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SUBTYPING IN CHRONIC SCHIZOPHRENIA: CLINICAL,
NEUROPSYCHOLOGICAL, AND STRUCTURAL INDICES OF DETERIORATION

City University of New York

PH.D. 1984

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by

ROBERT M. BILDER, JR.

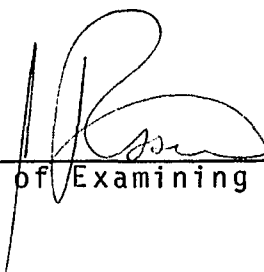
A dissertation submitted to the Graduate Faculty in
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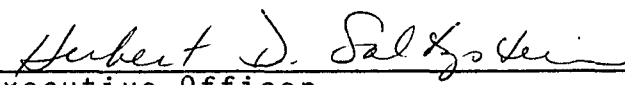
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This manuscript has been read and accepted for the graduate Faculty in Psychology in satisfaction of the dissertation requirement for the degree of Doctor of Philosophy.

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Abstract

SUBTYPING IN CHRONIC SCHIZOPHRENIA: CLINICAL, NEUROPSYCHOLOGICAL, AND STRUCTURAL INDICES OF DETERIORATION

by

Robert M. Bilder, Jr.

Adviser: Professor Jeffrey J. Rosen

Researchers have proposed that a "subtype" of chronic schizophrenia may exist that is marked by degeneration of both brain and behavior. This theoretical syndrome has been characterized as one in which: (a) "negative" symptoms and history of poor premorbid social adjustment are prominent, (b) neuropsychological deficits are conspicuous, and (c) structural abnormalities of the brain such as ventricular enlargement and cortical atrophy may be seen on computed tomographic (CT) scans.

The association of these characteristics was studied in a sample of 32 chronic schizophrenic or schizoaffective inpatients on a research unit. Correlations within and between predefined sets of symptoms did not support the hypothetical distinction between positive and negative symptoms. Although clusters of "core" negative and positive symptoms were identified, a nonspecific cluster including

both positive and negative components was prominent.

The core clusters of symptoms related to some of the other subtyping measures along hypothesized lines. The core negative symptoms (affective flattening, avolition/apathy, anhedonia) were related to poor premorbid social adjustment, neuropsychological deficits, and evidence of deterioration from previously higher levels of functioning. The core positive symptoms (delusions, hallucinations, breadth of psychosis) were unrelated to these defects. The nonspecific group of positive and negative symptoms (alogia, attentional impairment, formal thought disorder, and bizarre behavior) was associated with the most severe neuropsychological deficit and evidence of poor premorbid intelligence, but not with CT-scan abnormalities.

Evidence of ventricular enlargement and cortical atrophy was strongly correlated with indices of intellectual deterioration, and surprisingly, with higher estimates of premorbid intelligence and educational achievement. The results indicate that CT-scan abnormalities were related to better premorbid functioning; or conversely, that patients not manifesting structural degeneration of the brain had never developed adequate cognitive abilities.

Sample selection is probably critical to the interpretation of these findings and the results of other investigators. In this sample, a process characterized by symptoms of cognitive/attentional disturbance and

severe neuropsychological impairment was independent of the current definitions of positive and negative symptoms and unrelated to CT-scan abnormalities. This pattern of associations is discussed in the context of the abnormal development of cerebral systems.

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My thanks to those who have been active participants in the research activities that are reported here, and to those who so generously supported me through the last several years, will always be incomplete. The opportunity to express my gratitude to Rita Rudel, who was in fact responsible for my initial involvement in these projects, is now painfully absent. I can only hope to deserve someday the confidence she had in me.

It was Ronald Rieder who initiated and directed this research; his clarity of thought serves as a constant example. I will always be spoiled by having had the chance to collaborate with Anand Pandurangi and shall miss our heated debates about functional neuroanatomy. Without the professional and personal generosity of Harold Sackeim, I cannot imagine how this work could have been completed. He, if anyone, has demonstrated to me that rigor and the joy of scientific exploration are not incompatible.

The debt of thanks to my mentor, Jeffrey Rosen, can never be repaid. I can only feel lucky that he was tirelessly willing to guide me through these tortuous years. It is impossible to count the number of times he has dissolved my confusion and anxiety. It has been my honor to be exposed to the simultaneous genius and profound humanity of Louis Gerstman, who has so often seen what was beyond my

vision and been kind enough to show me. To Elkhonon Goldberg I owe the deepest intellectual debt; at every turn I rely on ideas that he has fostered, and I can only hope that my inevitable simplifications do not do him injustice. I am extremely grateful to Wilma Rosen for her selfless contributions of time, energy, and ideas; without her sane advice I doubt this work would have been completed.

A number of students participated in this research and I owe thanks to them all. Edward Moss in particular donated considerable energy to the project; I hope that he benefited from his involvement at least fractionally as much as I did. Mark Pesner, Fred Krellenstein, William Buonanotte, and John Jannes were also instrumental in the project's completion.

"In the beginning was the word"... and without the instruction in processing these, provided graciously by Jane Gruen and Timothy Barnum, along with good company and humor, this text might not have materialized until the return of the Comet Kehoutek.

A most special gratitude is due to Sukdeb Mukherjee. His unwavering support has more than any other factor allowed me to pursue and complete this work. To have had him as a teacher and friend is my supreme good fortune.

Last and most. My wife, best friend, and physician, Alison. Who has shared every torture, and loved me nevertheless. I'm coming home.

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"For the view that in the origin of dementia praecox degeneration [author's italics] plays a part, the circumstance is usually brought forward that in the patients from the beginning, physical and psychic signs of degeneration are frequently found."

- Emil Kraepelin, 1896 -

(transl. in Dementia praecox and paraphrenia. R.E. Krieger Publishing Co., Inc.: Huntington, NY, 1971, p. 235.)

The role of "degeneration" has assumed new importance in schizophrenia research. While deterioration of "psychic" functioning has been documented clinically for almost a century, it is now established that many schizophrenic patients show striking deficits of neuropsychological function and degenerative changes in brain structure. These clinical, neuropsychological, and structural signs of deterioration may serve to identify a homogeneous subgroup of schizophrenic patients. Isolation of such a subgroup could form a rational basis for future biological investigations of schizophrenia.

Past research has been plagued by the heterogeneity of the schizophrenic syndrome. Patients are diagnosed schizophrenic according to a taxonomy based entirely on symptoms. The lack of isomorphism between symptoms and etiopathology, a problem in all biomedical sciences, has been especially troublesome in psychiatry (Corning & Steffy, 1979). Schizophrenia may be best conceptualized as an umbrella classification sheltering a wide variety of disorders for which etiology is unknown (Kety, 1980). The heterogeneity of the schizophrenic syndrome prompted Jeste and his colleagues to propose a motto for schizophrenia research - "'Ex Uno Multi' or 'many from one'" (Jeste, Kleinman, Potkin, Luchins, & Wyatt, 1982, p. 200). The priority that they advocate is the subtyping of schizophrenia across multiple behavioral and biological dimensions.

Several promising efforts to subtype schizophrenia are based on the differences between those patients who show conspicuous deterioration of brain and behavior, and those who do not. Behavioral signs of deterioration have been derived using clinical psychiatric measures (such as assessments of symptoms and social functioning) and cognitive or intellectual measures (such as neuropsychological test performance). Degeneration of brain structure may now be assessed by the non-invasive technique of computerized tomography (CT). The presence of such signs of deterioration may be used to define a subtype. The absence of these signs, and the presence of different features, may be used to define a complementary subtype.

An example of subtyping that involves clinical, neuropsychological, and structural dimensions is presented in Table 1. This classification system is based on the work of many investigators. The contributions of Crow (1980); Jeste et al. (1982); Weinberger, Cannon-Spoor, Potkin, and Wyatt (1980); and Andreasen, Olsen, and Dennert (1982); are particularly significant. The validity of the dichotomy presented has not been established. Few studies have included all of the measures that are theoretically relevant to the subtypes, and much of the evidence supporting this subtyping scheme is indirect. I will first consider the clinical, neuropsychological, and neuroradiological findings that have led to the use of these measures in subtyping

Table 1
Features Used to Define Hypothetical Subtypes Within the
Schizophrenic Syndrome

Features	Subtype	
	"Negative" "Type II" "Defect"	"Positive" "Type I" "Productive"
<u>Clinical Symptoms</u> <u>& History</u>	Flat affect Apathy Impoverished speech Anhedonia Premorbid asociality	Delusions Hallucinations Formal thought disorder Bizarre behavior Adequate social adjustment
<u>Neuropsychological</u> <u>Performance</u>	Defective performance	Adequate performance
<u>Structural (CT)</u> <u>Findings</u>	Enlarged ventricles Cortical atrophy	No abnormality
Note. See text for details.		

efforts, and then review those interdisciplinary studies that suggest the existence of a particular subgroup of chronic schizophrenic patients marked by deterioration of both brain and behavior.

Clinical Psychiatric Subtyping Approaches

For over a century, clinicians have recognized the heterogeneity of psychiatric disease. Physicians observed systematic differences in the symptoms and the courses of "insanity" and formulated the earliest taxonomies of mental illness. Deterioration was the basis for some of the

earliest subtyping efforts. Morel (in 1856) introduced the designation démence précoce, emphasizing the role of symptomatic deterioration in what is now termed the schizophrenic syndrome. Kraepelin (in 1898) expanded on these observations and made the first clear differentiation of patients into groups according to the progression, or course, of the illness. He argued that the deteriorating clinical course of dementia praecox distinguished it from other psychiatric illness (i.e., manic-depressive psychosis).

Since the time of Kraepelin, clinical measures of symptoms and course have been used as the basis for many classifications of mental disorders in general and of schizophrenia in particular. Validation of these classification systems has consisted of determining:

1. how well patients fit into the categories. An ideal system would be comprehensive and the categories would be discrete. All cases should be accounted for and no intermediate or "mixed" cases should occur.

2. how much the system aids prediction. An ideal system would enable prediction of prognosis and the probability of response to treatment alternatives.

No classification system has yet been deemed satisfactory according to these tests of criterion-related and predictive validity. Some systems have been more, some less successful. The concept of deterioration has been

invoked in a variety of those systems that have been judged most successful.

At the symptom level, the concept of deterioration is reflected by such descriptors as "the defect state", "the poverty syndrome", or "the dementia of dementia praecox." In systems more dependent on analysis of the course of the disorder, deterioration is emphasized in the the designation of "chronic", "process", and "malignant" forms of schizophrenia.

The defect state and deteriorating process in schizophrenia have been contrasted to forms of the illness that are characterized by "florid" or "productive" symptomatology, and relative preservation of functioning between episodes. Numerous dichotomies have been proposed that follow from this basic distinction. Symptom-based dichotomies include productive vs nonproductive, paranoid vs nonparanoid, and affective vs nonaffective types. Dichotomies based on course include acute vs chronic, reactive vs process, and good- vs poor-outcome classifications.

Concerns about the reliability of diagnosis have led to the use of more purely symptom-based systems, and within these systems, a relatively greater emphasis on productive symptomatology (Andreasen, 1982). This approach is typified in the work of K. Schneider (1959, 1957) who identified eleven "First Rank Symptoms" that (in the absence of known physical illness) he considered to be pathognomonic of

schizophrenia. Each of the First Rank Symptoms is a productive one -- delusions, hallucinations, and bizarre behavior or thought disorder are noted for their presence. Nonproductive symptoms, such as apathy and withdrawal, were not considered to be significant for diagnosis.

The most widely used diagnostic systems, which rely primarily on observation of productive symptomatology, include: the Diagnostic and Statistical Manual of Mental Disorders (DSM-III; American Psychiatric Association, 1980); the Research Diagnostic Criteria (RDC; Spitzer, Endicott, & Robins, 1977); the New Haven Schizophrenia Index (Astrachan et al., 1972); the Carpenter-Strauss Criteria (Carpenter, Strauss, & Bartko, 1973). In these systems, a deteriorating course of illness is not central to classification, although generally a minimum duration of illness is specified for the diagnosis of schizophrenia.

Adoption of these systems has contributed to a narrowing of the concept of schizophrenia, particularly in excluding patients with very brief or predominantly affective disorders. The use of specific criteria for diagnosis has also made it easier to compare samples studied by different research groups. Nevertheless, it has become clear that considerable heterogeneity exists even among patients with more chronic forms of schizophrenia. Many patients are not easily classified into the diagnostic categories of these systems, and considerable variability

within diagnostic groups has been observed in studies of treatment response and outcome.

Dissatisfaction with the criterion-related and predictive validity of these classification systems has revived interest in the defect state of chronic schizophrenia. A fundamental distinction between positive (productive) and negative (defect state) symptoms has recently been invoked by several groups (Strauss, Carpenter, & Bartko, 1974; Crow, 1980). The positive symptoms of schizophrenia, such as delusions, hallucinations, thought disorder and bizarre behavior, have been contrasted to the negative symptoms of apathy, withdrawal, poverty of speech, and blunted affect. In the defect state, or "negative schizophrenia", it is proposed that positive symptoms may be very mild or not present at all.

Parallel to investigations of negative symptoms, interest has been renewed in the malignant course of some chronic schizophrenics. More attention has been paid to the permanence of symptoms after the onset of illness, to the age of patients at the time of onset, and to the psychosocial adjustment of patients prior to onset. The more malignant and unrelenting forms of illness have been associated with onset earlier in the life span, and with a pattern of premorbid social withdrawal and isolation (Gittelman-Klein & Klein, 1969). The latter pattern of premorbid social adjustment has been widely used in prediction of prognosis, and the syndrome of "premorbid

asociality" has been consistently associated with an unremitting course and poor outcome (Cannon-Spoor et al., 1982). In contrast, a pattern of adequate premorbid social adjustment has been associated with later onset and a less chronic course. In these patients, partial remission and periodic return to premorbid levels of functioning are sometimes seen.

These two means of clinical classification -- the positive/negative symptom distinction and the good/poor premorbid functioning distinction -- are now considered relevant to the identification of more homogeneous subtypes of chronic schizophrenia. The development and defining characteristics of these distinctions, and evidence concerning their validity as subtyping methods within the clinical dimension, will now be reviewed.

Positive and Negative Symptoms

A conceptual dichotomy between positive and negative symptoms was formulated by Hughlings-Jackson (1931). According to this theory, in a hierarchy of cerebral function, superordinate centers modulate (by inhibition) subordinate ones, while the subordinate centers provide "activation" necessary for all brain functions. Lesions of subordinate centers cause impairment of cerebral arousal and result in decrements of activity and responsivity in various brain centers. The behavioral concomitants of this cerebral dysfunction are "negative" or conspicuous by their absence.

Symptoms include lack of drive, loss of interest, decreased motor and speech activity, and withdrawal from social interactions. Lesions of superordinate centers, on the other hand, result in disinhibition of subordinate ones, leading to unmodulated cerebral activity and disorganization. Behavioral manifestations of this disturbance are "positive" symptoms such as disordered expression and thought, bizarre perceptual experiences, and active disturbances of affect.

The original dichotomy between positive and negative symptoms proposed by Hughlings-Jackson is similar, but not identical to that used in psychiatric research today. In current theories (such as that of Crow [1980]) the neuroanatomical basis of this distinction is not postulated. Instead, positive symptoms refer simply to those that are noted for their presence, while negative symptoms are those remarkable by their absence. Thus the presence of delusions, hallucinations, formal thought disorder, and bizarre behavior comprise positive symptoms. The absence of goal directed activity, interest in activities, social interaction, and affective engagement comprise negative symptoms.

A number of investigators have recently revived interest in this dichotomy (Strauss, Carpenter, & Bartko, 1974; Crow, 1980; Andreasen & Olsen, 1982) as a primary means of subtyping the schizophrenic syndrome. Evidence from psychopharmacological investigations has been important

in the development of these theories. Neuroleptic drugs appeared to affect only the positive symptoms of schizophrenia (Johnstone, Crow, Frith, Carney, & Price, 1978). Patients with predominantly negative symptoms failed to benefit from drug treatments (Letemendia & Harris, 1967). Furthermore, while positive symptoms were exacerbated by amphetamine-like drugs, negative symptoms showed little change (Kornetsky, 1976).

These indications that the positive/negative dichotomy might have a biological basis and be helpful for predicting treatment response stimulated a number of investigations. Most of these studies will be discussed later in the context of assessing the relationship between the positive/negative dichotomy and other subtyping measures. A methodological problem faced in most studies was that no consensus existed about how to define positive and negative symptoms. This problem was addressed by N. Andreasen and her colleagues.

Andreasen and Olsen (1982) suggested five characteristic features of the defect state, including: (a) Alogia, (poverty of speech, and poverty of content of speech); (b) Anhedonia/Asociality "(e.g., inability to experience pleasure or to feel intimacy, few social contacts)"; (c) Avolition/Apathy "(e.g., anergia, impersistence at work or school)"; (d) Attentional Impairment; and (e) Affective Flattening. Andreasen (1980, 1982) developed the Scale for the Assessment of Negative Symptoms (SANS), and together with Olsen, outlined

a set of specific criteria for classifying patients into positive, negative, and mixed groups (Andreasen & Olsen, 1982). Inclusion of the mixed group demonstrated the authors' recognition that the criterion-related validity of the positive/negative dichotomy was not perfect (i.e., patients would not fall exclusively into positive and negative groups, and in many cases a mixture of positive and negative symptoms would be found).

In a validation study of the positive/negative distinction, the symptoms used to define positive and negative schizophrenia did appear to cluster together along hypothesized lines. Correlational analysis of five negative and four positive symptom variables showed consistency within each set, especially among the negative symptoms (Cronbach's alpha for negative symptoms = .849; for positive symptoms = .397). Principal components analysis including the same variables revealed a single factor accounting for 42% of total symptom variance. This factor had strong positive loadings on each of the negative symptoms, as well as large negative loadings on each of the positive symptoms (Andreasen & Olsen, 1982). Despite the failure of the positive/negative symptom dichotomy to neatly classify patients, it appeared in this study that a continuum of symptoms exists on which positive and negative symptoms occupy opposite extremes.

The predictive validity of the positive/negative dichotomy was also assessed by Andreasen and Olsen (1982). Their findings will be discussed in review of the relationship between the positive/negative dichotomy and other subtyping measures.

Premorbid Social Adjustment

Kraepelin initially isolated a pattern of premorbid social functioning in his patients characterized by a "quiet, shy retiring disposition", and the absence of friends. Bleuler noted an additional feature, "lack of interest in the environment." Both Kraepelin and Bleuler felt that these poor premorbid functions were prodromal features of the illness.¹

Hoch (1910) was the first to suggest a relationship between these premorbid features and outcome. While the prognostic value of certain symptoms was addressed by others (e.g., Kant, 1944; Langfeldt, 1937), little attention was focused on the prognostic value of premorbid social functioning again until the 1960's. In these studies the absence of early "schizoid" traits was viewed as a positive prognostic sign (Stephens, Astrup, & Mangrum, 1966; Vaillant, 1964). Relatively strong associations were found

¹This view was opposed by Meyer (1950), who thought that such factors were not the initial signs of schizophrenia, but rather that such dysfunction had a predisposing role.

between the absence of early schizoid traits and later remission or recovery.

