null hypothesis. Among these tests, Right and Left handed Finger Tapping are significantly correlated as are the Word Fluency Test and the Trail Making Test, and the Wisconsin Card Sorting Test and the Categories Test.

Summary of Results

The results of this study failed to show the predicted relationship among the principal measures of interest in the schizophrenic sample. No significant correlations were found between any combination of the measures of VBR, eye tracking accuracy and neuropsychological performance. Although the schizophrenic group was impaired, relative to the controls, for eye tracking accuracy and on several neuropsychological tests, they did not differ from the control group with respect to lateral ventricle size. None of the individual schizophrenic patients had lateral ventricular enlargement as defined in the literature (a VBR$\geq$2 SD above the mean of the control group).

No relation was found between duration of hospitalization or substance abuse and any of the principal measures. Age was found to be correlated with WAIS-R Full Scale IQ such that older subjects tended to have higher IQ's.

Relationship among the tests in the neuropsychological battery conformed to previous findings of correlations between WAIS-R IQs and other neuropsychological measures, indicating

that the neuropsychological finding are not entirely anomalous. The predicted relationship among tests believed sensitive to frontal lobe functioning was not strongly supported: of 15 non-redundant correlations in the matrix of frontal lobe tests, only three were significant.

DISCUSSION

Group Differences

Before the central issue of the relationships between the three principal measures can be meaningfully addressed, it is useful to examine the pattern of impairments relative to the control groups.

The eye tracking performance of the schizophrenic group was significantly impaired relative to the control group (see Figure 2 for graphic display of the distributions of LRMS deviation in tracking for the schizophrenic and control groups). This replicates many previous findings in the literature (e.g. Holzman et al., 1974; Iacono et al., 1982; Levin et al., 1981).

The schizophrenic sample was found to perform significantly less well than an age matched group of non-schizophrenic psychiatric patients on six out of the 10 neuropsychological tests (see Table 9). The schizophrenic sample made significantly more errors on the Categories Test and Wisconsin Card Sorting Test. Both these tasks assess abstracting ability and conceptual flexibility. In addition, these tasks have a memory component. Subjects must remember from trial to trial the concept they are using to obtain correct categorization of items. Both these tests are considered sensitive to frontal lobe function. Performance on the Wisconsin Card Sorting Test has been repeatedly

demonstrated to be impaired in patients with frontal lobe lesions (Lezak, 1983). However, as Lezak (1983) points out, poor performance on the Wisconsin Card Sorting Test can result from a variety of intellectual deficits. The schizophrenic sample was slower than the psychiatric controls in completing the Trail Making Test. This test, which Lezak (1983) characterizes as being one of the neuropsychological tests most sensitive to the presence of brain damage, involves visual conceptual skills and visualmotor tracking. The schizophrenic sample was notably impaired relative to the psychiatric controls on both a visual and an auditory memory task. Finally, there was a significant difference between psychiatric controls and the schizophrenic patients on WAIS-R performance IQ.

The schizophrenic group did not differ from the psychiatric controls on Verbal IQ, Word Fluency, and Finger Tapping Right and Left. Further, it is interesting to note from Table 8 that neither the schizophrenics or the psychiatric controls were impaired relative to a normal sample on Word Fluency and Finger Tapping Right and Left. Both the Finger Tapping Test and the Word Fluency Test are timed, and require attention and considerable cooperation over repeated trials. The lack of difference between normals and both groups of patients would suggest that the deficits in other areas are not simply artifacts of inattention or insufficient effort. The finding that the schizophrenics and psychiatric

controls do not differ for Verbal IQ, Word Fluency, and Finger Tapping, would again suggest that the deficits evidenced by the schizophrenic sample relative to the psychiatric controls are not attributable simply to a generalized behavioral deficit in the schizophrenic sample. The similarities in Verbal IQs between the schizophrenic sample and the psychiatric controls suggest that the differences between the two groups on other tests are not likely to be a function of differences in general fund of knowledge or ability to comprehend and respond to verbal instructions.

In overview, the performance of the schizophrenic patients shows an interesting pattern of impairment relative to psychiatric controls. The schizophrenic sample does not differ significantly from psychiatric controls in general verbal ability. However, the schizophrenic patients are especially impaired on tests requiring abstract reasoning ability (Categories Test and Wisconsin Card Sorting Test); in tasks which require coordination of visuoperceptual skills and motor responses (Benton Visual Retention Test, most subtests on the WAIS-R Performance IQ scale and the Trail Making Test); and on the memory tasks in the battery (Benton Visual Retention Test and the Rey Auditory Verbal Memory Test). In the context of the literature reviewed for this study, the schizophrenic patients would be characterized as showing diffuse neuropsychological impairments despite some non-significant differences from psychiatric control. As a group,

schizophrenic patients were impaired on several frontal lobe tests; on WAIS-R Performance IQ; on memory tests which are associated with both temporal and parietal lobe functions (Kolb and Whishaw, 1980); and on spatial and constructional tasks requiring integration of perceptual and motor functioning which are associated with parietal lobe function.

The third principal measure in this study was lateral ventricle size. The schizophrenic sample and normal volunteer controls did not differ significantly on this variable (see Figure 1). The ranges of scores are virtually identical, although there is a tendency for the scores of the schizophrenic group to cluster above the mean of the distribution. This negative finding, with respect to lateral ventricle enlargement, runs counter to the hypotheses put forward in this study and to several studies in the literature, particularly the research conducted in the late 1970s and early 1980s. However, the findings are consistent with a number of published reports which have failed to detect lateral ventricular enlargement in schizophrenic patients. A communication by Smith and Iacono (1986) suggests that some previous reports of lateral ventricular enlargement in schizophrenics may have been an artifact of unrepresentatively small ventricular size in the control groups. Smith and Iacono (1986) report that the mean VBR of schizophrenic patient groups for seven studies which failed to find lateral ventricle enlargement was 6.75, while 14 studies which

reported ventricular enlargement in their sample had an overall mean VBR of 6.86. The studies which failed to find enlarged ventricles in their schizophrenic samples had control groups with a mean VBR of 6.34 whereas the 14 studies reporting positive findings had control groups with mean VBRs of 3.95. Thus, the difference between several studies with positive and negative findings appears to be a function of the ventricle sizes in the control groups and not in the schizophrenic patients. The sample of schizophrenic subjects assessed in this study has a mean VBR of 6.75, while the control group has a mean VBR of 6.53. These values are practically indistinguishable from those reported by Smith and Iacono (1986) for studies which failed to find ventricular enlargement.

A question which might be raised in response to the negative findings is whether the sample of schizophrenic subjects used in this study might not be an unusually intact group, which differs in some systematic way from samples used in previous research. This seems an unlikely explanation in virtue of a number of issues. First, the sample was found to be impaired for eye tracking accuracy and on a number of neuropsychological tests, relative to controls. Second, the sample consists of consenting consecutive admissions to a large, public mental institution. As several other studies in the literature report using consenting consecutive admissions to similar institutions, subject selection procedures should

not account for differences between this study and others. Third, although all subjects were under the age of 35, the average accumulated duration of hospitalization for the sample was two years, nine months. Half the subjects had spent between 2 and 4 years in mental institutions, and twenty percent of the sample had spent more than 4 years in hospital. Finally, individuals with histories of extensive substance abuse were not excluded from the sample provided they had not been specifically treated for drug or alcohol dependence. Although there may be good reasons to attempt to exclude substance abusers, high prevalence of substance abuse among young chronic schizophrenics would suggest that a sample composed only of individuals without a history of substance abuse would be a very unrepresentative sample. In any case, the inclusion of these individuals would be expected to increase the likelihood of finding ventricular enlargement in the sample if it has any effect at all. Thus overall, there is no reason to suspect that some aspect of the sample selection procedure, or particular subject variables, make this sample unrepresentative of young institutionalized chronic schizophrenics. Neither is there any indication that the characteristics of this particular sample would bias toward smaller ventricle sizes.