Although early schizoid features were consistently related to outcome, it was not clear whether a "good" vs. "poor" premorbid social functioning dichotomy existed, or patients might simply vary along a continuum. Original research on the Elgin Prognostic Scale by Wittman (1941) demonstrated a bimodal distribution of premorbid functioning in a large group of schizophrenics. Gittelman-Klein and Klein (1969) also found a distinct bimodal distribution of premorbid social functioning in a sample of 84 schizophrenics. Scores on a rating scale developed by the authors indicated that premorbid asociality was also strongly related to a variety of outcome variables, such as length of hospitalization and rate of relapse. The use of a "good/poor" premorbid social functioning dichotomy appeared therefore to be a valid subtyping measure² with prognostic significance. The poor-premorbid group demonstrated greater homogeneity of outcome than the good premorbid group. Almost all of the former group had unfavorable outcome. Among patients in the good premorbid group, about one third did poorly later, while the rest did relatively well according to outcome measures. Thus the good premorbid

²That good/poor premorbid functioning represents a true dichotomy is not universally accepted, and it has been suggested that further empirical studies are necessary to answer this question (Keith & Buchsbaum, 1978).

group appeared to be a more heterogeneous one.

Relationships Between Symptoms and Premorbid Social Adjustment

Two means of subtyping schizophrenia within the clinical dimension have been described. One, derived from observation of current symptoms, is the dichotomy between positive and negative symptoms. The other, derived from retrospective analysis of early social behavior, is the dichotomy between good and poor premorbid social adjustment.

Both dichotomies have been considered relevant to prediction of prognosis, although the validity of only one (the premorbid social functioning dichotomy) has been demonstrated in a prospective study (Gittelman-Klein & Klein, 1969). Indirect evidence supports the use of the positive/negative symptom dichotomy as a prognostic index. Lack of response to treatment is considered a poor prognostic sign, and patients with positive symptoms generally respond to treatment better than those with negative symptoms. Indeed, it is the positive symptoms of schizophrenia that are affected most by treatment; negative symptoms may remain the same (Angrist et al., 1980). Andreasen and Olsen (1982) reported that the negative group in their sample had more history of electroconvulsive therapy (ECT) than positive or mixed symptom groups. They suggest that "this frequent use of ECT in the patients with negative symptoms probably represents an aggressive but

obviously unsuccessful attempt to eradicate their negative symptoms" (p. 792).

If both negative symptoms and poor premorbid social functioning are relevant to the identification of a homogeneous subgroup of patients, then the two measures should be positively correlated. Some indirect evidence supports such an association. Before interest in the positive/negative symptom dichotomy had been generated, a relationship had been suggested to exist between premorbid asociality and the presence of nonparanoid symptoms. Of course, inferences about positive/negative symptoms that are based on studies of paranoid/nonparanoid features are valid only to the extent that these two distinctions overlap.

Several studies have supported the association of poor premorbid adjustment and the absence of paranoid diagnosis (Goldstein, Held, & Cromwell, 1968; Zigler & Levine, 1973). This relationship appeared to obtain, however, only if patients with very poor levels of premorbid adjustment were included (Zigler, Levine, & Zigler, 1976). Goldstein (1978) examined the relationship of premorbid adjustment and paranoid status in acute schizophrenia. He found a positive linear relationship between better premorbid adjustment and increasing paranoid symptomatology. Among patients with poorest premorbid adjustment, paranoid symptoms were largely absent. Among patients with best premorbid adjustment, however, more nonparanoid cases were found than were predicted by the linear model. In agreement with the

findings of Gittelman-Klein and Klein (1969), the patients with poor premorbid functioning comprised a more homogeneous group than those with good premorbid adjustment.

Cannon-Spoor, Potkin, and Wyatt (1982) found that a paranoid subgroup of chronic schizophrenics had relatively better premorbid social functioning than other subgroups of patients. Insofar as paranoid symptomatology is positive, these findings suggest that the relationship of positive symptomatology and good premorbid adjustment is not restricted to acute forms of the illness.

In a more direct investigation of this relationship, schizophrenics classified as "negative" on the basis of symptoms had significantly poorer premorbid social adjustment than groups classified as "positive" or "mixed" (Andreasen and Olsen, 1982).

If both dichotomies are tapping a single valid means of subtyping, then sociodemographic characteristics and course of illness might be expected to differ consistently between groups classified according to either dimension. Specifically, negative and poor-premorbid groups should manifest a more malignant course with earlier onset and lower educational attainment.

Andreasen and Olsen (1982) found that positive schizophrenics had more years of education than negative or mixed groups, but age at onset did not differ between groups defined on the basis of symptoms. In fact, "negative" schizophrenics in this sample were nonsignificantly older at

onset than either positive or mixed groups. In contrast, Cannon-Spoor, Potkin, and Wyatt (1982) found that earlier onset was associated with premorbid asociality. They point out, however, the difficulty of differentiating between "premorbid" and early "morbid" characteristics in assessing this relationship. A later study by Jeste et al. (1982) found no difference in age at onset between good and poor premorbid groups.

The positive/negative symptom dichotomy and the good/poor premorbid social adjustment dichotomy appear to be useful means of classification in the schizophrenic syndrome. That both dichotomies are tapping a fundamental distinction is suggested by observations that they are positively correlated and may have similar prognostic significance. Most evidence supporting the association of symptoms and premorbid social adjustment is indirect; that is, paranoid and nonparanoid samples must be taken to represent positive and negative groups, respectively. That both distinctions clearly identify patients with a similar course of illness remains in question.

The good/poor premorbid adjustment distinction has appeared to better represent a true dichotomy, while the positive/negative symptom distinction may better reflect a continuum. In both distinctions, however, homogeneity has appeared greater in the more deteriorated group (i.e., poor premorbid and negative symptom groups). This observation lends support to the idea that these two clinical

distinctions may serve to identify a valid subtype of chronic schizophrenia in which clinical deterioration is significant.

Neuropsychological Subtyping Approaches

Kraepelin and Bleuler felt that schizophrenic illnesses could be distinguished from "organic" mental disorders because in the former, disturbances of orientation, consciousness, and memory were not found. This view has not been sustained by the results of controlled neuropsychological investigations. Defects of intellectual and cognitive functioning have been found with regularity in controlled studies of schizophrenic samples (for many examples see Heaton, Baade, & Johnson, 1978). Deficits in neuropsychological functioning found in psychiatric samples have often been disregarded as artifacts of psychodynamic disturbances, the effects of institutionalization, drug or surgical treatments (Goldstein, 1978). Most of these studies, however, were flawed by criterion bias. Neurological diagnosis was generally used as the sole criterion for establishing the presence of "organicity." A negative neurological exam has been interpreted as demonstrating the absence of brain damage. Longitudinal studies and the use of additional validating criteria (e.g., CT-scans), have shown that neuropsychological assessment is

often more sensitive to the presence of brain disease than neurological examination (Hartlage, 1982).

Several recent reviews (Heaton et al., 1978; Goldstein, 1978; Malec, 1978) of many neuropsychological studies, documented similarities in performance between chronic schizophrenics and patients with neurologically diagnosed brain damage. This evidence has finally led to acceptance of the hypothesis that many chronic schizophrenic patients are indeed "organic."

Many of the earlier psychological-testing studies are difficult to interpret because they suffer from serious methodological problems. For example, in the 94 studies reviewed by Heaton et al. (1978): representativeness of the sample was not documented in 63%; neurological examination procedures or laboratory results were lacking in 85%; criteria for psychiatric diagnosis was not specified in 94%; the chronicity of the sample was not mentioned in 54%; and the age of the patients was reported in only 38% of reports.

Despite the methodological inadequacies of many studies, they are consistent in suggesting neuropsychological dysfunction in chronic schizophrenics that is qualitatively and quantitatively indistinguishable from that seen in patients with neurologically diagnosed brain disease. Some chronic schizophrenics perform many tasks at levels below those used clinically as "cutoffs" for the identification of brain damage. The profile of neuropsychological impairment in chronic schizophrenia has

been generally consistent with that of bilateral/diffuse cerebral dysfunction rather than localized cortical compromise (Klonoff, Fibiger, & Hutton, 1970; Flor-Henry, 1976; Taylor & Abrams, 1984). There have nevertheless been attempts to specify the nature of neuropsychological deficit in schizophrenia in regional terms.

Several investigators have proposed the existence of relatively dysfunctional dominant hemisphere systems, in this way accounting for the disorders of language and thought that are hallmarks of the syndrome. Noteworthy in this regard are the theories of Flor-Henry (1969, 1976, 1979, 1983), who characterized brain dysfunction in the schizophrenic disorders as that of the dominant fronto-temporal systems. Evidence supporting dominant hemisphere dysfunction in schizophrenia has been gleaned from analyses of incidence of schizophrenia-like psychoses in unilateral temporal-lobe epilepsy (Flor-Henry, 1969); in cases of unilateral brain insult (Davison & Bagley, 1969); and from prospective neuropsychological evaluations of patients with affective and schizophrenic psychoses (e.g., Flor-Henry, 1976). Support for the hypothesis of an anterior/dominant hemisphere dysfunction in the schizophrenic syndrome also comes from studies of cerebral metabolism (e.g., Buchsbaum, Ingvar, Kessler, Waters, Cappelletti, van Kammen, King, Johnson, Manning, Flynn, Mann, Bunney, & Sokoloff, 1982; Ingvar, 1976), and electroencephalography (e.g., Serafetinides, 1972, 1973;

Coger, Dimond, and Serafetinides, 1979). Other evidence from electrodermal, tachistoscopic, dichotic listening, and lateral eye-movement studies has been marshalled to support the dominant-hemisphere hypotheses of schizophrenic illness (see, e.g., Taylor, Redfield, and Abrams, 1981; Tucker, 1981, for reviews). Conflicting results have been reported (see, e.g., Newlin; Carpenter, & Golden, 1981), and alternative interpretations of these findings have been offered (e.g., defects of interhemispheric transfer (Beaumont & Dimond, 1973; Green, 1978)). Controversy has also centered on whether the dysfunction attributed to the left hemisphere reflects hypo- or hyper-activation (Gur, 1979; Gruzelier, 1981).

It is certainly possible that significant localized cerebral abnormalities are present in specific subgroups of patients, but the heterogeneity of the populations studied has obscured regional effects. A homogeneous subgroup of patients isolated from the schizophrenic spectrum might be more likely to manifest a core pattern of neuropsychological deficit. Unfortunately, there have been few systematic studies of neuropsychological differences between subgroups of chronic schizophrenic patients.

The course of neuropsychological deterioration in schizophrenia has received little attention, perhaps because even the existence of significant dysfunction was questioned for so long. Longitudinal studies have generally shown little or no deterioration of performance by groups of

schizophrenics on neuropsychological tests after the onset of the illness (Klonoff et al., 1970; Hamlin & Ward, 1973; Foulds & Dixon, 1962; Hamilton, 1963). It has been suggested, however, that significant deterioration may occur in subgroups of patients (Haywood & Moelis, 1963; Smith, 1964). Comparisons of pre- and post-morbid levels of cognitive or intellectual functioning are sparse. Some reports indicated that significant intellectual deficits were observed only after onset (Lubin, Geiseking, & Williams, 1962; Schwartzman & Douglas, 1962). Other investigations of high-risk samples (children of schizophrenics) have shown that "premorbid" deficits occur, but the majority of these studies have not progressed to enable comparisons of pre- and post-morbid intelligence (e.g., Rieder, Broman, & Rosenthal, 1977; Oltman, Weintraub, Stone, & Neale, 1978; Watt, Grubb, & Erlenmayer-Kimling, 1982). Retrospective analyses of school or army intelligence tests indicated that individuals who later developed schizophrenia had performed more poorly than their peers or siblings who remained well (Offord, 1974; Watt & Lubensky, 1976; Miner & Anderson, 1958; Lane & Albee, 1965).

Neuropsychological techniques have been developed in neurological settings that address the issue of deterioration from previously higher levels of functioning. If it is assumed that psychiatric disorders reflect (presently unknown) disturbances of the brain, then extending the use of these techniques to the study of

psychiatric populations would be valid insofar as such measures are not rendered unreliable by factors unrelated to neuropathology.

The most widely used bases for the formulation of indices of neuropsychological deterioration have been the Wechsler scales (Wechsler-Bellevue, Wechsler Adult Intelligence Scale or WAIS, and the revised edition of the latter, the WAIS-R). In calculating indices of deterioration, a primary distinction has been drawn between those tests which "hold", or remain relatively invariant, in the presence of brain damage, and those which "don't hold", or are particularly sensitive to the presence of brain damage (Wechsler, 1958; McFie, 1974). The observation that certain subtests of the WAIS do "hold" in the presence of brain damage has, in fact, prompted the use of these measures as indicators of premorbid level of intellectual functioning. For example, it was found in one series of investigations that those subtests best reflecting premorbid functioning in the presence of brain damage (as assessed by neurological exam) were Information, Vocabulary, Arithmetic, Picture Completion, and Object Assembly. Those found most sensitive to brain damage were Similarities, Digit Span, Digit Symbol, and Block Design (Norman, 1966; Bersoff, 1970). These choices of hold and no-hold subtests have been questioned by other investigators using different samples. A variety of "Deterioration Indices" and "Deterioration Quotients" have been derived, all based on the hold/no-hold

dichotomy (e.g., Wechsler, 1958; Hewson, 1949; McKeever & Gerstein, 1958; Wolff, 1960; L'Abate & Gale, 1969; Matthews, Shaw & Klove, 1966). These indices have generally been used, however, only to differentiate neurologically diagnosed groups from either asymptomatic control or mixed psychiatric samples with negative neurological findings. Use of deterioration indices to subtype within the schizophrenic syndrome has not yet been attempted.

Neuropsychological impairment has been found to occur in schizophrenia, especially in the more chronic forms. The possibility that regionally or functionally specific deficits may characterize a subgroup of patients has been suggested, but not adequately tested. Deterioration from previously higher levels of functioning has been shown to coincide with the onset of symptoms. Premorbid deficits have also been demonstrated. To concluded that greater deterioration and/or continuing deterioration may characterize a subgroup of patients requires further study.

Radiological Subtyping Approaches

Investigations in the 1950's and 1960's (Huber, 1957; Haug, 1962; Nago, 1963; Asano, 1967) using pneumoencephalography had indicated that some schizophrenic patients might have enlarged ventricles or atrophy of the cerebral cortex, but these studies were generally discounted on methodological grounds. It was argued that the

pneumoencephalographic technique could lead to enlargement of ventricular and sulcal spaces, and that the risks of the procedure prevented using normal controls. With the advent of the widespread availability of CT-scanning in the 1970's, noninvasive measurement of these structural features in psychiatric populations became possible, and simultaneously eliminated the source of some of these earlier criticisms.³

The first CT study of chronic schizophrenic patients was reported by Johnstone, Crow, Frith, Husband, and Kreef (1976). In their sample of older chronic schizophrenic inpatients (mean age = 54.9 years), significant enlargement of ventricular size (as measured by the ventricular-brain ratio or VBR; see Methods section for description) was found for the patients compared to controls⁴ matched for age and occupational attainment. Soon thereafter, a similar report was made by Weinberger, Torrey, Neophytides, and Wyatt (1979a), who studied a somewhat younger sample (mean age = 32.8 years). Review of the scans of these patients revealed that indices of cortical atrophy (CA) also were more frequent in the patients than controls (Weinberger, Torrey, Neophytides, & Wyatt, 1979b). The measures of CA

³Although CT-scanning is not "invasive," there is risk associated with exposure to radiation that still limits sample selection. In some studies, control subjects are selected from groups of non-psychiatric patients referred for CT-scans (e.g., car accident victims, headache sufferers). The choice of such control samples (at risk for CT-abnormalities) would tend to minimize spurious findings of CT-abnormalities in the index schizophrenic groups.

⁴In this study, controls were hospital staff volunteers.

were not correlated with ventricular enlargement (VE), suggesting that two independent pathological processes may exist. Golden, Moses, et al. (1980) also reported VE in a group of chronic schizophrenic patients, although this study did not include an independent control sample. Another study showed that younger subjects (aged 21-40) did not have VE (as measured by linear indices), while older subjects (aged 41-60) did have VE (Tanaka, Hazama, Kawahara, and Kobayashi, 1981).

These studies left in doubt whether CT-scan abnormalities might be found primarily in older patients, and perhaps associated with extended hospitalization or medication use. However, a recent study showed significant VE in 35 patients who had no previous episodes of illness or exposure to medication (Weinberger, Delisi, Perman, Targum, and Wyatt, 1983). Cortical atrophy (as measured by sulcal prominence) was also found, although less frequently than VE. Significant VE was also reported in a group of 46 psychotic patients, 19 of whom had no previous psychiatric history (Nyback et al., 1982). Schulz et al. (1983) also reported VE in a group of 15 schizophrenic adolescents, many of whom had received no somatic therapy. These reports clearly indicated that VE was not exclusively due to exposure to medication, institutionalization, or advanced age.

A number of other reports have appeared that generally confirm the findings of these studies (see Weinberger, et al., 1983 for an excellent review.) The frequency of abnormalities reported, however, does appear related to the CT-measure used, the population sampled, and the criteria for categorizing scans as abnormal. Three negative reports (in which no difference between schizophrenics and controls was indicated) serve to illustrate these effects.

Mundt et al. (cited in Weinberger et al., 1983) reported no differences between CT-scan findings in 68 chronic schizophrenics and a group of medically ill patients. No diagnostic criteria were specified in this report, and only linear measures of the third ventricle and frontal horn span were included. Benes et al. (1982) found no difference in either linear indices of VE or VBR between 40 patients and 23 symptomatic normal controls. In this study, however, the controls were all referred for CT-scans for clinical reasons, and only 10 of the 40 patients met diagnostic criteria for schizophrenia. Both groups were also young (mean age = 22 years). The third negative study (Jernigan et al., 1982) compared 30 male schizophrenics (meeting RDC and DSM-III criteria) to a sample of normal volunteers. Neither a volumetric index of VE nor VBR differed between patient and control groups. While this study was methodologically superior to the other two (i.e., specific diagnostic criteria were used, the control group was not symptomatic), the sample of patients was atypical.

First, the patients were selected from a relatively high-functioning population. Second, patients were excluded if they performed poorly on neuropsychological tests (Nasrallah, 1982). Thus, Jernigan et al. (1982) may have selected a schizophrenic sample that would be expected to show less evidence of CT-scan abnormality.

Differences in CT-scanners, methods used in obtaining the scans, and methods for reading scans have all been suggested to influence outcome, and the use of independent control groups at each center has been advocated (Jernigan et al., 1982; Zatz & Jernigan, 1983). Despite such differences in technique, control measures of VBR reported by different groups have been strikingly consistent (Weinberger et al., 1983; Zatz & Jernigan, 1983).⁵ Linear measures have been said to be less reliable than the areal (e.g., VBR) or volumetric indices of VE (Jernigan et al., 1982), but a similar frequency of findings has been reported using the linear indices when other factors (e.g., sample composition) are controlled (Nasrallah, 1982). Cortical atrophy has been less investigated, and assessment of inter-center differences is thus difficult. Within centers, however, measurements of CA are highly reliable, and different methods of assessing CA (e.g., subjective rating

⁵One conspicuous exception has been reported by Jernigan et al., 1982. Scans were sent to two different centers for blind measurement of VBR; one center reported VBR-values consistent with automated measures of VE, while the other center reported considerably higher values.

scales, linear and areal measurements of fissures and sulci) are strongly correlated (Rieder et al., 1979).

Sample selection seems to have the greatest influence on the frequency of CT abnormalities that are reported. In groups composed primarily of patients with more malignant or severe forms of schizophrenic illness, VE may be present in almost all patients. The initial report by Johnstone et al. (1976) involved older patients who had been ill for many years (age > 55; mean duration of hospitalization > 30 years). In this group, 94% of patients had VBR's exceeding the control range. Golden et al. (1980) found 60% of a chronic schizophrenic sample ($N = 42$) to have VE in comparison to published norms. This sample included 22 patients referred for CT-scans to rule out "organicity." Thus, although this sample was younger than that of Johnstone et al. (1976), it probably included more patients with a high probability of CT abnormality than would be expected in a random sample of chronic schizophrenics. In younger, higher functioning samples, abnormalities are less frequently observed (Weinberger et al., 1983; Nyback et al., 1982; Schulz et al., 1983) or may not be found at all (Jernigan et al., 1982; Benes et al., 1982).

Woods and Wolf (1983) recently suggested that the effects of age and especially duration of illness may be important determinants of VE. As these authors pointed out, the fact that previous studies have not detected significant correlations between VE and age or duration of illness does

not rule out such an association. No study has yet included patients with a sufficiently broad range of age and illness duration to allow adequate multivariate assessment of the relationship of these variables with VE.

In samples that may be more representative of the general schizophrenic population, the prevalence of VE appears to range between 20% and 50% (e.g., Weinberger et al., 1979a; Jeste et al., 1982). Cortical atrophy may be less prevalent in similar populations, with the normal range exceeded by 10% to 30% of patients (Weinberger et al., 1979b; Rieder, Mann, Weinberger, VanKammen, & Post, 1983). The frequency of either CA or VE in similar samples appears to be in the 50%-60% range (Weinberger et al., 1983; Donnelly et al., 1980).

Thus, CT scan abnormalities (VE, CA) have been demonstrated in many chronic schizophrenic patients, and these abnormalities are not necessarily related to age, duration of illness, or medication use. The frequency with which such findings are found, however, may depend on technique and seems to depend heavily on sampling considerations.

In discussing premorbid social functioning, the importance that identification of a bimodal distribution has for establishing the validity of a dichotomy for use in subtyping was mentioned. A bimodal distribution of VBR was reported by Andreasen, Olsen, et al. (1982). One mode of schizophrenic VBR's was near that of the normal control

values; the other occurred at the upper limit of the normal range. This finding lends support to the possibility that VBR is a meaningful classification method reflecting a pathological process common to a subgroup of schizophrenics. No such report has been made for indices of CA, but as was mentioned earlier, CA has been less studied and thus no conclusions about the presence or absence of a bimodal distribution of CA can be made.

A variety of other CT abnormalities have been reported, including atrophy of the cerebellar vermis (Weinberger, Kleinman, Luchins, Bigelow, & Wyatt, 1980), reversal of the normal asymmetry between the hemispheres (Luchins, Weinberger, & Wyatt, 1979, 1982; Luchins, Morihisa, Weinberger, & Wyatt, 1981), and decreased densities of certain parenchymal regions (Golden, Graber, Coffman, Berg, Newlin, & Bloch, 1981), as well as increased densities in others (Dewan, Pandurangi, Lee, Ramachandran, Levy, Boucher, Yozawitz, & Major, 1983). Most of these findings, however, have not been replicated, and are of uncertain prevalence and significance at this point (Jernigan, Zatz, Moses, & Cardelino, 1982; Luchins, 1982).

CT-scan abnormalities, including VE and CA, have also been reported in non-schizophrenic populations (e.g., Jacoby & Levy, 1980; Pearlson & Veroff, 1981; Rieder et al., 1983). It appears, therefore, that structural abnormalities are not unique to the schizophrenic syndrome, but may occur also in other psychiatric disorders.

Interdisciplinary Subtyping Approaches

This proliferation of reports that structural abnormalities may be found in the brains of psychiatric patients has invigorated the search for an "organic" etiology in at least a subgroup of chronic schizophrenics. Several centers quickly capitalized on the opportunity to use CT-scanning as a basis for biological subtyping in schizophrenia. In an influential paper, Crow (1980) proposed that there are two "Types" of schizophrenia. He proposed that the "Type I" patients, without CT scan abnormalities, were those manifesting more positive symptoms and less neuropsychological impairment. The defect in these patients is a potentially reversible biochemical one because they have a good response to neuroleptic medications and have a more favorable prognosis. According to this scheme, "Type II" patients, with irreversible brain damage seen on CT-scans, are those who show more negative symptoms and greater neuropsychological impairment - that is, the defect state. The Type II patients should show relatively poor responses to neuroleptic medications and have unfavorable prognoses. The possibility that premorbid asociality, which had already been related to poor prognosis, might also be related to the CT-scan findings and be part of the Type II syndrome, was independently proposed by Weinberger et al. (1980). Intensive research over the

past three years has been directed at determining the validity of these proposed subtypes.

Relationships between clinical and CT-scan findings

The evidence supporting the use of the positive/negative symptom and good/poor premorbid social functioning dichotomies in subtyping the schizophrenic syndrome has been discussed. In addition, the findings of neuropsychological dysfunction indicated that severe deficits are regularly found in at least a subgroup of schizophrenic patients. To the extent that both clinical psychiatric and neuropsychological approaches are valid indices of a Type I/Type II distinction such as that elaborated by Crow (1980) and Weinberger et al. (1982), we would expect an association to exist between these indices of clinical and neuropsychological impairment.

Indirect evidence supports such an association. Neuropsychological impairment has been found consistently most severe in patient groups described as "chronic", "process", or "nonparanoid" (Klonoff, Fibiger, & Hutton, 1970; Watson, Thomas, Anderson, & Felling, 1968; Lilliston, 1973). Each of these descriptors has been directly related to negative symptomatology and premorbid asociality.

Severity of neuropsychological impairment has also been associated with earlier hospital admission, longer hospital stays, and slower recovery (Depue & Dubicki, 1974; Depue, Dubicki, & McCarthy, 1975; Depue, Dubicki, & Fowles, 1974).

Each of these factors indicating malignant course of illness has been associated with poor premorbid social functioning.

There is little direct evidence supporting association of negative symptoms and neuropsychological deficit. This may reflect the fact that use of the positive/negative dichotomy per se is relatively recent. As was pointed out, neuropsychological impairment has regularly been found in "negative symptom" groups defined according to other dichotomies (e.g., process/reactive, paranoid/nonparanoid). Johnstone et al. (1976, 1980) reported trends for an association between severity of cognitive impairment, the presence of negative symptoms, and the absence of positive symptoms; but the associations were not statistically significant.

Scores on the Mini Mental State Exam (Folstein & McHugh, 1975) were lower in a negative symptom group than in either positive or mixed groups (Andreasen and Olsen, 1982). This study is unique in that specific criteria for categorizing patients into positive and negative symptom groups were used.

Schizophrenics with the syndrome of premorbid asociality (Klein & Rosen, 1973) performed worse than other schizophrenic groups on tests of intelligence, perceptual and motor functions, and auditory-visual integration (Belmont, Birch, Klein, et al., 1964; Quitkin & Klein, 1969; Quitkin, Rifkin, & Klein, 1976). These findings, together with evidence that patients with the syndrome of premorbid

asociality have poorer prognosis and drug response, led Quitkin, Rifkin, and Klein (1976) to suggest that schizophrenia with premorbid asociality may be a distinct subtype with "organic" etiology.

Jeste et al. (1982) did not report neuropsychological test performance to discriminate between patients in good and poor premorbid groups. It is not possible to determine from the evidence they present, however, whether this relationship was directly tested. Other recent investigations of premorbid adjustment (e.g., Cannon-Spoor et al., 1982; Weinberger, Cannon-Spoor, et al., 1980) have not assessed relationships to neuropsychological test performance. The amount of evidence from earlier studies that supports the association of poor premorbid social adjustment to neuropsychological impairment is sufficient, however, to suggest that a relationship is probably present.

Many investigators have suggested that schizophrenia is characterized by dominant hemisphere dysfunction (see, e.g., Flor-Henry, 1983; Gur; 1978; Gruzelier, 1980; Taylor & Abrams, 1981). As was suggested earlier, regional neuropsychological deficits may be more prominent in a subgroup of schizophrenics defined according to clinical measures. Unfortunately, there have not been many studies comparing the performance of subgroups of schizophrenic patients on tasks that would specify the nature of regional dysfunction.

Some studies suggest that left hemisphere dysfunction is more prominent in certain subgroups of schizophrenic patients. Findings of left-ear advantage in dichotic listening tasks (indicating left hemisphere dysfunction or relative right hemisphere superiority) have been found greater in paranoid than nonparanoid patients (Nachson, 1980; Gruzelier, 1976, 1980, 1981). Electroencephalographic (EEG) evidence of left hemisphere disturbance has been found in patients described as "acute" (Rochford et al., 1976) or paranoid (Goldstein, Temple, & Pollack, 1976). Serafetinides (1972, 1973) reported an association of chlorpromazine response (which has been related to primarily positive symptom profile) and left hemisphere voltage increases (normalization) in the EEG. Gordon, Goldstein, & Sobol (1982) found that schizophrenic patients with evidence of "OBS or alcohol abuse" had less asymmetrical left/right dysfunction on a battery of neuropsychological tests than patients without such a history.

In each of these studies, the more "positive" group has shown greater left hemisphere abnormality, or greater hemisphere asymmetry. These studies, however, have not involved direct measures of positive and negative symptoms, but instead have considered differences between paranoid and nonparanoid, acute and chronic, neuroleptic responsive and nonresponsive, or "organic" and "nonorganic" subgroups. Thus, interpretation is limited by the lack of demonstrated

isomorphism between each of these classifications and the positive/negative distinction.

It has, on the other hand, been suggested that nonparanoid (negative?) patients may show relatively greater disturbance of the dominant hemisphere (e.g., Magaro [1983]). Studies that show greater left hemisphere impairment in a more deteriorated group of patients, however, generally fail to account for overall performance differences between the groups. It is therefore difficult to conclude that any hemisphere-specific findings are greater in negative symptom groups.

A similar problem confounds analysis of deficits in poor premorbid adjustment groups, in that performance is generally inferior to that of good premorbid groups. Until more research has been conducted that accounts for overall performance differences between groups, the hemisphere-specific findings in subgroups of schizophrenics must be interpreted cautiously.

Relationships between Clinical and CT-findings

According to the Type I/Type II distinction (Crow, 1980), CT-scan abnormalities should be associated with a negative symptom profile. An association between negative symptoms and ventricular enlargement has been reported by one group (Andreasen, Olsen, Dennert & Smith, 1982). In their comparison of two groups (with the sixteen smallest

and sixteen largest VBR's selected from a sample of 52 schizophrenics⁶), all negative symptom indices (SANS means) were higher in the large ventricle group, and most positive symptom means were higher in the small ventricle group, although the groups differed significantly on only one symptom, Bizarre Behavior, which was higher in the small ventricle group. When the three most discriminating positive symptoms (Delusions, Hallucinations, and Bizarre Behavior) were combined into a summary index, this index was significantly greater in the small ventricle group. A similar index of negative symptoms derived from the sum of scores on Alogia, Avolition, and Anhedonia did not differ significantly between the small and large ventricle groups. A "Summary" score, the difference between positive and negative symptom indices, also differed significantly between the groups, but did so no more strongly than the positive symptom index alone.

Johnstone et al. (1978) reported an association between negative symptoms and intellectual impairment (which was associated with ventricular enlargement), but the association of negative symptoms and VE itself was nonsignificant. Jeste et al. (1982) reported a significant positive correlation between VE and non-response to

⁶The mean VBR of the "small" ventricle group, calculated from data presented in a companion paper (Andreasen, Olsen, et al., 1982) was 1.94, a value exceeded by 37 of 47 controls.

neuroleptics (indirectly supporting the association of Type II profile and VE). A similar report was made by Smith, Largen, Calderon et al. (1983). When comparing paranoid and nonparanoid groups, however, they found no differences in either CT-scan or neuropsychological status.

The data presented are consistent in suggesting that CT-scan abnormalities and negative symptoms may be related, but the association has not been demonstrated to be particularly robust. The data in support of an association between premorbid adjustment and CT-scan status are still less convincing.

Chronic schizophrenics with CT-scan abnormalities evidenced poorer premorbid functioning than those without abnormalities (Weinberger, Cannon-Spoor, et al., 1980), but this finding has not been replicated. A later report by Jeste et al. (1982; which may have included some of the same patients used in the Weinberger et al. [1980] study), found an overrepresentation of abnormal VBR's in their poor-premorbid group, although the difference in VBR between poor- and good-premorbid groups was not significant.

Andreasen, Olsen, Dennert, and Smith (1982) found no difference in premorbid social functioning (assessed by the Phillips Scale) between their large and small ventricle schizophrenic groups. In contrast to the predicted relationship between course of illness (i.e., early onset) and VE, the authors found their large ventricle group to have significantly later onset of illness.

In the face of these limited and somewhat contradictory data, the proposed relationship of poor premorbid social functioning and CT-scan abnormalities must be viewed as tentative.

Relationship of Neuropsychological and CT-scan Findings

Three different groups of investigators have documented an association between abnormal CT-scans and neuropsychological impairment. The first of these studies (Johnstone et al., 1976) revealed a significant inverse relationship between ventricular size and overall performance on a brief neuropsychological battery (Withers-Hinton Tests of the Sensorium; $r = -.70$; $p < .01$) in a group of 18 elderly (mean age = 54.9) chronic schizophrenic patients. The authors stated that the CT-abnormal patients were particularly worse on those items of the battery that tap memory and attentional functioning, but provide no supporting statistical evidence. A reanalysis of the scans from the same sample to examine measures of CA (sulcal size) revealed no significant differences in neuropsychological performance between groups with and without CA (Johnstone et al., 1978).

Rieder, Donnelly, Herdt, and Waldman (1979) selected from a sample of 17 younger (ages 20-35) chronic schizophrenic and schizoaffective patients, four patients with, and four age-matched patients without, evidence of CA (sulcal prominence). All patients were relatively "high-

functioning" (all participated in a "day socialization program", and mean WAIS Full Scale IQ's were near 100 for each group). All patients were administered the Halstead-Reitan Battery and the WAIS. The CA-positive group performed worse than the CA-negative group on only one individual HRB subtest (Trail Making Test, Part B); but the Average Impairment Rating and the percentage of ratings in the impaired range was also significantly higher in the CA-positive group. The groups did not differ significantly in performance on any WAIS subtest, but the CA-positive group had significantly lower Performance IQ.

Donnelly, Weinberger, Waldman, & Wyatt (1980), studied 35 chronic schizophrenic inpatients. The WAIS and HRB were administered to 15 patients who had CT-scans (excluded were 4 patients over age 50; 1 patient with a history of alcohol abuse, 5 patients who failed to satisfy RDC for chronic schizophrenia, and notably, 10 who were uncooperative to testing). Considering both VE (VBR) and sulcal prominence (of the Sylvian or longitudinal fissures, or superior surface), they compared those patients manifesting at least one abnormality ($n = 8$) with those manifesting no abnormalities ($n = 7$). The CT-abnormal group performed significantly worse on 10 of 13 HRB subtests, and 8 of 11 WAIS subtests. There was no analysis of differences in neuropsychological performance associated with different CT-scan findings. The authors were able, however, to

correctly classify 80% of their sample into CT-positive and CT-negative groups using a preset cutoff score (HRB average impairment index = 1.55). A significant association between IQ and CT-scan status was also reported, with CT-positive patients showing lower IQ's.

Jeste et al. (1982) also reported a significant positive correlation ($r = .40$) between VE and the HRB Average Impairment Index. Golden et al. (1980), using the Luria-Nebraska Neuropsychological Battery (LNNB) reported significant correlations between 8 of the 14 LNNB scales and ventricular size (range of r 's = .33 -- .58). The eight LNNB variables significantly correlated with VBR were entered into a multiple regression formula, and a multiple correlation of 0.72 between VBR and LNNB scores was calculated. The senior author devised a set of "rules" which enabled 90% correct classification of subjects into VE-positive and VE-negative groups. Of course, the opportunities to take advantage of chance in performing multiple regression with eight variables and only 42 subjects are great, and the "rules" for identifying VBR positive patients were post hoc derivations. Nevertheless, similarly high classification values were obtained in a cross validation study (Golden, MacInnes, et al., 1982).

These studies consistently found greater neuropsychological impairment in those patients manifesting CT-abnormalities; however, certain questions which are critical to an understanding of the significance of the

CT-scan findings are unanswered. Only the Donnelly et al. (1980) and the Johnstone et al., (1978) studies reported on both CA and VE measures, and only in the Johnstone et al. (1980) study is it possible to infer that the neuropsychological abnormalities are more strongly associated with one type of CT-finding (VE) than the other (CA). Further, these studies do not address the possibility that regional neuropsychological abnormalities may be associated with either the presence or absence of the structural deficits reported. These studies also failed to assess the possibility that the groups may differ in premorbid cognitive or intellectual functioning, or that one group may show greater deterioration from a previous level than the other.

The evidence reviewed points to an association of CT-scan abnormalities, neuropsychological impairment, and some of the historical/symptomatic variables generally thought to represent the Type II profile. A relationship is reasonably well established, however, only with respect to CT-scan and neuropsychological indices of impairment. The Jeste et al. (1982) study included most of the measures that have been considered important in subtyping efforts (VE, CA, neuropsychological test results, and indices of premorbid adjustment). The distinction between positive and negative symptoms was not specifically addressed, however, and neither CA nor neuropsychological impairment were used to classify patients. Furthermore, in this study, the

relationships were not as strong as had been reported in some earlier studies. In addition, the sample used in this study overlaps (to an unknown degree) with several other studies (i.e., Weinberger, Bigelow, et al., 1980, Weinberger, Kleinman, et al., 1980, Weinberger et al. 1982; Cannon-Spoor et al., 1980), and therefore, these findings cannot be interpreted as replication of previous work. Andreasen et al. (1982) also reported a variety of the relevant measures, but measures of CA were absent, and their findings with respect to premorbid functioning contradict the most popular hypotheses.

Statement of the Problem

A multidimensional approach to the subtyping of the schizophrenic syndrome that incorporates measurement of clinical, cognitive, and structural brain abnormalities has been advocated. The existence of a subtype of chronic schizophrenia characterized by negative symptoms, poor premorbid social adjustment, impairment of neuropsychological functioning, and atrophy of the brain has been hypothesized. Unfortunately, there have been few direct investigations of the relationships between these abnormalities.

The association between negative symptoms and poor premorbid social adjustment is supported indirectly by the

relationships of each to unfavorable prognosis and poor response to treatment. Both negative symptom profile and premorbid asociality have been related to neuropsychological impairment. The relationship of negative symptoms to CT-scan findings is sparsely documented, while the association of premorbid asociality and CT-scan findings is unclear in the face of conflicting results.

Neuropsychological impairment has been consistently associated with CT-scan abnormalities, but the different associations of VE and CA to cognitive deficit are unknown. Although some investigators have theorized that schizophrenia is characterized by a regionally specific pattern of neuropsychological dysfunction, few attempts have been made to determine whether such a pattern may exist in a subset of patients defined according to clinical or radiological measures. Techniques have been developed for the retrospective estimation of premorbid intelligence and deterioration from that level, but such estimates have not been related to symptoms, premorbid social functioning, or CT-scan findings, despite hypothetical relationships of these variables to the course of the illness.