In summary, this schizophrenic group was found to have impaired smooth pursuit eye tracking performance and to perform significantly less well then psychiatric controls on

several neuropsychological tests. These findings are consistent with the predictions of greater impairment hypothesized in this study, and with previous research findings in schizophrenic samples. The schizophrenic sample did not show lateral ventricular enlargement relative to the normal volunteer controls. Although this negative finding is in contradiction to the study hypothesis and to a proportion of previous literature, it is consistent with findings of more recent studies. The average VBR for the sample of patients is similar to the mean VBRs for many controlled studies that have obtained both positive and negative findings. Thus, while ventricular enlargement was not found, neither would it be said that the present sample has smaller ventricles than many of the previously reported samples of schizophrenic patients.

Relationships Among VBR, LRMS Deviation in Eye Tracking, and Neuropsychological Test Performance

The principal purpose of this study was the investigation of relationships among the measures of lateral ventricle size, eye tracking accuracy, and neuropsychological test performance within the group of chronic schizophrenic patients. It was hypothesized that there would be correlations between the measures such that low attainment on one measure would tend to be associated with low attainment on each of the other measures. None of the predicted relationships between VBR,

eye tracking or any of the neuropsychological tests were found in this study.

VBR and eye tracking. No significant relationship was found between these measures. The correlation between these variables was less than zero and in direction opposite to that predicted.

There are two studies which have assessed the relationship between lateral ventricle size and eye tracking (Weinberger and Wyatt, 1982; and Bartfai et al., 1985); the findings were thought by the investigators to be suggestive of a relationship between large ventricle size and impaired tracking. Both studies have methodological flaws which make it difficult to interpret the data with respect to the association between eye tracking and ventricular size. The Weinberger and Wyatt (1982) report was based on an investigatory project. Two groups of patients selected on the basis of having "large" and "normal" ventricles, were given an eye tracking task which involved watching a swinging pendulum. They found that 30% of the patients with normal ventricles had markedly disordered eye tracking (a rating greater than 3 on a 5 point scale), while 64% of the patients with large ventricles had disordered tracking. Unfortunately they do not describe the patients, nor give an indication of the mean VBRs for each group. The Bartfai et al. (1985) study had a small sample (n=18) and used a rather unsophisticated measures of both eye tracking and lateral ventricle size. They found few

patients with evidence of enlarged lateral ventricle anterior horns, but they concluded that there was a tendency for the most impaired trackers to have a larger anterior horn index than patients with better tracking. Their finding of association between lateral ventricle size and eye tracking was not statistically significant when they compared groups or when they correlated ventricle size and eye tracking ratings ($r=.35$, $df=15$, not significant at 0.05, one tailed).

The possibility that a relationship between ventricle size and eye tracking exists, but was undetected by this study cannot be completely ruled out. None of the subjects in the schizophrenic sample showed lateral ventricular enlargement relative to the control group. If eye tracking impairment and ventricular enlargement are associated only when ventricular enlargement is extreme, then this study would fail to demonstrate the relationship. It should, however, be noted that the schizophrenic group in this study has a mean ventricular size that is comparable to that found in other samples of schizophrenic patients, who, by virtue of comparison with different control samples have been labeled as having significant ventricular enlargement. The group of patients in this study did exhibit eye tracking impairment. The ranges and distributions for VBR and LRMS are approximately normal. Therefore, there is no reason to believe that this particular sample would be any less likely to demonstrate a true relationship between ventricle size and

eye tracking than other samples of schizophrenic patients for whom measures of ventricular size are available.

In summary, there was no significant relationship between larger lateral ventricles and impaired eye tracking. The literature relevant to this relationship is small. One study found that more patients with large ventricles tracked poorly than did patients with small ventricles. The other study failed to show a significant relationship between the two. Although it is possible that this study failed to find the predicted relationship due to the absence of extreme ventricular enlargement in the patients, this argument is not felt to be a strong challenge to the validity of the present findings as applied to schizophrenic patients who, as a group, do not show extreme ventricular enlargement. It can be concluded that, although it is possible that in a sample with more ventricular enlargement a correlation between VBR and eye tracking might emerge, it is clearly not the case that bad eye tracking is causally associated with ventricular enlargement.

VBR and Neuropsychological Test Performance. There were no significant relationships between VBR and performance on any of the neuropsychological tests (see Table 10).

The issues involved in discussion of this finding are very similar to those discussed in some detail in the previous section on the relationship between VBR and eye tracking. As this sample was not found to have abnormally enlarged ventricles relative to the control group, this investigation

is not able to address the issue of the effect of abnormally large ventricles on neuropsychological performance. However, as was pointed out in discussion of VBR and eye tracking, this sample showed lateral ventricle sizes in the same range as several other studies of schizophrenic patients which have reported ventricular enlargement. There are clear indications that the sample exhibits impairment on a number of neuropsychological tests. Examination of the ranges of scores for the schizophrenic patients (see Table 8) show that all the ranges span the means for both psychiatric controls and literature norms. Taking the above issues into consideration, it would seem that there is no reason to expect this particular study to be less likely than others to demonstrate a true relationship between ventricle size and neuropsychological performance in schizophrenic patients, if one exists.

Examining the literature related to the association between lateral ventricle size and neuropsychological test performance suggests only moderate support for an association between cognitive functioning and lateral ventricle size. The studies which report the strongest association between VBR and cognitive functioning are those of Johnstone et al. (1976) and Golden et al. (1980a and 1982). The average VBR for patients in the Johnstone et al. (1976) (n=18) study was 18.7. The measure of cognitive functioning was the Withers-Hinton scale, which is similar in content to a neurological mental state

exam. These investigators found a correlation of -.70 between ventricle size and Withers-Hinton scores. A more recent report by this research group (Owen et al., 1985) which uses a much larger sample (although it appears that the subjects reported on in the 1976 study are also part of the group described in the 1985 paper) found a significant curvilinear relationship between Withers-Hinton scores and ventricular size. Both papers present anomalous findings compared to other research. It seems likely that the ventricle sizes reported in their first study are derived from measurement techniques which differ from those used in most VBR studies. The curvilinear relationship between ventricular size and Withers-Hinton scores is puzzling. The two other studies which show a relationship between VBR and neuropsychological functioning are those of Golden et al. (1980a and 1982). They report multiple correlation coefficients between the Luria Nebraska Battery and VBR of 0.72 (for VBR and eight scales from the Luria Nebraska), and 0.76 (for VBR and 14 scales from the Luria Nebraska). According to the description of their method, the multiple correlation coefficients were calculated using only those scales which significantly correlated with VBR. Thus, unlike the present study, the Golden et al. studies found a sizable correlational relationship between VBR and neuropsychological functioning. There are at least six published reports which have failed to find relationships between lateral ventricular size and various measures of

cognitive functioning. The results of this study are consistent with the majority of research on lateral ventricle size and cognitive functioning. The findings of Golden et al. would benefit from systematic replication by a group independent of the Nebraska group. Should their findings be replicated it may imply that investigators, including the present author, have used tests which are insensitive to variations in ventricle size, and that the Luria Nebraska Battery has some special qualities which make it very sensitive to the effects of ventricular enlargement on cognitive functioning.

Eye Tracking and Neuropsychological Test Performance. There were no relationships between eye tracking accuracy and performance on any of the neuropsychological tests (see Table 10). The hypotheses for this study proposed two alternative forms for relationships between eye tracking and neuropsychological performance. One pattern which might have emerged would involve an association of eye tracking with impairment on many of the neuropsychological tests. This would suggest that eye tracking impairment might be related to global neuropsychological deficits, and hence, might serve as an indicant of "diffuse" brain dysfunction, which some investigators believe to be a characteristic of a subgroup of schizophrenics. On the other hand, some investigators believe that both eye tracking impairment and schizophrenia involve disruptions of frontal lobe functioning. If this were to be

the case, one might have expected eye tracking impairment to be particularly related to deficits on the frontal lobe tests in the neuropsychological test battery. Neither of these patterns emerged.

There is little previous research on the relationship between neuropsychological tests and eye tracking. Bartfai et al. (1985) found correlations between eye tracking and two tests which were used in this study -- the Trail Making Test and Finger Tapping-Right. These findings were not replicated in this study. Holzman (1974) and Cegalis and Sweeny (1979, 1982) failed to find significant correlations between IQ measures and eye tracking proficiency.