The aim of the present study was to investigate the pattern of relationships among the clinical, neuropsychological, and structural indices of deterioration that have been proposed to mark a subtype of chronic schizophrenic patients. An additional goal was to explore the potential relationships between regionally or

functionally specified neuropsychological deficit and the other subtyping measures; and to determine whether estimates of premorbid intellectual functioning and deterioration might be related to premorbid social functioning, present symptoms, or CT-scan status.

Based on the literature reviewed and speculating along the lines of Crow (1980) and Weinberger, Cannon-Spoor, et al. (1980), the following hypotheses were advanced:

¶ Negative symptomatology, indicated by assignment to the "negative" group according to the criteria of Andreasen and Olsen (1982), or assessed on the continuous subscales of the SANS, will be associated with: (a) poorer premorbid social adjustment; (b) greater neuropsychological dysfunction; and (c) more CT-scan abnormalities.

¶ Poor premorbid social functioning will be associated with (a) earlier age at onset; (b) lower levels of educational attainment; (c) more negative and less positive symptomatology; (d) greater neuropsychological dysfunction and lower premorbid ability; and (e) greater ventricular enlargement.

¶ Patients will manifest impairments on standard intelligence tests and a disproportionate number will perform below "cutoff" levels on tests used to identify brain damage.

¶ Estimated premorbid intellectual functioning will be positively correlated to age of onset and educational

attainment.

¶ Estimated deterioration from previous levels of functioning will be positively correlated to age, duration of illness, age at onset, and educational attainment.

¶ Neuropsychological dysfunction will be positively correlated to (a) negative symptoms, (b) poor premorbid social adjustment, and (c) the presence of abnormalities on CT-scans.

Exploratory analyses within and between sets of clinical, neuropsychological, and structural dimensions were also planned to:

1. assess the consistency of measures within dimensions;
2. assess possible relationships of symptoms, clinical history, and CT-scan findings to patterns of functional neuropsychological impairment and deterioration from estimated levels of premorbid intelligence, and
3. to determine whether different indices of structural brain atrophy, such as VE and CA, might be differentiable by clinical or neuropsychological measures.

Methods

Subjects

Psychiatric inpatients at Creedmoor Psychiatric Center (CPC) between the ages of 20 and 48 satisfying Research Diagnostic Criteria (RDC; Spitzer & Endicott, 1977) for Chronic Schizophrenia ($n = 30$) or Schizoaffective Disorder ($n = 2$) served as subjects. Both Schizoaffective patients were diagnosed as Mainly Schizophrenic.⁷ Exclusion criteria were: known neurological disease, mental retardation, and/or history of alcoholism or substance abuse. Patients who had major exposure to radiation (over 6 rads) in the preceding year, had received electroconvulsive therapy during the preceding six months, or had positive tests for pregnancy were excluded.

Prior to the initiation of the study it was decided that the results would be based on the the first 32 admissions to the protocol. Among 38 patients tentatively admitted to the protocol on the basis of chart review and

⁷These patients were included to increase the range of symptomatology that might be observed while still restricting the sample to chronic patients. In terms of the hypotheses advanced in this study, no differential predictions were made for this group.

brief interview, six patients were excluded. For each of these cases, it was found during extended evaluation and history review, that RDC for Chronic Schizophrenia or Schizoaffective disorder could not be fulfilled at the "definite" or "probable" level. In two cases, substance abuse could not be ruled out as being significant etiologically (amphetamine, 1; phencyclidine, 1). One patient had temporal lobe epilepsy. Another patient met RDC for Affective Disorder, and two others met RDC for "Unspecified Functional Psychosis". The total sample size was thus 32. Among these patients, not all information could be obtained for every patient due to lack of cooperation (e.g., refusal of neuropsychological testing). Data were also rejected in certain cases where the examiner/rater could not assign definite values (e.g., insufficient historical data for premorbid ratings; ambiguities in CT-scan landmarks).

Basic demographic and diagnostic characteristics of the sample are presented in Table 2. Data for individual patients are included in Appendix 1. The sexes were equally represented. Among the non-white patients, eight were black, one was of Hispanic and the other of Oriental descent. Education level is specified in Table 2 using Hollingshead and Redlichs' (1958) criteria. The modal education of patients was 12 years (i.e., completion of high school). Most patients were from middle class families

Table 2
Sample Characteristics

Sex:	Male = 16	Female = 16
Race:	White = 22	Nonwhite = 10
RDC Diagnosis:	Chronic Schizophrenia = 30	Chronic Schizoaffective = 2

	mean $\pm$ s.d.	range
Age (years)	32.5 $\pm$ 7.6	20 - 48
Education level ^a	4.0 $\pm$ 1.3	1 - 7
Age at onset ^b	19.8 $\pm$ 4.1	14 - 29
Illness duration ^b	12.5 $\pm$ 7.4	2 - 26

^aDetermined according to the criteria of Hollingshead and Redlich (1958). The scale runs from 0 (no formal education) to 7 (completed graduate or professional school).

^bCalculated from time (in years) at which symptoms were first present.

(Hollingshead-Redlich level 3 or 4) and had been raised in the New York metropolitan area. Every patient had a previous history of psychiatric hospitalization, most had been hospitalized at CPC for at least the preceding year (range of present hospitalization 6 months to 26 years).

The frequency of RDC diagnostic subtypes for the index episode (episode leading to current hospitalization) was: paranoid (13); disorganized [hebephrenic] (6); catatonic (2); undifferentiated (8); mixed (1); and schizoaffective -- mainly schizophrenic (2). The diagnostic subtype of each patient is shown in Appendix 1.

All patients were prescribed regimens of neuroleptic medications by staff psychiatrists at CPC during the course of clinical and neuropsychological evaluations. One patient received imipramine (25 mg/day) in addition to haloperidol.

Four received Cogentin, and one Benadryl, in addition to neuroleptics. The chlorpromazine equivalent dosage received by each patient at the time of evaluation is included in Appendix 1.)

Procedures

Screening and Selection

Prospective subjects were identified by staff psychiatrists at CPC or research fellows from the Department of Psychiatry, Columbia University College of Physicians & Surgeons and New York State Psychiatric Institute (NYSPI). A research fellow (Anand K. Pandurangi, M.D.; AKP) explained the nature of the procedures involved in the research protocol⁸ to the patients and obtained informed consent. Copies of the consent forms are included in Appendix 2. Satisfaction of inclusion and exclusion criteria was determined on the basis of interview (Schedule for Affective Disorders and Schizophrenia [SADS; Endicott, Spitzer, & Robins, 1978]) and chart review, EEG, neurological examination, and pregnancy testing of females. Interview, history taking, and chart review were performed by AKP.

⁸The conduct of this research was reviewed and approved by the Institutional Review Boards at NYSPI and CPC.

Outline of Assessment Procedures

After admission to the protocol and transfer to the Intensive Psychiatric Care Unit (IPCU), each patient spent the first week in a period of acclimatization to the unit. After this period of acclimatization, the patient first underwent clinical psychiatric evaluations, followed by neuropsychological and CT examinations. Clinical, neuropsychological, and CT exams were usually performed within two weeks of each other. After completion of all examinations, the patient was given the opportunity to participate in an "informing" session in which his primary therapist and the treating physician were included. The nature of the results were discussed with the clinical staff members in advance of such sessions.

Clinical Assessments

After admission and acclimatization to the IPCU, clinical examinations were conducted by AKP. The clinical evaluations were the source of demographic and diagnostic data, the basis for measures of positive and negative symptoms, and documentation of the course of illness and premorbid social functioning. In addition to routine clinical interview, history taking, and chart review, the clinical evaluation included ratings on several published interview schedules and scales. These included: the Schedule for Affective Disorders and Schizophrenia (SADS), the extension of the SADS specifically geared to assessment

of psychosis and disorganization (SADS-PD), the Brief Psychiatric Rating Scale (BPRS), the Scale for the Assessment of Negative Symptoms (SANS), the Premorbid Adjustment Scale (PAS), and the Global Assessment Scale (GAS). Each of these is discussed below in relationship to the the assessment of positive and negative symptoms and premorbid social adjustment.

Assessment of positive and negative symptoms. Interest in the positive symptoms of schizophrenia is clearly reflected by the content of most instruments developed to measure schizophrenic symptomatology. While the Schedule for Affective Disorders and Schizophrenia (SADS, Endicott & Spitzer, 1978) was not developed primarily for use with schizophrenic samples, the recent extension of the SADS (Psychosis-Disorganization Scale or SADS-PD; Endicott, 1983) incorporates in greater detail the content areas reflective of positive schizophrenic symptoms that were absent from the original instrument. These two instruments (SADS, SADS-PD) together provide an account of delusions, hallucinations, formal thought disorder, and bizarre behavior that are the hallmarks of positive schizophrenia as defined by Crow (1980) and Andreasen and Olsen (1982).

Although these instruments provide adequate measurement of positive symptoms, none was specifically designed to address the positive/negative dichotomy. While most instruments currently used to measure psychiatric symptomatology place greatest emphasis on the positive or

productive symptoms, no index of positive symptoms has received strong support. The classification system developed by Andreasen et al. (1982) is the only one which has been defined in a study of positive/negative symptoms. This classification system was used in the data analyses to be presented, but additional continuous indices of positive symptomatology were also derived. Items from the SADS and SADS-PD that were used to derive these indices are presented in Table 3.

Table 3
Variables Comprising the Scale for Positive Symptoms (SPOS)

Variable	Source/Description
Delusions	SADS Item 26/Severity of Delusions
Hallucinations	SADS Item 27/Severity of Hallucinations
Bizarre Behavior	SADS Item 36/Bizarre Behavior
Positive Formal Thought Disorder	(Sum of items measuring "positive formal thought disorder")
	SADS Item 33/Impaired Understandability Due Disorder to Thought Disorder
	SADS-PD Item 1/Loosening of Associations
	SADS-PD Item 3/Illogical Thinking
SPOS	Sum of standardized (mean=0, sd=1) scores on Delusions, Hallucinations, Bizarre Behavior, and Positive Formal Thought Disorder

Three of the four "cardinal" features of positive schizophrenia are represented by individual items -- Delusions, Hallucinations, and Bizarre Behavior. The fourth feature -- Positive Formal Thought Disorder (PFTD) -- was formed by summing raw scores on three items (Impaired Understandability due to Thought Disorder, Loosening of

Associations, and Illogical Thinking).

These four variables (Delusions, Hallucinations, Bizarre Behavior, and Positive Formal Thought Disorder) were standardized to mean = 0 and sd = 1, then summed to form a scale of positive symptomatology (the Positive Symptom Summary Scale). Each of the variables listed in Table 3 is rated on a scale (from 0 -- 7) from least severe (or not present) to most severe.

Ratings on items from the SADS-PD, which are rated on a scale (0 -- 3) from absent to definitely present, were summed to form an index of the "breadth" of psychosis (BROADPSY; see Table 4). This index is a direct function of the number of symptoms and not their severity.

Table 4
Items Included in the "Breadth of Psychosis Scale"
(BROADPSY)

SADS-PD Items

- | | |
|----|---|
| 6 | Delusions of reference |
| 7 | Delusions of being controlled or influenced |
| 8 | Delusions of mind being read |
| 9 | Thought broadcasting |
| 10 | Thought insertion |
| 11 | Thought withdrawal |
| 12 | Persecutory delusions |
| 13 | Delusions of jealousy |
| 14 | Delusions of guilt or sin |
| 15 | Grandiose delusions |
| 16 | Somatic delusions |
| 17 | Auditory hallucinations |
| 18 | Visual hallucinations |
| 19 | Somatic or tactile hallucinations |
| 20 | Olfactory hallucinations |
-

Note. BROADPSY is the sum of raw scores (0 -- 3) on each of the above items.

The measurement of negative symptoms was recently investigated by Nancy Andreasen and her colleagues (Andreasen, 1982; Andreasen & Olsen, 1982), who have developed the Scale for the Assessment of Negative Symptoms (SANS). The SANS contains 30 items, 25 of which are ratings of individual symptoms, the other five items are "global" ratings in each of the five symptom complexes (Alogia, Affective Flattening, Avolition/Apathy, Anhedonia/Asociality, and Attentional Impairment). An initial validation study of the scale demonstrated high interrater reliability (intraclass correlation for items, range = .860 - .925; for subscales = .860 - .925; for composite score = .920); and high internal consistency (Cronbach's coefficient alpha; range for subscales = .632 - .844; composite score = .885). The subscales, and the variables included in each subscale of the SANS are listed in Table 5.

Each item is rated on a scale (0 -- 5) from not present to severe. Item scores were summed within each subscale to derive subscale scores. The total of all raw subscale scores is a "composite" index of the breadth and severity of negative symptomatology. The sum of global ratings for each subscale (the SANS Global Total Score) was used as an index of the overall severity of dysfunction of negative symptoms (i.e., global ratings on a subscale may be high even when scores are high on only one or two items within that subscale). This use is in some ways similar to the division

Table 5
Scale for the Assessment of Negative Symptoms (SANS)

SANS Measure	Items included in measure
Affective Flattening (8 items)	1. unchanging facial expression 2. decreased spontaneous movements 3. paucity of expressive gestures 4. poor eye contact 5. affective nonresponsivity 6. inappropriate affect 7. lack of vocal inflections 8. subjective complaints of emotional emptiness or loss of feeling
Alogia (5 items)	1. poverty of speech 2. poverty of content of speech 3. blocking 4. increased latency of response 5. subjective rating of alogia
Avolition/Apathy (4 items)	1. grooming and hygiene 2. impersistence at work or school 3. physical anergia 4. subjective complaints of avolition and apathy
Anhedonia (5 items)	1. recreational interests and activities 2. sexual interest and activity 3. ability to feel intimacy and closeness 4. relationships with friends and peers 5. subjective awareness of anhedonia-associability
Attentional Dysfunction (3 items)	1. social inattentiveness 2. inattentiveness during mental status testing 3. subjective complaints of inattentiveness
SANS Global Total Score: Sum of Global Ratings (1 rating on each of the 5 subscales)	
Negative Symptom Summary Scale: Sum of Raw Scores on each of the SANS subscales	

of positive symptoms into a severity index (the Positive Symptom Summary Scale) vs breadth of psychosis index (BROADPSY).

Assessment of premorbid social functioning. Although the validity of assessing premorbid functioning (as a predictor of outcome) had been corroborated by several different groups using different instruments (Phillips, 1953; Wittman, 1941; Gittelman-Klein & Klein, 1969; Goldstein, 1977), a workshop at the Center for Studies of Schizophrenia (Keith & Buchsbaum, 1978) that was convened specifically to address certain deficiencies in the existing assessment techniques, resulted in the development of a new scale that:

"(1) was useful for research purposes, (2) conceptualized successful premorbid adjustment in terms of the attainment of certain developmental goals that were viewed as necessary milestones for healthy functioning, and (3) considered attainment of these goals as specific age-related tasks." (Cannon-Spoor, Potkin, & Wyatt, 1982, p. 471).

The resulting Premorbid Adjustment Scale (PAS) assesses four content areas at each of four life periods (where appropriate). The content areas include: social accessibility-isolation, peer relationships, ability to function outside the nuclear family, and capacity to form intimate socio-sexual ties. The four life periods are: childhood (up to 11 years), early adolescence (12-15 years),

late adolescence (16-18 years), and adulthood (19 years and older). In addition to the four content scales, a "General" scale is included to estimate the highest level of premorbid functioning, the time span and characteristics of onset, and other general information (e.g., education, occupational functioning). Higher PAS scores indicate poorer premorbid adjustment.

Inter-rater reliability of this scale was found to be high for experienced raters (intraclass correlation = .85, $p < .0001$). Validation of the scale has been demonstrated by discrimination between groups of schizophrenic patients and normal controls, and significant positive correlations have been shown to exist between higher PAS scores and a variety of variables including insidious onset, length of hospitalization, and CT-scan abnormalities (Weinberger, Cannon-Spoor, Potkin, & Wyatt, 1980). Comparisons to the widely used Phillips Scale revealed that the PAS scores were more strongly related to length of hospitalization, early onset of illness, and type of illness (with nonparanoid illness associated with higher PAS scores). Thus the PAS has appeared to be a valid and reliable index of premorbid social adjustment that bears out the most critical hypotheses regarding the relationship of such functioning to outcome and type of illness.

The variables included in each section of the PAS are listed in Table 6. Scores for each item are (with a few

Table 6
Premorbid Adjustment Scale (PAS)

Period: Items Assessed

Childhood

1. Sociability
2. Peer relationships
3. Scholastic performance
4. Adaptation to school

Early Adolescence (age 12-15)

1. to 4. as above
5. Social-sexual aspects of life

Late Adolescence (age 16-18)

1. to 5. as above

Adulthood (age 19 and above)

1. Sociability & Withdrawal
2. Peer relationships
3. Aspects of adult social-sexual life
 - a. married, presently or formerly;
 - b. never married, over 30;
 - c. never married, age 20-29.

General

1. Education
 2. Employment (6 mos. - 3 yrs. pre-hosp. admission)
 3. Employment (change, 6 mos. - 1 yr. pre-hosp. adm.)
 4. Employment (changes, 6 mos. - 3 yrs. pre-hosp. adm.)
 5. Establishment of Independence
-

exceptions) on a scale (0 -- 6) from good functioning to severely poor functioning. The total score on the PAS, which is based only on those time periods preceding onset of symptoms and adjusted proportionally to the number of items assessed, was used as an index of poor premorbid social adjustment.

Two other clinical assessment instruments were included

in an effort to characterize "global" levels of present functioning and psychopathology. The Global Assessment Scale (GAS) is simply a Likert scale with 0 representing gross impairment in virtually all areas of functioning and 100 representing an exceptionally high level of functioning in all social and occupational pursuits. This scale was included in order to characterize patients without specific reference to symptoms or history.

The Brief Psychiatric Rating Scale (BPRS), widely used in psychiatric research and employed in several previous studies involving CT-scanning or neuropsychological assessment (e.g., Nasrallah, et al., 1982; Golden et al., 1983), was also administered. This scale was included simply as a "global" measure of psychopathology.

The number of patients rated, and descriptive statistics for each of the clinical measures are provided in Table 7. Ratings for one patient were excluded for all measures, and ratings for one other patient were excluded for the SANS, due to the impression of the rater that these were unreliable.

Given inequalities of mean scores and variances between measures, all were standardized (mean = 0; sd = 1) before entry into subsequent analyses.

Table 7
Univariate Statistics for Clinical Measures

Measure	n	mean $\pm$ sd	min	max
SPOS ^a	30	0.0 $\pm$ 0.8	-1.6	1.4
Delusions	31	3.6 $\pm$ 1.3	1	6
Hallucinations	31	3.2 $\pm$ 1.5	1	5
Bizarre Behavior	30	2.9 $\pm$ 1.2	1	5
PFTD	31	7.3 $\pm$ 3.8	3	16
BROADPSY	31	20.2 $\pm$ 6.8	2	32
SANSUM	30	42.2 $\pm$ 20.2	13	80
Affective Flat'g	30	12.4 $\pm$ 7.6	0	28
Alogia	30	4.8 $\pm$ 5.1	0	19
Avolition/Apathy	30	8.6 $\pm$ 3.5	4	16
Anhedonia	30	11.4 $\pm$ 5.3	3	20
Atten. Impairm't	30	4.2 $\pm$ 3.4	0	14
SANSQT	30	7.7 $\pm$ 4.2	2	18
PAST	30	50.5 $\pm$ 14.4	28	78

Note. SPOS, Positive Symptom Summary Scale; PFTD, Positive Formal Thought Disorder; BROADPSY, Breadth of Psychosis Scale; SANSUM, Negative Symptom Summary Scale; SANSQT, SANS Global Total Score; PAST, Premorbid Adjustment Scale Total Score. See text for descriptions.

^aSPOS is sum of standardized (to mean = 0, sd = 1) scores on positive symptom variables.

^bPFTD is sum of three items -- Impaired Understandability, Loosening of Associations, and Illogical Thinking (raw scores).

Neuropsychological Assessments

Neuropsychological testing was performed either by me or by one of four graduate students trained by me. All examiners were blind to the results of clinical and CT-scan evaluations. The entire set of neuropsychological test instruments selected for use in this study (see following section) was divided into two "components." The "standard" component (including such tests as the WAIS-R, Raven Standard Progressive Matrices, Purdue Pegboard, Mini-Mental

State Exam) was generally administered in one session. An "extended" component included thirty tests considered more relevant to the functioning of more specific neuropsychological systems. The 30 tests were divided (on the basis of function tested and difficulty) into 6 groups with 5 tests per group, and four counterbalanced administration orders were constructed to maximize the temporal separation of tests with similar task demands and difficulty. The four counterbalanced orders were assigned to patients sequentially on the basis of the subjects' admission to the study protocol. The extended component was usually administered in one or two sessions (total time 3-4 hours) but in some cases more sessions were required. Breaks were allowed at the patients' request whenever necessary to obtain cooperation, but never in mid-test.

Selection of instruments. Certain critical problems emerged in the selection of neuropsychological test instruments for this study. Existing "batteries" of tests, for which extensive normative data are available, or that had been used in previous CT-studies, all contain deficiencies in their measurement of brain-behavior relationships. Of interest was not only global neuropsychological deficit, but also determination of patterns of functional deficit, regional brain dysfunction, and neuropsychological indices of deterioration that might relate to the clinical and structural indices of

deterioration. The two most popular neuropsychological batteries (the Halstead-Reitan Battery or HRB, and the Luria-Nebraska Neuropsychological Battery or LNNB) are inadequate in their ability to isolate patterns of regional brain dysfunction.

The HRB, validated on neurological populations, has the demonstrated capacity to differentiate patients with brain damage from normals and certain psychiatric groups (Reitan & Davison, 1974; Heaton, Baade & Johnson, 1978). In addition, the HRB has proved to be a valid discriminator of severe lateralized dysfunction, and to provide some information as to process (i.e., acute vs chronic or long-term illness [Russell, Neuringer, & Goldstein, 1970]). Nevertheless, the HRB was not designed specifically to assess the integrity of different functional systems of the brain. In fact, the most discriminating of the instruments included in the HRB (e.g., Category Test, Tactual Performance Test, Trail Making Test), each depend on many different neuropsychological functions. The HRB also fails to include adequate measures of memory and language functions.

The LNNB, on the other hand, while including many different neuropsychological tasks, does not assess any single function in detail. It has been stated by one reviewer (Spiers, 1981,1982) that the LNNB assesses no neuropsychological function. Another battery of tests (Hinton-Withers Tests of the Sensorium [Hinton & Withers,

1971; Withers & Hinton, 1971]), which has been used in an interdisciplinary study (Johnstone et al., 1976), is convenient to administer due to its brevity, but measures no neuropsychological function in sufficient detail to allow either functional or regional specification.

Some batteries of neuropsychological tests have been developed to assess specific neurologically defined populations (e.g., the Boston Diagnostic Aphasia Examination [Goodglass & Kaplan, 1972], the Neuropsychological Battery for Epilepsy [Dodrill, 1978]), or certain limited functions (e.g., Boston Remote Memory Battery [Albert, Butters, & Levin, 1979]). None of these was appropriate for this study.

To avoid the shortcomings of any of the aforementioned batteries, it was decided to determine in advance of the study a list of functions and functional brain regions, and then to select instruments from existing batteries and the experimental literature to fit this list.

The List of Neuropsychological Instruments that follows is divided into "functional" categories. The assignment of a particular test to a particular function is sometimes arbitrary, as certain tests involve multiple functions, and the functions themselves overlap. The tests were selected by:

1. considering overall brain functioning as divisible into differentiable "functional systems" in the sense used

by Luria (1980);

2. determining the nature of individual tasks that might best represent the different aspects of these systems;

3. choosing from the available neuropsychological and psychometric assessment procedures those instruments that would best represent the kind of tasks identified in step 2, and satisfy several criteria. The criteria included:

(a) documentation of impairment of key neurologically impaired groups with respect to other neurologically defined, psychiatrically defined, or normal control groups,

(b) psychometric properties, including sufficient length and internal consistency to assure reasonable levels of reliability; and

(3) instructions and task demands be of minimal complexity.

Some compromise of these principles was unavoidable. In certain cases, new tests were designed, or available tests modified, to fill in the gaps in what is intended to be a relatively comprehensive battery with maximal sensitivity to local brain dysfunction.

In addition to this battery of tests with regional specificity, certain additional measures were included because they had been shown to discriminate well between groups with "functional and organic" illnesses, or between groups of chronic schizophrenic patients with and without

CT-scan abnormalities. The Wechsler Adult Intelligence Scale (Revised Edition; WAIS-R) was also included for a variety of reasons. First, it is the most widely used test in clinical and research settings. Second, in many past studies where neurologically defined samples have been employed, patterns of brain-behavior relationships and indices of deterioration from previously higher levels of premorbid functioning have been derived. Third, it served to allow comparison of overall level of intellectual/cognitive functioning between this study and others.

I will first describe the group of tests with presumed regional/functional specificity. The representation of each functional group by various tests will be discussed with special reference to the relationship of each functional group to the hypothesized underlying brain system. A list of references for each test is provided in Appendix 3.

Tests of motor functions. These tests are relevant particularly to the functioning of frontal lobe systems, as has been amply demonstrated in stimulation and lesion studies showing the somatotopic organization of precentral gyrus with respect to the control of single motor units. The hierarchical organization of the frontal lobes, with elementary motor processes represented at the most posterior limit (central sulcus) and successively superordinate levels of organization being represented at

successively more anterior frontal regions, is reflected by the choice of tests. The most elementary level of motor control is tested in a simple test of strength (Hand Grip Strength), as well as in tests of simple repetitive finger, forearm, and foot movements (Finger Oscillation Test and three tests of the Motor Performance Battery). A higher level of organization of motor activity is required in those tasks which require alternating or sequential movements (three tests of the Motor Performance Battery). Sex differences on motor tasks are well known; males are faster and stronger than females (see Fromm-Auch & Yeudall, 1983; and Gardner, 1979, for descriptions of the magnitude of differences on the tasks used here). All motor tasks were therefore corrected for sex differences before entry into subsequent analyses and composite scales.

Tests of verbal functions. Verbal tasks are relevant particularly to the functioning of the "dominant" temporal lobe, as well as those regions of the dominant frontal lobe (frontal operculum, third frontal convolution) that have been demonstrated to be involved in the "expressive" aspects of speech, from articulation of phonemes to verbal fluency. The latter aspects are measured in simple tests of verbal fluency (Controlled Word Association) and in measures of articulation in several tasks (Word Reading, Sentence Reading). "Receptive" language tests were selected to represent the hierarchical organization of the temporal

lobe, from the level of phonemic discrimination (Wepman Speech Sound Discrimination Test), to the levels of word finding (Oldfield-Wingfield Picture Naming, Responsive Naming subtest of the Boston Diagnostic Aphasia Examination), and comprehension (Complex Ideational Material subtest of the Boston Diagnostic Aphasia Examination). The integration of frontal and temporal processes in language has been seen somewhat differently by different investigators. Geschwind's (1965) concept of "conduction aphasia", the hypothesized result of lesions to the arcuate fasciculus or disconnection of frontal and temporal neocortices, would lead to the conclusion that such integration would be best reflected by tests of verbal repetition. Luria's (1980) concept of the "frontotemporal system" invokes the idea that frontal lobe mechanisms serve an "executive" function in the organization of linguistic production, and would be best measured by the comprehension and production of syntactic elements. These two hypotheses have more than superficial similarities; an appreciation of the rules governing the sequential organization of language would appear directly related to the ability to repeat strings of words that exceed in length the span of immediate memory for unrelated auditory signals, given that semantic organization ("chunking" into meaningful components) is held constant. Both types of task (Sentence Repetition, Syntactic Comprehension) were included.

Tests of somatosensory/visuospatial functions. These tests are considered together here because both have been found relevant to the functioning of the parietal and parieto-occipital zones. The somatotopic representation of somesthetic functioning on post-central gyrus has been demonstrated in a fashion analogous to that for motor functions and the precentral gyrus. Deficiencies at the most elementary level of somesthetic functioning (i.e., anesthesia, two-point discrimination deficits) will be screened for in the routine neurological examination. In the neuropsychological examination, more complex functions will be tested. The test for graphesthesia (Finger Tip Number Writing Perception), and tests of identification, differentiation, and sequential differentiation of stimulation of the fingers (Kinsbourne-Warrington Tests for Finger Agnosia) are the additional measures of somesthetic function. One additional test is included which is not a test of somesthetic function (Right-left Discrimination), but like the other tests, has been found sensitive to dysfunction of the parietal neocortices. The tests of graphesthesia and finger gnosis may reflect unilateral dysfunction of the contralateral lobe, while right-left disorientation is impaired primarily following damage to the dominant parietal lobe (Luria, 1973). Constructional praxis is considered to be a hallmark feature of parietal lobe function, and a test of copying line

drawings (Rosen Drawing Test) is included to assess this function, as are certain WAIS-R subtests (Block Design, Object Assembly). While deficits on certain visuospatial/constructional tasks have been found to be sensitive to dysfunction of either parietal lobe, certain tasks have been found particularly sensitive to dysfunction primarily of the non-dominant parietal and/or temporo-parietal cortices. Included among these are tests of perceptual synthesis, in which the subject is required to identify real objects which are fragmented or distorted (Closure). Another task found to be sensitive to non-dominant temporo-parietal functioning is facial recognition (Benton Facial Recognition Test). One additional task particularly sensitive to dysfunction of non-dominant temporal functioning (Spatial Block Span & Learning) requires the subject to imitate a sequence of movements (taps) performed by the examiner over a spatial array (of blocks). The learning of spatial sequence is measured by calculating the differential performance of the subject on sequences which are repeated and those that are not. A final task, requiring the subject to discriminate overlapping line drawings (Poppelreuter Figure Analysis) has been found particularly sensitive to lesions of the most posterior parietal and parieto-occipital zones.

Tests of executive functions & behavioral programming.

These tasks are most sensitive to dysfunction of the

prefrontal divisions of neocortex although they also tend to be sensitive to lesions elsewhere in the brain. The simpler of these tasks (Competing Programs) requires the subject to perform in a responsive way to conflicting instructions (e.g., when the examiner holds up one finger, the subject must hold up two fingers; and vice versa). The other task of executive functioning (Wisconsin Card Sorting Test) requires the subject to form strategies, and then switch strategies, given only minimal instructions and feedback from the examiner. This task has been demonstrated to be particularly sensitive to lesions of the frontal lobes, although performance may also be impaired in the presence of other (diffuse or axial) disturbances.

Tests of learning & memory functions. These tests are most sensitive to dysfunction of mesiotemporal and limbic/diencephalic regions. In addition to the Wechsler Memory Scale, which includes two subtests of verbal learning (paragraph recall and word-pair Associate Learning) and one subtest of visual learning (Visual Reproduction), several tests are included to represent more thoroughly measures of verbal and non-verbal learning and memory. A list learning test which uses the technique of selective reminding (Buschke Learning & Memory Evaluation) has been used extensively in studies of populations with limbic/diencephalic damage, and is relatively more sensitive

to dominant hemisphere dysfunction. Two tests of nonverbal learning and memory (relatively more sensitive to dysfunction of non-dominant limbic regions) are included. One is a test of memory for geometric and nonsense figures (Kimura Recurring Figures Test) the other, a test of memory for faces (Associate Learning - Visual).

Tests of attentional functions. These tests have less localizing significance than most of the tests previously described, yet may be particularly impaired with dysfunction affecting the axial structures of the brain. In the case of axial disturbance, overall "cortical tone" may be most affected, and therefore deficits may be observed primarily in tasks that involve sustained attention and concentration. Tasks involving simple registration of stimuli, or execution of familiar routines, may remain relatively unimpaired. Nevertheless, the attentional tests may show deficiencies when any part of the brain is impaired, as each depends on multiple functions. As a group, these tasks are the most sensitive to brain damage, and have generally been most successful in attempts to discriminate between "organic" and "functional" groups.⁹ The simplest of the attentional tasks are those which require only the identification and "cancellation" of letter

⁹This is also true for tests of executive functioning, especially the Wisconsin Card Sorting Test.

groups, number groups, or geometric forms (Target Detection Tasks). Included are tasks which require cancellation of single targets (only one target-type per page), and dual targets (two target-types per page). Such tasks require sustained attention and may be sensitive to unilateral neglect. Also included is the Trail Making Test, in which subjects are required to connect sequentially a series of numbered targets (Part A); or to connect in alternating ascending sequence a series of both letters and numbers (Part B). The WAIS-R also includes subtests which are sensitive to attentional dysfunction, most noteworthy are the Digit Symbol and Digit Span subtests. These will be considered with the other attentional tests.

Additional tests. It was mentioned earlier that certain tests would be included despite the fact that that they are not clearly relevant to the functioning of particular neuropsychological systems. Such measures were included to allow comparisons to other studies and better characterize our sample, to enable the use of conventional indices of deterioration, or because they have been used widely in non-psychiatric settings to differentiate between brain-damaged and non-brain-damaged groups. The Wechsler Adult Intelligence Scale - Revised Edition (WAIS-R) is the most widely used instrument to assess intelligence, and has also been used more widely than any other instrument to assess neurologic and psychiatric populations. We will use

the WAIS-R:

1. as a measure of intellectual functioning (i.e., Full Scale IQ),
2. to determine Verbal-Performance IQ discrepancies, previously found to relate to CA (Rieder et al., 1979),
3. to calculate "Deterioration Indices", and estimates of premorbid intellectual functioning. A series of such measures was calculated according to the rules established by Wechsler (1958), DeWolfe (1971), and on the basis of data presented in McFie (1975). This approach involved simply subtracting standardized scores on subtests sensitive to brain damage from a standardized estimate of premorbid intelligence. The estimate of premorbid intelligence was formed from scores on the Information and Vocabulary subtests of the WAIS-R, each of which has been found particularly insensitive to the effects of localized brain lesions (Russell, 1972). Three subtests most sensitive to localized lesions were selected from the McFie (1975) presentation by taking those subtests showing greatest decrement in the presence of local brain damage, then ranking them in terms of both magnitude of decrement and frequency of decrement across the categories of brain damage. The sensitivity of each subtest to focal lesions of left, right, or either hemisphere are shown in Table 8 in terms of these rank-sums.

Table 8
Deviations of Wechsler Subtests Accompanying Localized Lesions¹

Subtest	Sum of Rank Deviation		
	Total	L. Hem.	R. Hem.
Digit Symbol	42	20	22
Digit Span	35.5	21	14.5
Picture Arrangement	34.5	13.5	21
Arithmetic	29.5	17.5	12
Block Design	29.5	10	19.5
Similarities	22	16	6
Vocabulary	13.5	6	7.5
Picture Completion	9.5	4	5.5

Note. (Calculations performed on data presented in J. McFie, Assessment of Organic Intellectual Impairment. New York: Academic Press, 1975.)

¹Brain damage was localized to one of six regions: frontal, temporal, or parieto-occipital in either left or right hemisphere.

The Digit Symbol subtest had clearly highest overall rank; indicating greatest sensitivity to focal lesions anywhere in the brain. Roughly equivalent in overall rank were the Digit Span and Picture Arrangement subtests, but as may be seen in Table 2, each appeared more sensitive to compromise of a particular hemisphere (Digit Span, left; Picture Arrangement, right). Weighted standardized scores on each of these subtests were subtracted from the "premorbid index" to form a global deterioration index (D1), a deterioration index theoretically more sensitive to left hemisphere lesions (DLEFT) and a deterioration index theoretically more sensitive to right hemisphere lesions (DRIGHT). The formulae obtained using this approach are presented in the

following section.

The Raven Standard Progressive Matrices (RSPM) are included as an additional measure of intellectual functioning that is less sensitive to the effects of motor slowing and language dysfunction. The standardized raw scores on the WAIS-R and RSPM will be summed to form an index of Global Intellectual Functioning.

The Mini-Mental-State Exam (MMS) has been used in a variety of studies as a brief measure of cognitive functioning, and is included here primarily to determine whether such a brief measure can be useful in predicting CT-scan or neuropsychological abnormalities.

The Purdue Pegboard has proved useful in the discrimination of brain-damaged from non-brain-damaged groups, and is used widely in clinical neuropsychology as an indicator of "organicity." It was included, like the MMS, to determine its value as a brief measure in the prediction of CT-scan or neuropsychological findings.

Handedness was assessed with a modified form of the Edinburgh Handedness Inventory. Subjects were asked to "pretend" to perform each of 20 activities that involve one or the other hand. For several activities, ambiguous responses are possible (e.g., swinging a baseball bat, the "upper" hand is considered dominant, yet some patients simply clasped their hands such that neither hand was clearly uppermost). Performance of at least 14 of 20

activities unambiguously with a given hand was used as the criterion for handedness. Foot and eye preference were also assessed. Regardless of handedness, language dominance was assumed to be left in the calculation of regional neuropsychological scales. Given that even among left handers, the prevalence of right hemisphere dominance for language is less than 50% (Goodglass & Quadfasel, 1954; Penfield & Roberts, 1959), this assumption should lead to fewer incorrect assignments than that of right hemisphere dominance for language in left handers.

Using the above criteria, three patients were left handed (performed more than 14 of 20 activities on modified Edinburgh Handedness Inventory with their left hand). The remainder were right handed (performing more than 15 activities with the right hand). Two right handed and one left handed patient displayed opposite foot preference. Five right handed and two left handed patients showed opposite eye preference. The handedness of each subject is shown in Appendix 1.

Missing Neuropsychological Data

Among the 32 patients in the sample, two patients refused all testing. One patient who was ethnically Chinese, and had (according to records) been raised speaking English, nevertheless demonstrated such striking impairments on tests of language and inconsistencies on other measures

requiring comprehension, that her native language abilities were questioned. Neuropsychological results from this patient were not included in analyses. Among the remaining 29 patients, 22 completed all measures. All non-missing data were included. The total n for analyses involving neuropsychological tests thus ranges from 22 to 29.