In summary, the hypothesis that impaired eye tracking would be related to impairment on neuropsychological tests was not confirmed. Although there was no concordance for impairment on the neuropsychological measures and on the measure of eye tracking, subjects were impaired on both relative to controls. Given the score ranges and approximately normal distributions for most of the measures it seems improbable that the data analyses would fail to uncover systematic relationships if they were present.

Subject variables

The possibility of confounding relationships between duration of institutionalization, substance abuse, and age and the principal measures was examined. There were no

significant correlations between duration of institutionalization and VBR, LRMS, age or any of the neuropsychological tests. Past history of substance abuse, for approximately one third of the sample, is not believed to have affected the findings. There were no differences between the group of substance abusers and a group of ten patients with little or no drug or alcohol use for VBR, eye tracking, or WAIS-R Full Scale IQ. Age was related to only one variable in the study; WAIS-R Full Scale IQ and age were correlated .40. In this particular sample the older subjects tended to have some of the higher IQ's measured in the group.

There was no control for medication effects on eye tracking or neuropsychological test performance. However, it is interesting to note that the schizophrenic patients were not impaired relative to normals on a test of motor speed and coordination (Finger Tapping), or on a timed test of verbal fluency (Word Fluency). This suggests that the schizophrenic patients were not abnormally slowed in either motor responses or production of verbal responses - both of which occur if medications are causing significant sedation (Heaton & Crowley, 1981).

Correlations within the Neuropsychological Test Battery

The pattern of positive and negative correlations within the test battery are directionally consistent with scoring (ie. attainment vs. error scored tests produce correlations in

the expected directions). There were significant correlations between five of the non-IQ tests and the IQ scales. The individual tests which do and do not correlate with the two IQ scales are, in the main, consistent with theories of the abilities these tests measure. For instance the Benton Visual Retention Test and the Trail Making Test both correlate with Performance IQ and not Verbal IQ. These two tasks involve visuoperceptual and motor performance, as do several tasks which contribute to the Performance IQ score. Conceptual reasoning tests (Categories Tests and Wisconsin Card Sorting Test) and the verbal fluency test (Word Fluency) correlated with Verbal IQ. The fact that the Finger Tapping Test does not correlate with IQ is also a finding which would be expected.

Demonstrating these relationships in this sample is useful, indicating that the subjects' performance shows some of the expected inter-correlation typically found among these tests in many different patient samples. The subjects in this study were institutionalized patients many of whom were actively psychotic at the time of testing. It is conceivable that the test performance of these individuals might be highly erratic, precluding any systematic relationship between the neuropsychological tests and other measures. The relationships between the various tests in the battery and the consistency of the directions of the correlation coefficients makes it unlikely that failure to find relationships between

neuropsychological performance and the other measures is due to erratic or random test behavior by the patients.

Although the consistency in responses is thought to be sufficient to rule out the likelihood of random or invalid test behavior, several expected correlations did not emerge. More covariation was expected between tests sensitive to frontal lobe function. The fact that there is not a stronger relationship between these tasks might be the result of numerous factors. First, several of the tests designated as 'frontal tests' are known to involve complex cognitive functions which are not exclusive to the frontal lobes; hence, the 'frontal tests' may not be specifically measuring frontal lobe functioning in these patients. Second, it is highly likely that the 'frontal tests' are not equally sensitive to frontal lobe functioning, or are sensitive to different aspects of the functioning of the frontal lobes, and therefore should not be expected to intercorrelate highly. Finally, it is possible that there is not a specific frontal lobe dysfunction in the subjects who participated in this study and hence, there is no reason to expect covergence of performance among the frontal tests. As no objective criterion of frontal lobe integrity is available for these subjects, it is not possible to choose between the above alternatives.

Finally it is noteworthy that Verbal and Performance IQs are not significantly correlated. In the WAIS-R standardization sample of 300 subjects age 25-34, the

correlation between Verbal and Performance IQ was .76. In this sample it is .25. In comparison with the psychiatric control group the schizophrenic patients do not differ in Verbal IQ but did significantly less well on Performance IQ. The low correlation between the two scales may reflect a selective impairment of some of the abilities assessed by the WAIS-R Performance Scale. The pattern of significant depression of Performance IQ relative to Verbal IQ is consistent with the sort of impairment found in diffuse brain damage.