Neuropsychological Scales

Each of the following scale scores was calculated as the sum of standardized raw scores on the individual variables that comprise each scale, with equal weight assigned to each component of a given scale. When WAIS-R, Wechsler Memory Scale, and Boston Diagnostic Aphasia Examination (BDAE) subtests were included in scales, raw scores were used. The neuropsychological scale titles are printed in capital letters to differentiate them from other tests or scales in which only the initial letters are capitalized (e.g., ATTENTION is the neuropsychological scale measuring attentional function, while Attentional Impairment is a subscale of the SANS). All neuropsychological scales (except the deterioration indices) are formed such that higher scores represent better functioning. The deterioration indices are formed such that higher scores represent more deterioration.

GLOBAL = Full Scale IQ (WAIS-R)
 + Raven Standard Progressive Matrices (total score)

PREMORBID = Information (subtest of WAIS-R)
 + Vocabulary (subtest of WAIS-R)

Global Deterioration Index [D1] = PREMORBID
 - (2 X Digit Symbol Subtest of WAIS-R)

Deterioration Index (left hemisphere) [DLEFT] = PREMORBID
 - (2 X Digit Span Subtest of WAIS-R)

Deterioration Index (right hemisphere) [DRIGHT] = PREMORBID
 - (2 X Picture Arrangement Subtest of WAIS-R)

MOTOR (RIGHT) = Hand Grip Strength (right hand)
 + Finger Oscillation (right hand)
 + Motor Performance Battery (right body, total time)

MOTOR (LEFT) = Hand Grip Strength (left hand)
 + Finger Oscillation (left hand)
 + Motor Performance Battery (left body, total time)

MOTOR = MOTOR (LEFT) + MOTOR (RIGHT)

SOMATOSENSORY (RIGHT) = Graphesthesia (right hand)
+ Finger Gnosis Test (right hand)

SOMATOSENSORY (LEFT) = Graphesthesia (left hand)
+ Finger Gnosis Test (left hand)

SOMATOSENSORY = SOMATOSENSORY (LEFT)
+ SOMATOSENSORY (RIGHT)
+ Right Left Discrimination Test

PERCEPTUAL = Spatial Block Span
+ Facial Recognition Test
+ Closure Test
+ Poppelreuter Figure Analysis

LANGUAGE = Controlled Word Association Test
- Auditory Discrimination Test (error score)
+ Sentence Repetition Test
+ Syntactic Comprehension Test
+ Picture Naming Test
+ Responsive Naming Test
+ Complex Ideational Material (subtest of the BDAE)
+ Similarities (subtest of WAIS-R)

MEMORY = Logical Memory (subtest of Wechsler Memory Scale)

- + Visual Reproductions (subtest of Wechsler Memory Scale)
- + Associate Learning (subtest of Wechsler Memory Scale)
- + Associate Learning -- Visual
- + Recurring Figures (mean net score)
- + Selective Reminding Test (recognition; hits)
- + Selective Reminding Test (recall; consistent long-term retrieval)

ATTENTION = Digit Symbol (subtest of WAIS-R)

- + Digit Span (subtest of WAIS-R)
- Trail Making Test, Part B (total errors)
- Trail Making Test, Part B (total time)
- Target Detection Test (total time)
- + Target Detection Test (total hits)

EXECUTIVE = Competing Programs Test

- + Wisconsin Card Sorting Test (Categories Achieved)
- Wisconsin Card Sorting Test (Perseverative Errors)
- + Picture Arrangement (subtest of WAIS-R)

ANTERIOR LEFT = MOTOR (RIGHT)

- + Digit Span (subtest of WAIS-R)
- + Controlled Word Association Test

ANTERIOR RIGHT = MOTOR (LEFT)

+ Picture Arrangement (subtest of WAIS-R)

+ Spatial Block Span

POSTERIOR LEFT = ((LANGUAGE - Controlled Word Association
Test) / 7) + SOMATOSENSORY (RIGHT) / 2))

POSTERIOR RIGHT = (PERCEPTUAL / 4)

+ ((SOMATOSENSORY (LEFT) / 2)

LEFT = ANTERIOR LEFT + POSTERIOR LEFT

RIGHT = ANTERIOR RIGHT + POSTERIOR RIGHT

ANTERIOR = MOTOR + EXECUTIVE

POSTERIOR = POSTERIOR LEFT + POSTERIOR RIGHT

Computed Tomography (CT) Scan Assessments

CT-scanning facilities were provided by the Institute for Basic Research in Mental Retardation (IBR) at Staten Island. All scans were performed on the same machine (General Electric Model 7800). Fast scans (250 ms/slice) were performed to minimize radiation exposure while still

providing adequate resolution. For each patient, twelve transverse slices were taken at 10 mm intervals parallel to the orbito-meatal line, starting at 0 mm offset, generating a 256 X 256 pixel matrix. Digital recordings of the scans were maintained at IBR; hard copies (photoemulsions) were prepared at IBR and kept at the NYSPI. Two indices of ventricular enlargement (VE) were used; the ventricular-brain ratio (VBR), and the frontal horn index (FHI). Cortical atrophy (CA) was assessed by sulcal prominence ratings (SPR). We will consider the methods for obtaining each of these measures in turn.

Measurement of VE. The technique of Andreasen and Olsen (1982) was used to determine the VBR. In this technique, the slice showing the lateral ventricles at their largest extent is selected; tracings are then made under cursor control along the outer margins of each lateral ventricle, and along the inner table of the skull. The area within each tracing is automatically output through algorithms provided in the software of the 7800. The VBR was calculated simply as $[(\text{ventricular area}/\text{inner table area}) \times 100]$.

Other investigators (e.g., Weinberger et al., 1980; Rieder et al., 1983; Nasrallah et al., 1982; Golden et al., 1980) have used almost identical techniques, but mechanical planimetry was used to determine ventricular and inner table

areas rather than measuring these directly from the scanner viewing screen. The reliability of measurements made using this technique has been found to be high (on the order of .95; e.g., Jernigan, Zatz, Moses, & Berger, 1982).

An alternative measure of VE, originally used by Hahn and Rim (1976), is derived from linear measurements rather than areal ones. In this technique, the slice showing the frontal horns of the lateral ventricles at their largest is selected, and the distance between the most lateral extensions of left and right frontal horns is calculated. A similar distance measure is obtained from left to right inner skull tables, at the same anterior/posterior level at which the maximal frontal horn distance was calculated. The frontal horn index (FHI) is calculated as $FHI = [(maximal\ frontal\ horn\ distance / inner\ table\ distance) \times 100]$. As was the case for areal measurements, these distance measurements were output via algorithms provided in the software of the 7800.

Measurement of cortical atrophy (CA). The method for determining the degree of cortical atrophy was a modification of that described by Rieder et al. (1979). In this technique, the CT-scan slices showing the superior cerebral convexity best (usually the second and third highest slices) are viewed, and the prominence of cortical sulci are rated on a 6 point scale, with a rating of 0 representing normal appearance and a rating of 5

representing severe atrophy, with intermediate ratings representing intermediate (mild, moderate) levels of sulcal prominence. In the Rieder et al. (1979) study, interrater reliability was found to be high (intraclass correlation = .93). Interrater reliability of the modified scale was determined on a sample of 22 scans from the present study, rated by three observers (RMB, AKP, and Ronald O. Rieder [ROR]). Intraclass correlation was .95 for these raters, and the reliability for a single viewer's sulcal prominence ratings (SPR's) was .87. The means of SPR's made by two viewers (ROR and RMB; both blind to patient identity) were used as the index of cortical atrophy.

Results

Organizational Format

The results are presented in three main sections: Positive/Negative Symptoms, Neuropsychological Performance, and CT-scan Findings.

The section on positive/negative symptoms begins with analyses involving the positive and negative group classifications of Andreasen and Olsen (1982). Assessment of group differences on basic subject variables (e.g., age, sex) is followed by assessment of group differences in neuropsychological performance and CT-scan measures. The individual positive and negative symptoms are considered next. Before presenting correlations of the symptoms with other measures, the consistency of the negative and positive sets of variables is assessed. First, correlations within each set are presented; next, the correlations between sets of symptoms are shown. The results of the correlational analyses within and between sets of symptoms are summarized in a principal components analysis. The factors more concisely illustrate the "clustering" of symptoms found in correlational analysis, and should be helpful in interpreting subsequent results. Correlations of the symptoms with subject variables, premorbid adjustment scale

scores, neuropsychological tests and scales, and CT-scan findings are then shown.

The section on neuropsychological performance begins with presentation of psychometric findings that describe the overall level of intellectual functioning of the sample, and the number of patients that performed tasks at levels below those used as "cutoffs" for the identification of brain damage. The correlations between neuropsychological measures and the subject variables, as well as PAS scores, are then shown. After presentation of these findings, the relationships between symptoms and neuropsychological performance, which were detailed in the section on symptoms, are reviewed. This review is followed by presentation of correlations between neuropsychological performance and CT-scan measures. The section ends with analyses of the consistency of neuropsychological scales and indices.

The final section, on CT-scan findings, begins with presentation of the distributions of each CT-measure, and assessment of the comparability of these results to normative data and the findings of other clinical investigations. The relationships between CT-scan findings and other measures, including subject variables, clinical measures, and neuropsychological performance, are then reviewed. Finally, the consistency of the CT-measures and the possibility that VE and CA are dissociable, are assessed.

Positive and Negative Symptom Groups

Group Differences in Subject Variables

Patients were classified into positive, negative, and mixed groups according to the criteria of Andreasen and Olsen (1982). The sex composition and demographic/course characteristics of positive, negative, and mixed symptom groups are shown in Table 9. Analysis of variance to test

Table 9
Characteristics of Positive, Negative, and Mixed Groups

	POS	NEG	MIX	F	p
Sex (No. F,M)	4,6	5,7	5,5	.34	ns
Age (yrs)	34.2	30.1	33.6	.96	ns
Education Level ^a	3.9	4.1	4.0	.05	ns
Onset Age (yrs)	19.3	20.0	20.1	.09	ns
Duration Ill (yrs)	14.8	10.1	13.5	1.18	ns

Note. The values are means; F statistics are for each main effect independently.

^aHollingshead/Redlich Criteria (0--7).

the effects of classification on each of the these variables revealed no significant effects.

Patients in the negative symptom group had higher PAS scores (poorer premorbid social adjustment) than patients in the positive symptom group. The mean PAS average score ($\pm$ sd) of patients classified as negative according to the criteria of Andreasen and Olsen (1982) was significantly

greater than that of patients classified as positive (55.7 ± 13.2 vs 42.9 ± 10.1 ; $t = 2.45$, $df = 17.5$, $p < .02$, one-tailed). The mean PAS score of the mixed group (50.5) was intermediate between that of the positive and negative groups, and was not significantly different from either. In a one-way ANOVA to test the effect of group membership (including the mixed group) on PAS scores, there was not a significant effect of group [$F(2, 27) = 2.02$, $.05 < p < .10$].

The hypothesis that poor premorbid social adjustment would be positively correlated to age at onset was not supported ($r = -.03$, $df = 29$, $p > .5$). The correlation between PAS score and education level was negative ($r = -.37$, $df = 29$, $p < .05$, two-tailed), as was hypothesized.

Group Differences on other Subtyping Dimensions

Neuropsychological findings. It was hypothesized that patients classified as negative would show more evidence of neuropsychological impairment than patients classified as positive. Those neuropsychological tests on which patients classified as negative performed differently from patients classified as positive are presented in Table 10. Only differences significant at the .10 level (t -tests without pooled variance, df approximated, two-tailed) are listed. The negative group performed more poorly on the Digit Symbol subtest of the WAIS-R, and this difference was significant

Table 10
Neuropsychological Test Measures Performed Differently by
Positive and Negative Symptom Groups

Measure	Group Mean $\pm$ sd		<u>t</u>	<u>df</u>	<u>p</u>
	Positive	Negative			
DSYMRW	41.2 $\pm$ 7.2	29.5 $\pm$ 7.1	-3.64	17.2	.002
DSYMCSS	7.2 $\pm$ 1.8	4.9 $\pm$ 1.2	-3.85	14.8	.002
WMSVR	8.8 $\pm$ 2.3	6.2 $\pm$ 3.1	-2.07	17.0	.054
FOSCR	49.5 $\pm$ 9.0	37.8 $\pm$ 12.4	-2.38	17.0	.029
FOSCL	43.7 $\pm$ 9.7	34.3 $\pm$ 11.1	-1.97	16.3	.066

Note. DSYMRW, Digit Symbol subtest of the WAIS-R, raw score; DSYMCSS, Digit Symbol subtest of the WAIS-R, age corrected scaled score; WMSVR, Wechsler Memory Scale, Visual Reproduction subtest; FOSCR, Finger Oscillation Test, right hand; FOSCL, Finger Oscillation Test, left hand.

both for raw and age corrected scaled scores (see Table 10). The negative symptom group also performed worse on the Visual Reproduction subtest of the Wechsler Memory Scale, and on both left and right hand administrations of the Finger Oscillation Test.

Comparisons of scores of positive and negative groups on each of the neuropsychological scales were all nonsignificant (t-test, p > .10, two-tailed). Trends were seen for the negative group to perform worse on the PREMORBID (t = -1.23) and ATTENTION (t = -1.52) scales, and to have higher scores than the positive group on the Global Deterioration Index (t = 1.41). The positive group tended to show worse performance on the RIGHT POSTERIOR scale, and

to have higher scores on the the index of left hemisphere deterioration ($t = -1.53$).

CT-scan findings. It was hypothesized that the negative symptom group would show more evidence of VE and CA than the positive group. Mean values of each CT-scan index for positive and negative groups, along with tests of the differences between means, are presented in Table 11. FHI and SPR were nonsignificantly greater in the negative group (see Table 11). VBR was non-significantly greater in the positive group.

Table 11
Comparison of CT-scan Measures in Positive and Negative Symptom Groups

Measure	Mean Value ($\pm$ sd)		t	df	p
	POS	NEG			
VBR	7.6 $\pm$ 4.4	6.7 $\pm$ 1.0	-.56	8.6	.59
FHI	23.9 $\pm$ 5.4	25.7 $\pm$ 5.4	.53	12.4	.60
SPR	1.9 $\pm$ 1.3	2.6 $\pm$ 1.5	1.23	18.7	.23

Note. T-statistics without pooled variance; df estimated; p values are for two-tailed tests.

Thus, differences between positive and negative symptom groups were found in scores on the PAS, with the negative group showing more evidence of poor premorbid social adjustment. The negative group also performed more poorly than the positive group on three independent neuropsychological tests, and for no test did the negative group perform better than the positive group. Group

differences were not found, however, on mean neuropsychological scale scores. Furthermore, positive and negative groups did not differ on any CT-scan index.

Individual Positive and Negative Symptoms

Analyses of the individual symptom measures were more revealing than those of symptom-defined groups. Evidence was found suggesting that positive and negative symptoms as defined by Andreasen (1982) may be neither homogeneous within their own sets nor definitive of a dichotomous continuum. This evidence was found: (a) in correlational analysis within and between sets of positive and negative symptoms; and (b) in the correlations of the symptoms with other subtyping measures.

Consistency of Symptoms

Correlations within symptom sets. The intercorrelations of SANS subscale and summary scores is presented in Table 12. The highest intercorrelations of SANS subscales were those between: (a) Alogia and Attentional Impairment ($r = .79$, $p < .0001$); and (b) Affective Flattening and Avolition/Apathy ($r = .78$, $p < .0001$). These correlations were significantly greater than any other intersubscale correlations (t -test for the difference of correlated coefficients of correlation; smallest $t_{dr} = 1.71$, $df = 27$, $p < .05$). Anhedonia was more

Table 12
Intercorrelations of SANS Subscales and Summary Scores

Scale	2	3	4	5	6	7
1. Affective Flat'g	.43*	.78††	.60†	.47**	.87††	.80††
2. Alogia	--	.36	.41*	.79††	.69††	.72††
3. Avolition/Apathy		--	.61†	.40*	.80††	.72††
4. Anhedonia			--	.57†	.78††	.65††
5. Attent. Impairm't				--	.78††	.78††
6. SANSUM					--	.93††
7. SANSGT						--

Note. $n=30$; SANSUM, Sum of SANS Subscales; SANSGT, SANS Global Total Score.

* $p < .05$ ** $p < .01$ † $p < .001$ †† $p < .0001$

weakly correlated with the other subscales and with SANS Global Total Score. Although Anhedonia appeared to relate more strongly to Avolition/Apathy ($r = .61$) or Affective Flattening ($r = .60$) than to Alogia ($r = .41$) the differences between these correlation coefficients were not significant.

The positive symptom variables comprising the Positive Symptom Summary Scale also appeared to manifest heterogeneity (see Table 13). There was one strong cluster of subscales, represented by items measuring Positive Formal Thought Disorder and Bizzare Behavior. The correlations of Delusions and Hallucinations with all other symptoms were only moderate (see Table 13). Comparison of correlation coefficients revealed that the correlation between Positive Formal Thought Disorder and Bizarre Behavior was significantly greater than the correlations of either

Table 13
Intercorrelations of Positive Symptom Measures and Summary Scores

Measures	2	3	4	5	6
1. Delusions	.51**	.51**	.40*	.76††	.50**
2. Hallucinations	--	.51**	.35	.74††	.46**
3. Bizarre Behavior		--	.82††	.88††	.05
4. PFTD			--	.83††	.07
5. SPOS				--	.33
6. BROADPSY					--

Items/PFTD	2	3	4
1. Impaired Understandibility	.70††	.90††	.97††
2. Loosening of Associations	--	.53**	.82††
3. Illogical Thinking		--	.90††
4. PFTD			--

Note. PFTD, Positive Formal Thought Disorder; SPOS, Positive Symptom Summary Scale; BROADPSY, Breadth of Psychosis Scale.
* $p < .05$ ** $p < .01$ † $p < .001$ †† $p < .0001$ (two-tailed)

variable with Delusions or Hallucinations (smallest $t_{dr} = 2.71$, $df = 27$, $p < .001$). It should also be noted that the Breadth of Psychosis Scale was only moderately correlated with the Positive Symptom Summary Scale, and appeared to have no linear relationship with either Bizarre Behavior or Positive Formal Thought Disorder.

Correlations between symptom sets. Correlations within positive and negative symptom sets showed that neither set was homogeneous. Further analyses between sets of positive and negative symptoms fail to support the hypothesis that such symptoms define opposite ends of a continuum. If this had been the case, then most correlations between sets would have been negative. The correlations between positive

symptom measures and SANS subscales is displayed in Table 14. There were no significant negative correlations. Only

Table 14
Intercorrelations of Positive and Negative Symptom Measures

SANS Measure	Positive Symptom Measure					
	DEL	HALL	BIZB	PFTD	SPOS	B'PSY
Affective Flat'g	.25	.06	.12	.13	.18	-.14
Alogia	.10	-.02	.44*	.59†	.34	-.19
Avolition/Apathy	.32	.19	.15	.14	.25	-.07
Anhedonia	.24	.27	.18	.12	.24	-.03
Attent. Impairm't	.26	.29	.59**	.62†	.54**	-.15
SANSGT	.21	.14	.44**	.43*	.38*	-.32

Note. SANSGT, SANS Global Total Score. DEL, Delusions; HALL, Hallucinations; BIZB, Bizarre Behavior; PFTD, Positive Formal Thought Disorder; B'PSY, Breadth of Psychosis Scale. *p < .05 **p < .01 †p < .001 (all two-tailed)

the Breadth of Psychosis Scale had a consistent pattern of negative correlations with the SANS subscales. The Positive Symptom Summary Scale and some of its components, however, were positively correlated with the SANS Global Total Score and certain SANS subscales, contradicting the hypothetical dichotomy between positive and negative symptoms.