Statistical Issues

The analyses of the data in this study were conducted using multiple t-tests and correlations. Except for the examination of inter-correlations in the neuropsychological test battery, other multiple comparisons were done against Bonferroni corrected probability values. This approach seems the most appropriate one for a study examining many inter-relationships in a relatively small sample. Further, the literature on the relationships between the measures is relatively small, contains inconsistencies, and does not have a well developed theoretical base for linking the measures. In accord with this it seems advisable to use a conservative approach to Type I error. This study failed to demonstrate any statistically significant relationships among the principal measures. Examining the correlation tables makes it

clear that there are no consistent trends to suggest that the data are related as hypothesized, but miss significance by a slim margin. In fact, were the Bonferroni procedure not used, the interpretation of results would not change. Of the twenty correlation coefficients between the neuropsychological tests and VBR and eye tracking, two would be significant at a liberal p-value of .05 one tailed (Performance IQ is correlated -.33 with eye tracking and the Categories Test in correlated .37 with eye tracking). The purpose of the investigation was to assess the possibility of using VBR, eye tracking accuracy, and neuropsychological test performance, as a sort of battery for investigation of hypotheses related to biological subgrouping of schizophrenic patients. The weak relationships between two of the neuropsychological tests and eye tracking do not provide convincing evidence that performance on these measures share a common etiology, or that either would be particularly useful to predict the occurrence of the other.

Conclusion. There is no indication from the present study that lateral ventricular enlargement, eye tracking impairment, and neuropsychological test deficits would, as a group, form a useful set of measures for identification of a subgroup of chronic schizophrenic patients for further research.

The sample did not show lateral ventricular enlargement as predicted. In light of the most recent research

literature, significant lateral ventricular enlargement in schizophrenics may be less common than earlier findings suggested. Several investigators are suggesting that the third ventricle, not the lateral ventricles, are abnormal in schizophrenic patients (e.g. Boronow et al., 1985). Third ventricle size was not analyzed in this report.

Although the present sample showed deficits in both eye tracking and neuropsychological performance, these impairments were not related. It might be that measurement of a relationship between these two variables was hampered by using a sample which was excessively impaired on both. This is thought to be unlikely. Despite the overall impairment of the group on both measures, it does not appear that the ranges of scores were so restricted as to preclude the demonstration of a relationship. The most parsimonious interpretation of the findings on eye tracking and neuropsychological performance would be that performance on these variables is unrelated in schizophrenic patients.

Nonetheless, it may be that the sample in this study is a subgroup in itself, and hence the measures are related by simple virtue of their co-occurrence in this group. The possibility exists, that had these measures of eye tracking and neuropsychological performance been applied to a broadly heterogeneous sample of schizophrenic patients, a subgroup of individuals with abnormal attainment on both would emerge and the measures would be found to be related. Further research

along these lines might be useful. Were such work to be done, it would be advisable to collect information on a wider range of clinical parameters than were considered in this study. It may be that links between the variables are mediated by subject characteristics which went unmeasured in this study.

Finally, little specific information is known about factors which covary with neuropsychological deficits in schizophrenia. These deficits clearly exist in the chronic patient group in this study, and in many others reported in the literature. Longitudinal investigation of neuropsychological deficits would be particularly interesting. Some of the patients who participated in this study had been neuropsychologically assessed earlier in the course of their illness. In some cases it appeared that there had been little change in their performance over a period of years. It would be very interesting to investigate the prevalence of neuropsychological deficits in first episode patients on whom follow-up assessments of both clinical and neuropsychological functioning were carried out.

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APPENDIX A

Testing the Identity Matrix Hypothesis

The calculation of the X^2 value used in testing the overall null hypothesis that a matrix of correlations is an identity matrix is done with the following formula:

$$X^2 = (N-3) \quad {}_{j<i} \quad Zij^2$$

where Zij^2 are the squares of the Fisher Z transformations for the non-redundant correlation coefficients in the matrix and N-3 corresponds to the sample size minus 3. The degrees of freedom for the critical X^2 value are the number of non-redundant correlations in the matrix.