In addition to the significant correlation between the Positive Symptom Summary Scale and the SANS Global Total Score, the Positive Symptom Summary Scale was also significantly correlated to the Attentional Impairment subscale of the SANS. There was also a trend for the Positive Symptom Summary Scale to be positively correlated to the Alogia subscale of the SANS ($p < .10$, two-tailed).

The SANS Global Total Score was significantly correlated with both Bizarre Behavior and Positive Formal Thought Disorder.

The correlations between individual SANS subscales and individual positive symptoms illustrate that Alogia and Attentional Impairment were significantly correlated only to Positive Formal Thought Disorder and Bizarre Behavior (see Table 14). Reaffirming the results of correlational analyses within symptom sets, the three negative symptom measures that were most independent of the others (Affective Flattening, Avolition/Apathy, and Anhedonia) were least related to any of the positive symptoms. Similarly, those positive symptom variables originally found most independent (Delusions, Hallucinations, and Breadth of Psychosis Scale) were nonsignificantly correlated to the negative symptom measures.

To illustrate this pattern of relationships, the results of principal components analysis of the ten clinical variables (Affective Flattening, Alogia, Avolition/Apathy, Anhedonia, Attentional Impairment, Delusions, Hallucinations, Bizarre Behavior, Positive Formal Thought Disorder, and Breadth of Psychosis Scale) are shown in Table 15. The initial solution produced three principal components with Eigenvalues greater than 1.0, that together accounted for 78% of the variance. The rotated (Varimax)

Table 15
Principal Components Analysis of Positive and Negative
Symptoms

	<u>Eva</u>	<u>Prb</u>	<u>Cumc</u>
Initial Solution			
Factor 1	4.16	.416	.416
Factor 2	2.18	.218	.633
Factor 3	1.50	.150	.783

Rotated Factor Pattern¹

<u>Variable</u>	<u>Factor</u>		
	<u>1</u>	<u>2</u>	<u>3</u>
Delusions	.25	.24	.77
Hallucinations	.26	.10	.76
Bizarre Behavior	.80	.01	.45
PFTD	.88	-.02	.36
BROADPSY	.17	-.12	.79
Affective Flat'g	.13	.90	-.01
Alogia	.80	.36	-.27
Avolition/Apathy	.08	.90	.07
Anhedonia	.19	.81	.07
Attent. Impairm't	.81	.45	-.02
Variance Explained	2.93	2.68	2.22

Note. PFTD, Positive Formal Thought Disorder; BROADPSY, Breadth of Psychosis Scale.

¹Rotation method was Varimax (Statistical Analysis System, 1982).

^aEigenvalue

^bProportion of variance explained.

^cCumulative proportion of variance accounted for.

factor pattern is also shown in Table 15. The first factor, with high loadings on Bizarre Behavior, Positive Formal Thought Disorder, Alogia, and Attentional Impairment, appears to represent a general (i.e., common to both positive and negative symptom scales) "cognitive disturbance" factor. Factor 2 had high loadings on those three negative symptom variables least related to positive

symptoms (Affective Flattening, Avolition/Apathy, and Anhedonia). This factor appears to represent the most distinct or "core" negative symptoms. The third factor, with high loadings on Delusions, Hallucinations, and the Breadth of Psychosis Scale (those positive variables least related to negative symptoms), appears to reflect the most distinct, or "core" positive symptoms.

Correlations of Symptoms with Subject Variables

Age at onset was positively correlated with the Avolition/Apathy subscale of the SANS ($r = .39$, $df = 29$, $p < .05$, two-tailed). All other correlations between the symptom measures and age, sex, education, age at onset, and duration of illness were nonsignificant.

The correlations between PAS average scores and the SANS subscales and summary scores are shown in Table 16.

Table 16
Correlations between Negative Symptom Measures and Premorbid Adjustment Scale

<u>SANS Measure</u>	<u>r with PAS</u>
Affective flattening	.49**
Alogia	.13
Avolition/Apathy	.38*
Anhedonia	.24
Attentional Impairment	.24
Sum of Subscales	.43*
Sum of Global Ratings	.45*

Note. Values are PM correlations with PAS average score.
 $n=29$.

* $p < .05$ ** $p < .01$ (two-tailed)

Both summary scales and two subscales (Affective Flattening and Avolition/Apathy) were significantly associated with PAS scores. Other subscales were nonsignificantly positively correlated to PAS scores.

The correlations between PAS scores and positive symptom measures were all nonsignificant (see Table 17).

Table 17
Correlations between Positive Symptom Measures and Premorbid Adjustment Scale

Symptom Measure	r with PAST
Delusions	.08
Hallucinations	-.12
Bizarre Behavior	.21
PFTD	.10
SPOS	.10
BROADPSY	-.13

Note. PFTD, Positive Formal Thought Disorder; SPOS, Positive Symptom Summary Scale; BROADPSY, Breadth of Psychosis Scale. Values are PM correlations with PAS average score. n=29.

The hypothesized relationship between poor premorbid social adjustment and negative symptomatology was thus accepted when Andreasen's classification system was used, but only when "pure" positive and negative patients were included in the analyses. Further, PAS scores were related to Affective Flattening and Avolition/Apathy, but not to Alogia or Attentional Impairment.

Correlations of Symptoms with Other Subtyping Measures

Correlations of symptoms with neuropsychological findings. Correlations were performed between each of the neuropsychological test variables and each of the variables composing negative and positive symptom scales. Those correlations significant at the .05 significance level (two-tailed) are presented in Tables 18 and 19.

The significant neuropsychological test correlates of the negative symptom measures are shown in Table 18. Alogia and Attentional impairment were strongly related to poor performance on a variety of tests requiring attentional, memory, language, and executive functions. Affective flattening, Avolition/Apathy, and Anhedonia were related to impaired performance on fewer tests. These were generally "non-specific" tests of attentional and visuomotor functions (e.g., Digit Symbol, Purdue Pegboard) commonly associated with either diffuse brain dysfunction or focal dysfunction in one of many brain regions. Other impairments on more specific tests of motor skill (Finger Oscillation Test, right hand) and executive functions (Competing Programs Test) raise the possibility that a more specifically anterior dysfunction may relate to these core negative symptoms. Nevertheless, the Competing Programs Test was the only test among those significantly correlated with Affective Flattening and Avolition/Apathy that was not

Table 18
Significant Neuropsychological Test Correlates of SANS
Subscales

<u>SUBSCALE</u>	<u>r</u>
<u>AFFECTIVE FLATTENING</u>	
Competing Programs Test, total score.....	-.58
Digit Symbol subtest, WAIS-R, raw score.....	-.52
Purdue Pegboard Test, right hand, 2nd 30" score.....	-.48
Digit Symbol subtest, WAIS-R, ACSS.....	-.46
Finger Oscillation Test, right hand mean score.....	-.44
Purdue Pegboard Test, right hand, 60" score.....	-.43
<u>ALOGIA</u>	
Prosopo-affective Agnosia Test, total score.....	-.53
Digit Symbol subtest, WAIS-R, ACSS.....	-.51
Recurring Figures Test, geometric forms, correct rejs.	-.49
Similarities subtest, WAIS-R, raw score.....	-.47
Comprehension subtest, WAIS-R, raw score.....	-.46
Full Scale IQ, WAIS-R.....	-.46
Competing Programs Test, raw score.....	-.45
Comprehension subtest, WAIS-R, ACSS.....	-.45
Digit Symbol subtest, WAIS-R, raw score.....	-.44
Vocabulary subtest, WAIS-R, raw score.....	-.43
Verbal IQ, WAIS-R.....	-.42
Picture Completion subtest, WAIS-R, raw score.....	-.41
Similarities subtest, WAIS-R, ACSS.....	-.41
Performance IQ, WAIS-R.....	-.41
Buschke Selective Reminding Test, total hits.....	-.40
Target Detection (Cancellation) tests, total time.....	.40
Vocabulary subtest, WAIS-R, ACSS.....	-.39
<u>AVOLITION/APATHY</u>	
Purdue Pegboard Test, right hand, 2nd 30" score.....	-.51
Purdue Pegboard Test, right hand, 60" score.....	-.48
Purdue Pegboard Test, left hand, 60" score.....	-.46
Competing Programs Test, total score.....	-.43
Purdue Pegboard Test, left hand, 2nd 30" score.....	-.43
Digit Symbol subtest, WAIS-R, raw score.....	-.42
<u>ANHEDONIA</u>	
Object Assembly subtest, WAIS-R, ACSS.....	-.53
Object Assembly subtest, WAIS-R, raw score.....	-.49
Spatial Block Span, longest span.....	.47
Verbal - Performance IQ Difference.....	.40
Target Detection (Cancellation) Tests, total time.....	.40

continued

Table 18 (continued)
 Significant^a Neuropsychological Test Correlates of SANS
 Subscales

SUBSCALE	r
<u>ATTENTIONAL IMPAIRMENT</u>	
Prosopo-Affective Agnosia Test, total score.....	-.56
Digit Symbol subtest, WAIS-R, ACSS.....	-.51
Responsive Naming subtest, BDAE, total score.....	-.48
Mini-Mental State Exam, total score.....	-.48
Syntactic Comprehension test, total score.....	-.48
Recurring Figures Test, nonsense shapes, total hits...	-.47
Digit Symbol subtest, WAIS-R, raw score.....	-.46
Buschke Selective Reminding Test, long-term recall....	-.46
Target Detection (Cancellation) tests, total time.....	.42
Picture Completion subtest, WAIS-R, raw score.....	-.42
Performance IQ, WAIS-R.....	-.41
Picture Completion subtest, WAIS-R, ACSS.....	-.40
<u>SANS GLOBAL TOTAL SCORE (SANS GT)</u>	
Competing Programs Test, total score.....	-.52
Recurring Figures Test, geometric net score.....	-.51
Digit Symbol subtest, WAIS-R, raw score.....	-.46
Digit Symbol subtest, WAIS-R, ACSS.....	-.43
Responsive Naming subtest, BDAE, total score.....	-.43
Syntactic Comprehension Test, total score.....	-.42
Target Detection (Cancellation) Tests, total time.....	.42
Target Detection (Cancellation) Tests, false alarms...	.41
Recurring Figures Test, mean net score.....	-.40
Prosopo-affective Agnosia Test, total score.....	-.40
Performance IQ, WAIS-R.....	-.39
Picture Arrangement subtest, WAIS-R, ACSS.....	-.38

Note. For WAIS-R subtests, ACSS indicates age corrected scaled score. BDAE, Boston Diagnostic Aphasia Exam.

^aAll correlations are significant at $p < .05$, two-tailed.

dependent on speed. Thus it may be more parsimonious to interpret these findings as related to slowing rather than specifically to anterior brain dysfunction. The significant correlates of the SANS Global Total Score included a

combination of executive, attentional and visuomotor functions along with some more specific tests of language dysfunction (Responsive Naming Test, Syntactic Comprehension Test).

A different pattern of neuropsychological test results was significantly correlated to positive symptoms and scales (see Table 19). Significant correlates of the Positive Symptom Summary Scale included three tests specifically dependent on language ability (Responsive Naming Test, Auditory Discrimination Test, and Wechsler Memory Scale - Memory Quotient), and the test for graphesthesia (right hand and total score). Among the variables included in the Positive Symptom Summary Scale, Positive Formal Thought Disorder and Bizarre Behavior were quite strongly associated with deficits on language tests, and with several less specific tests of attentional, memory, executive, and perceptual functions. Hallucinations and delusions were correlated significantly to only a few variables (which might be expected by chance given the number of correlations performed). Hallucinations scores were related to lower grip strength (left hand) and poorer graphesthesia (right hand and total scores); Delusions scores were significantly associated with fewer errors on Part B of the Trail Making Test, and with more categories achieved (better performance) on the Wisconsin Card Sorting Test. Delusions was unique among the symptom variables in relating to better

Table 19
Significant^a Neuropsychological Test Correlates of Positive Symptom Measures

<u>SCALE</u>	<u>r</u>
<u>DELUSIONS</u>	
Trail Making Test, Part B, total errors.....	-.48
Wisconsin Card Sorting Test, categories achieved.....	-.40
<u>HALLUCINATIONS</u>	
Hand Grip Strength, left hand, mean of 3 trials.....	-.43
Graphesthesia Test, right hand score.....	-.43
Graphesthesia Test, total score (both hands).....	-.39
<u>BIZARRE BEHAVIOR</u>	
Responsive Naming Test, total score.....	-.57
Buschke Selective Reminding Test, total hits.....	-.55
Wechsler Memory Scale, Memory Quotient.....	-.47
Wechsler Memory Scale, Associate Learning.....	-.45
Associate Learning Visual, Form 2.....	-.43
Vocabulary subtest, WAIS-R, raw score.....	-.43
Recurring Figures Test, geometric forms, correct rejs.	-.43
Auditory Discrimination Test, validity errors.....	.41
Wechsler Memory Scale, Logical Memory subtest.....	-.40
Target Detection (Cancellation) tests, false alarms...	.40
Graphesthesia Test, right hand score.....	-.39
<u>POSITIVE FORMAL THOUGHT DISORDER</u>	
Responsive Naming Test, total score.....	-.64
Auditory Discrimination Test, error score.....	-.62
Wechsler Memory Scale, Memory Quotient.....	-.55
Vocabulary subtest, WAIS-R, raw score.....	-.53
Prosopo-affective Agnosia, total score.....	-.52
Similarities subtest, WAIS-R, raw score.....	-.52
Buschke Selective Reminding Test, total hits.....	-.51
Arithmetic subtest, WAIS-R, ACSS.....	-.49
Wechsler Memory Scale, total raw score.....	-.48
Recurring Figures Test, geometric forms, correct rejs.	-.46
Wechsler Memory Scale, Associate Learning.....	-.45
Poppelreuter Figure Analysis, total score.....	-.44
Vocabulary subtest, WAIS-R, ACSS.....	-.44
Verbal IQ, WAIS-R.....	-.43
Wisconsin Card Sorting Test, perseverative errors.....	.43

continued

Table 19 (continued)
Significant^a Neuropsychological Test Correlates of Positive Symptom Measures

<u>SCALE</u>	<u>r</u>
<u>POSITIVE SYMPTOM SUMMARY SCALE</u>	
Responsive Naming Test, total score.....	-.60
Auditory Discrimination Test, error score.....	.43
Graphesthesia Test, right hand score.....	-.42
Wechsler Memory Scale, Memory Quotient.....	-.41
Graphesthesia Test, left hand score.....	-.40

BREADTH OF PSYCHOSIS SCALE

Motor Performance Battery, left body, mean time.....	.43
--	-----

Note. For WAIS-R subtests, ACSS indicates age corrected scaled score.

^aAll correlations are significant at $p < .05$, two-tailed.

performance on neuropsychological tests. Breadth of Psychosis Scale related significantly to only one measure. The correlation between the Breadth of Psychosis Scale and the Motor Performance Battery (left hand) indicates an association with slow left hand performance.

Correlations of each neuropsychological scale with negative and positive symptom measures were performed (Table 20). SANS Global Total Scores were significantly correlated with lower scores on the ATTENTION and LANGUAGE scales ($r = -.54$, $df = 22$, $p < .01$; and $r = -.41$, $df = 24$, $p < .05$, respectively). Examination of individual SANS subscales revealed that the correlation of language impairment with negative symptomatology held only for the Alogia and

Attentional Impairment subscales (see Table 20). These

Table 20
Correlations between Neuropsychological Scales and SANS
Subscales

Neuropsych. Scale	n	SANS Subscale				
		AFF	ALOG	AVOL	ANHE	ATT
GLOBAL	25	-.14	-.46*	-.22	-.50*	-.33
PREMORBID IND.	28	-.03	-.39*	.08	.15	-.33
DET'N INDEX	27	.48*	.05	.48*	.24	.13
" " (left)	28	-.03	-.35	.01	-.22	-.26
" " (right)	28	.29	-.07	.32	.28	.01
MOTOR	25	-.06	-.06	-.15	-.14	.05
SOMATOSENSORY	25	.06	-.20	-.17	-.11	-.24
PERCEPTUAL	25	.19	-.11	.10	.27	-.14
LANGUAGE	25	-.14	-.46*	-.15	-.17	-.52**
MEMORY	23	-.23	-.47*	-.13	-.21	-.53**
ATTENTION	23	-.44*	-.49*	-.47*	-.11	-.47*
EXECUTIVE	24	-.28	-.29	-.16	-.14	-.31
ANTERIOR LEFT	24	-.20	-.26	-.18	.08	-.27
ANTERIOR RIGHT	25	-.07	-.15	-.10	.05	-.18
POSTERIOR LEFT	24	.01	-.33	-.20	-.19	-.43*
POSTERIOR RIGHT	24	.21	-.19	.00	-.04	-.18
LEFT	21	-.12	-.51*	-.17	-.24	-.57**
RIGHT	21	.04	-.35	-.06	-.09	-.36
ANTERIOR	24	-.23	-.26	-.20	-.22	-.18
POSTERIOR	23	.41	-.26	-.06	-.09	-.33

Note. All values are PM correlation coefficients. AFF, Affective Flattening; ALOG, Alogia; AVOL, Avolition/Apathy; ANHE, Anhedonia; ATT, Attentional Impairment.

*p < .05 **p < .01 †p < .001 ††p < .0001

subscales also were correlated selectively to the GLOBAL, MEMORY, and LEFT scales. The Affective Flattening and Avolition/Apathy subscales of the SANS, on the other hand, were correlated selectively with the Global Deterioration Index. This may be due in part to the fact that the latter subscales were not related to lower PREMORBID scale scores, in contrast to Alogia (which was significantly associated

with lower PREMORBID scores,) and Attentional Impairment (which tended to show a similar relationship). The only neuropsychological scale that was consistently related to SANS subscales was ATTENTION; this scale was significantly associated with all SANS subscales except Anhedonia.

The correlations between neuropsychological scales and each of the positive symptom measures are shown in Table 21. The Positive Symptom Summary Scale was significantly

Table 21
Correlations between Neuropsychological Scales and Positive Symptom Measures

Neuropsychological Scale	n	Positive Symptom Measures				
		DEL	HALL	BIZB	PFTD	B'PSY
GLOBAL	25	.20	.09	-.15	-.28	.04
PREMORBID IND.	28	.09	.29	-.34	-.45*	.17
DET'N INDEX	27	.23	.34	-.08	-.17	.26
" " (left)	29	.01	.33	-.25	-.17	.22
" " (right)	28	.16	.36	-.24	-.17	.33
MOTOR	25	-.15	-.30	-.35	-.15	-.34
SOMATOSENSORY	25	.17	-.19	-.22	-.28	.06
PERCEPTUAL	25	.13	-.09	-.26	-.36	.07
LANGUAGE	25	.04	.08	-.48*	-.64†	-.33
MEMORY	23	.08	-.13	-.54**	-.52**	.23
ATTENTION	23	.00	.06	-.17	-.28	-.00
EXECUTIVE	24	.33	.08	-.04	-.18	.16
ANTERIOR LEFT	24	.13	.09	-.26	-.36	-.13
ANTERIOR RIGHT	25	.07	-.30	-.19	-.24	-.25
POSTERIOR LEFT	24	-.01	-.27	-.55**	-.61**	-.03
POSTERIOR RIGHT	24	.20	-.10	-.25	-.27	.09
LEFT	21	-.08	-.26	-.72†	-.70†	-.12
RIGHT	21	.11	-.25	-.51*	-.50*	-.01
ANTERIOR	24	.10	-.19	-.33	-.24	-.16
POSTERIOR	23	.09	-.21	-.46*	-.48*	.04

Note. All values are PM correlation coefficients. DEL, Delusions; HALL, Hallucinations; BIZB, Bizarre Behavior; PFTD, Positive Formal Thought Disorder; B'PSY, Breadth of Psychosis Scale.