In the case of the 10x10 matrix of coefficients for the neuropsychological battery, there are 45 non-redundant correlations. The sum of the squared Fisher Z transformations for these 45 correlations is 3.73. When this value is multiplied by N-3 (N-3=30-3, in this sample) the obtained value for the X^2 is 100.7. This is compared to a tabled value of X^2 with 45 degrees of freedom (p=.05) which equals 61.656, therefore the null hypothesis can be rejected.

This method is proposed by Steiger (1980) as a way of obtaining experiment wise error rate protection.

APPENDIX B1

MARKERS AND PREDICTORS (MAP) PROJECT CONSENT FORM

Investigators:

William G. Iacono, Ph.D.

Karen Tallman, B.Sc.

Consent to be interviewed:

A research project involving psychological testing, physiological records and a CAT scan has been described to me. I understand that before anyone is included in the research study they are interviewed. This interview is carried out because the research project needs to carefully select people with certain types of problems. Information that will be helpful to my treatment may be conveyed to my therapist (or to _____). Otherwise all the information obtained in this project will be kept confidential and used only for the purposes of this study. I understand that I will be paid $5.00 at the end of the interview whether I am selected for the research project or not. I also understand that I may withdraw from the interview at any time without prejudice to present and future care and treatment.

In signing this form I hereby acknowledge receiving a copy of my own use.

_____ Witness

_____ Signature

_____ Print Name

_____ Date

APPENDIX B2

MARKERS AND PREDICTORS (MAP) PROJECT CONSENT FORM

Investigators:

William G. Iacono, Ph.D.

Karen Tallman, B.Sc.

The research project you have been asked to participate in has three parts. None of the things we will be doing will cause you any pain. One part of the study will take place at Riverview and the other two parts will happen at the University of British Columbia. The testing done at the university takes about two and a half hours. A member of the project staff will drive you to the University, stay with you during the testing and then drive you back to Riverview. You will be away from the hospital for about 5 or 6 yours on the day you go to the University for testing.

Please read the rest of this form carefully so you understand what you will be doing if you decide to participate in the study.

PART ONE: Psychological Testing at Riverview: about 3 hours

In this part of the study, you will be given tests of memory, word definitions, concept puzzles, had coordination tasks and other more difficult for you. You will be asked to concentrate and try your best to answer each question. We will take a rest at the end of each hour.

PART TWO: Physiological Recording at U.B.C.: about 2 hours

In this part of the study your body responses such as eye movements, heart beat, brain waves and the activity of your sweat glands will be measured while you perform several simple tasks. These tasks include comfortably relaxing while listening to belief tones, watching brief flashes of light, 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. To make these recordings, sensors will be attached to your arms, legs, and head but no discomfort or danger to you is involved. In another part of this study a drop of oil similar to cooking oil will be placed on your skin near your fingernails and a photograph of your skin will be made.

PART THREE: CAT Scan at U.B.C. about 1/2 hour

In this part of the study, pictures of your head will be made with a machine called a CAT or body image scanner. 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. A CAT scan is very much like an X-ray and makes it possible to look at the structures of brain structures that are related to the kinds of problems you had been having or that are related to the measures of eye movements, sweat gland, and brain wave activity.

We hope you have carefully read the description of the three parts of the study. This is a good time to ask questions if there is anything you don't understand. If you feel you understand what you will be doing, and if you still wish to take part in the project pleas read and sign the following consent form.

I have read the above explanation of a research project and been given a copy of this consent form for my own use. I understand the project will involve psychological testing, physiological recordings and a CAT scan. I am aware that I will travel by car to the University of British Columbia with one of the research staff. Information that will be helpful to my treatment may be conveyed to my therapist (or to _____). Otherwise, all the information obtained in this project will be kept confidential and used only for the purposes of this study. I understand I am free to ask questions about the procedure at any time. By signing this form, I agree to participate, although I realize I am free to withdraw from this study at any time without prejudice to present and future care and treatment. When I finish all parts of the study I will be paid $35.00.

_____ Witness

_____ Signature

_____ Print Name

_____ Date