*p < .05 **p < .01 †p < .001 ††p < .0001

related to LEFT and LEFT POSTERIOR scales. It can be seen that Bizarre Behavior and Positive Formal Thought Disorder were the major contributors to this relationship, and that these two measures alone were significantly correlated with poor performance on tests of language and memory functions. The POSTERIOR and RIGHT hemisphere scales were also associated with Bizarre Behavior and Positive Formal Thought Disorder, but comparison of correlation coefficients demonstrated that Bizarre Behavior, Positive Formal Thought Disorder, and the Positive Symptom Summary Scale were each significantly more correlated with impairment of LEFT than RIGHT hemisphere scales (smallest $t_{dr} = 1.93$, $df = 18$, $p < .05$, one-tailed). Positive Formal Thought Disorder was also significantly correlated with lower scores on the Premorbid Scale. Delusions and Hallucinations were not significantly correlated with any of the neuropsychological scales, although there were trends for Hallucinations to be associated with higher scores on each of the deterioration indices.

Correlations of symptoms with CT-scan findings. The correlations between the three CT-scan measures and each of the clinical symptom measures are shown in Table 22. The only significant correlations represent an inverse relationship between Alogia and VBR (higher VBR, less Alogia), and a direct relationship between the Breadth of Psychosis Scale and SPR. Both correlations oppose the

Table 22
Correlations between Symptom Scales and CT-scan Measures

Symptom Scales	CT-scan Measures		
	VBR	FHI	SPR
Negative			
Affective Flattening	.25	.19	.34
Alogia	-.37*	.14	-.05
Avolition/Apathy	.22	.33	.22
Anhedonia	.22	.29	.17
Attentional Impairment	-.23	.15	-.01
Sum of SANS Subscale Scores	-.05	.29	.19
SANS Global Total Score	.04	.27	.08
Positive			
Delusions	-.03	-.09	.06
Hallucinations	.35	.17	.26
Bizarre Behavior	-.19	-.09	-.18
Positive Formal Thought Disorder	-.18	-.09	-.01
Positive Symptom Summary Scale	.01	-.04	-.01
Breadth of Psychosis Scale	.10	.10	.37*

Note. All values are PM correlations.

*p < .05 (two-tailed)

hypothesized relationship. There were, however, nonsignificant positive correlations between the CT measures and Affective Flattening, Avolition/Apathy, and Anhedonia. Moreover, among the negative symptom measures, these three were the most positively correlated with each CT index.

Summary of Findings in the Positive/Negative

Symptom Dimension

Comparisons of positive and negative symptom groups showed that the negative group evidenced poorer premorbid social adjustment and more impairment on some

neuropsychological tests, but the groups did not differ on any neuropsychological scale or CT index.

The analyses using individual symptom measures revealed three separable "clusters" of symptoms. This clustering of symptoms, apparent in correlations within and between sets of symptoms, was corroborated by the correlations between symptoms and the other subtyping measures. The "cognitive disturbance" cluster of symptoms, which included both positive (Positive Formal Thought Disorder, Bizarre Behavior) and negative (Alogia, Attentional Impairment) elements, was associated with the most widespread neuropsychological impairment and evidence of poor premorbid intellectual functioning, but not with premorbid social functioning or CT-scan status. The "core negative" cluster, including symptoms of Affective Flattening, Avolition/Apathy, and Anhedonia, was related most to poor premorbid social adjustment and evidence of deterioration from previously higher levels of intellectual functioning, as well as with a circumscribed set of neuropsychological (attentional) functions. This core negative cluster was more associated than others with CT abnormality, although these correlations were not significant in themselves. The "core positive" cluster of symptoms, including Delusions, Hallucinations, and the Breadth of Psychosis Scale, was least associated with any of the other subtyping measures.

Neuropsychological Performance

Level of Neuropsychological Functioning

It was hypothesized that patients would manifest impairments on standardized tests of intelligence and that a disproportionate number would score below "cutoff" levels used to identify "brain damage".

The sample's performance on widely used tests of intellectual ability and on instruments used for the prediction of brain damage is depicted in Tables 23 and 24.

Table 23
Intelligence Test Results for Sample

Wechsler Adult Intelligence Scale - Revised

Verbal Subtests	ACSS Mean $\pm$ sd	Performance Subtests	ACSS Mean $\pm$ sd
Information	8.1 $\pm$ 3.6	Picture Completion	6.2 $\pm$ 2.5
Digit Span	8.6 $\pm$ 2.4	Picture Arrangement	6.4 $\pm$ 2.0
Arithmetic	7.0 $\pm$ 2.6	Block Design	7.1 $\pm$ 2.1
Vocabulary	8.7 $\pm$ 3.5	Object Assembly	5.8 $\pm$ 2.2
Comprehension	7.4 $\pm$ 3.7	Digit Symbol	5.7 $\pm$ 1.6
Similarities	7.6 $\pm$ 4.5		

Verbal IQ = 88.4 $\pm$ 15.4 (70 - 133)

Performance IQ = 75.4 $\pm$ 7.8 (61 - 96)

Full Scale IQ = 81.2 $\pm$ 11.2 (67 - 112)

Raven Standard Progressive Matrices

Total Score = 29.9 $\pm$ 13.5 (7 - 56)

Median percentile score = 18th

Note. ACSS is age corrected scaled score. (n = 28-29)

Performance on the WAIS-R and Raven Standard Progressive Matrices is shown in Table 23. The mean WAIS-R Full Scale IQ of the patients (81.2) was in the lower end of the Low Average range of intellectual ability (Wechsler, 1981), and three patients had Full Scale IQ's in the range of Mild Mental Retardation. (See Appendix 1 for the IQ scores of each subject). Raven Standard Progressive Matrices total score indicated that the samples' performance exceeded that of only 11% -- 30% of the population (see Table 23).

On tests widely used as "screening" instruments for the identification of brain damage, from 70% to 96% of the sample was classified as brain damaged according to standard cutoff scores (see Table 24). Every patient was identified

Table 24
Classification of Patients by Instruments Used to Predict
"Brain Damage"

Instrument	Cutoff Score	Number scoring		Percent "B. D."
		Below	Above	
Purdue Pegboard ^a				
Preferred	<26	27	1	96
Non-preferred	<22	21	7	75
Both	<18	20	8	71
Trail Making Test ^b				
Part A	>40 s	19	8	70
Part B	>92 s	21	6	78
Finger Tapping Test ^c	<50	20	7	74

^aScores are number of pegs placed in two 30-second trials.
(Smith & Goldberg, 1979).

^bTime to complete (Reitan, 1964).

^cScore is mean of best 3 trials that are within 5 taps
(Halstead, 1948).

as "brain damaged" according to at least one of these measures. Four patients were classified as brain damaged according to all measures.

Correlations of Neuropsychological Measures with Subject Variables

Correlations of each of the neuropsychological scales to age, education, age at onset and duration of illness are shown in Table 25.

Table 25
Correlations of Neuropsychological Scales with Demographic and Course Variables

Neuropsychological Scale	n	Variables				
		Age	Educ	OnAge	Durn	Sex
GLOBAL	26	.31	.72††	.27	.18	-.21
PREMORBID IND.	29	.49*	.63†	.22	.40*	-.09
DET'N INDEX	28	.47*	.43*	.22	.39*	.00
" " (left)	29	.45*	.21	.03	.46*	.03
" " (right)	29	.25	.33	.17	.17	.07
MOTOR	26	-.08	-.16	.37	-.32	.02
SOMATOSENSORY	26	-.08	.43*	.16	-.19	.08
PERCEPTUAL	26	.09	.34	.24	-.06	.25
LANGUAGE	26	.27	.60**	.08	.25	.16
MEMORY	24	.08	.20	.13	.01	-.14
ATTENTION	24	.03	.24	.39	.17	.18
EXECUTIVE	25	.07	.29	.21	-.04	-.01
ANTERIOR LEFT	25	.06	.24	.25	-.09	-.02
ANTERIOR RIGHT	26	-.08	.12	.46*	-.37	-.05
POSTERIOR LEFT	25	.11	.53**	.17	.02	.23
POSTERIOR RIGHT	25	.00	.44*	.22	-.15	.19
LEFT	22	.20	.34	.28	.06	.13
RIGHT	22	.08	.31	.39	-.16	.21
ANTERIOR	25	-.02	-.02	.41*	-.27	.04
POSTERIOR	24	.11	.51*	.22	-.02	.25

Note. All values are PM correlation coefficients; for sex, F = 0, M = 1.

*p < .05 **p < .01 †p < .001 ††p < .0001

It was hypothesized that estimates of premorbid intelligence would be directly related to age at onset and educational attainment. The index of premorbid intelligence (PREMORBID) derived from the WAIS-R was nonsignificantly correlated to age at onset ($r = .22$, $p > .10$), but was strongly related to educational level ($r = .63$, $p < .005$). An unexpected finding was that age, and duration of illness (which is highly correlated with age), were significantly associated with PREMORBID, suggesting that older patients had once functioned intellectually at a higher level than younger patients.

It was also hypothesized that estimates of deterioration from previous levels of functioning would be directly related to age, duration of illness, age at onset and educational attainment. Both the Global Deterioration Index and the Index of left hemisphere deterioration were positively correlated to age and duration of illness. Only the Global Deterioration Index was also significantly correlated to educational level. Given the unanticipated relationship between age and PREMORBID, however, it is not clear that older patients had actually deteriorated more, or instead had deteriorated from a higher level. The correlation of age and the Global Deterioration Index partialling PREMORBID was not significant ($r_{\text{age Global Deterioration Index.PREMORBID}} = .30$, ns), suggesting that the latter hypothesis may be correct. Although it was

not specifically hypothesized, there were predictable relationships of other scales (GLOBAL, LANGUAGE, LEFT POSTERIOR) with educational level. Less predictable relationships of Education with SOMATOSENSORY and RIGHT POSTERIOR scales were also significant. There were also direct relationships between onset age and the "anterior" scales (RIGHT ANTERIOR, ANTERIOR) that appeared due more to motor than to "executive" functions. Among all scales, those including motor, memory, and "right-hemisphere" related tasks appeared to be most correlated to later onset.

All neuropsychological scales and test variables were analyzed for sex effects. As can be seen in Table 25, none of the neuropsychological scales is significantly related to sex. Among individual test variables, only the Closure Test and the Finger Gnosis Test (right hand administration) were performed differently by the sexes, with males scoring higher in both instances. Uncorrected motor tests were all significantly different, with males faster (Finger Oscillation Test, Motor Performance Battery) and stronger (Hand Grip Strength) than females, but these expected differences were all controlled with the use of sex corrected scores, as can be seen in Table 25 (i.e., $r_{\text{sex MOTOR}} = .02$).

Correlations of neuropsychological measures with PAS scores. It was hypothesized that PAS scores would be positively correlated with impairment on neuropsychological

tests, and inversely related to estimates of premorbid intelligence.

Correlations were performed between PAS average scores and each neuropsychological variable. Those neuropsychological variables significantly ($p < .05$, two-tailed) correlated to PAS average scores are listed in Table 26, ranked by absolute value of r .

Table 26
Neuropsychological Variables Significantly Correlated with
PAS Average Scores

Neuropsychological Variables	n	r^a	p^b
Wechsler Memory Scale, Logical Memory	26	-.51	.008
Syntactic Comprehension Test	27	-.49	.009
Digit Symbol subtest, WAIS-R, ACSS	27	-.48	.011
Digit Symbol subtest, WAIS-R, raw score	27	-.38	.048

Note. ACSS is age corrected scaled score.

^aPM correlation with PAS average score.

^bProbabilities of PM correlation coefficients are for two-tailed tests.

PAS scores were significantly related to impaired performance on three independent tests. Two of these were related to language ability (memory for passages from the Wechsler Memory Scale, Syntactic Comprehension Test). Third was the Digit Symbol subtest of the WAIS-R, and impairment on this test was evident on either raw or age corrected scaled scores.

The correlations between PAS scores and the neuropsychological scales were all nonsignificant (see Table

27). The correlation coefficient between PAS average score and the premorbid index was negative, as predicted, but not significantly different from zero ($r = -.26$, $p > .10$).

Table 27
Relationships of Neuropsychological Scales to Premorbid Adjustment Scale

Neuropsychological Scale	r with PAST
GLOBAL	-.25
PREMORBID INDEX	-.26
DET'N INDEX	.14
" " (left)	-.22
" " (right)	-.07
MOTOR	-.05
SOMATOSENSORY	.12
PERCEPTUAL	.29
LANGUAGE	-.27
MEMORY	-.19
ATTENTION	-.26
EXECUTIVE	-.05
ANTERIOR LEFT	-.16
ANTERIOR RIGHT	-.03
POSTERIOR LEFT	-.08
POSTERIOR RIGHT	.27
LEFT	-.17
RIGHT	.18
ANTERIOR	-.04
POSTERIOR	.14

Note. All values are PM correlation coefficients.

Correlations of the Neuropsychological Measures with Other Subtyping Measures

Review of neuropsychological correlates of symptoms and premorbid social adjustment. Neuropsychological differences between positive and negative groups, and the

neuropsychological correlates of individual symptoms and PAS scores were already presented. It was shown that:

1. more neuropsychological impairment was found in the negative than in the positive symptom group;

2. widespread neuropsychological deficits were associated with the "cognitive disturbance" cluster of symptoms;

3. a more circumscribed pattern of neuropsychological impairment (chiefly attentional dysfunction), and evidence of intellectual deterioration, were associated with the core group of negative symptoms;

4. either no associations, or correlations with better performance, were found with core positive symptoms; and

5. PAS scores were significantly correlated with impairments in several tests of language, and the Digit Symbol subtest of the WAIS-R, but not with any neuropsychological scales.

Correlations of neuropsychological findings with CT-scan findings. It was hypothesized that increased neuropsychological impairment would be positively correlated to VE and CA. Correlations between each neuropsychological variable and each CT-scan variable were performed. Correlations significant at the .05 level (two-tailed) are presented in Table 28, in rank order of absolute value of r .

Although many tests were strongly related to the CT-scan measures, the most consistent findings were that

measures of general intellectual ability, language ability, and premorbid functioning were positively correlated to the indices of VE and CA. No neuropsychological test measure was inversely related to VBR. FHI was correlated to impaired performance on only two test measures, one a measure of speed in attentional tasks (Target Detection

Table 28
Significant^a Neuropsychological Test Correlates of CT-scan Measures

VBR	r
Full Scale IQ, WAIS-R.....	.60
Information subtest, WAIS-R, ACSS.....	.60
Verbal IQ, WAIS-R.....	.58
Wechsler Memory Scale, Logical Memory subtest.....	.58
Comprehension subtest, WAIS-R, ACSS.....	.57
Information subtest, WAIS-R, raw score.....	.57
Comprehension subtest, WAIS-R, raw score.....	.57
Vocabulary subtest, WAIS-R, ACSS.....	.56
Vocabulary subtest, WAIS-R, raw score.....	.54
Similarities subtest, WAIS-R, ACSS.....	.54
Mini Mental State Exam total score.....	.52
Recurring Figures Test, nonsense forms, total hits...	.50
Controlled Word Association Test, total score.....	.48
Performance IQ, WAIS-R.....	.44
Picture Completion subtest, WAIS-R, ACSS.....	.40
Digit Symbol subtest, WAIS-R, ACSS.....	.40
Similarities subtest, WAIS-R, raw score.....	.40
Word Reading subtest, BDAE, total score.....	.40
Wechsler Memory Scale, Memory Quotient.....	.40
FHI	r
Sentence Reading Test, BDAE, total score.....	.53
Target Detection (Cancellation) Tests, total time....	.49
Vocabulary subtest, WAIS-R, raw score.....	.43
Information subtest, WAIS-R, ACSS.....	.43
Hand Grip Strength, left hand, mean of 3 trials.....	-.43
Vocabulary subtest, WAIS-R, ACSS.....	.40
Information subtest, WAIS-R, raw score.....	.39

continued

Table 28 (continued)
Significant^a Neuropsychological Test Correlates of CT-scan Measures

SPR	r
Picture Naming, total score.....	.60
Controlled Word Association, semantic total score...	.59
Information subtest, WAIS-R, ACSS.....	.59
Information subtest, WAIS-R, raw score.....	.57
Comprehension subtest, WAIS-R, ACSS.....	.52
Finger Oscillation Test, right hand, mean score.....	-.51
Comprehension subtest, WAIS-R, raw score.....	.51
Verbal IQ, WAIS-R.....	.50
Vocabulary subtest, WAIS-R, raw score.....	.49
Controlled Word Association Test, total score.....	.49
Arithmetic subtest, WAIS-R, raw score.....	.48
Full Scale IQ.....	.47
Arithmetic subtest, WAIS-R, ACSS.....	.46
Vocabulary subtest, WAIS-R, ACSS.....	.45
Word Reading Test, BDAE, total score.....	.44

Note. All values are PM correlation coefficients. ACSS indicates age-corrected scaled score. BDAE, Boston Diagnostic Aphasia Examination.

^aAll correlations are significant at the .05 level, two-tailed.

Tests, total time), the other was the measure of Hand Grip Strength (left hand). SPR was significantly correlated with poorer performance only on the Finger Oscillation Test (right hand).

Neuropsychological scale profiles for each CT measure are shown in Table 29. All three CT indices were positively correlated with the PREMORBID scale. Both VBR and SPR were also positively correlated with the GLOBAL scale. FHI and SPR were each significantly correlated with the Global Deterioration Index, and SPR was more strongly related than

Table 29
Relationships of Neuropsychological Scales to CT-scan
Measures

Neuropsychological Scale	n	CT-scan Measure		
		VBR	FHI	SPR
GLOBAL	25	.43*	.24	.44*
PREMORBID INDEX	28	.57**	.42*	.55**
DET'N INDEX	27	.30	.55**	.64†
" " (left)	29	.44*	.32	.28
" " (right)	29	.25	.34	.49**
MOTOR	25	.01	-.38	-.40*
SOMATOSENSORY	25	.25	.04	.11
PERCEPTUAL	25	.36	.30	.24
LANGUAGE	25	.31	.21	.42*
MEMORY	23	.27	.37	.23
ATTENTION	23	.15	-.38	-.08
EXECUTIVE	24	.28	.05	-.10
ANTERIOR LEFT	24	.29	-.28	-.11
ANTERIOR RIGHT	26	.05	-.22	-.32
POSTERIOR LEFT	24	.23	.12	.31
POSTERIOR RIGHT	24	.36	.17	.27
LEFT	21	.46*	.02	.13
RIGHT	21	.37	.01	.05
ANTERIOR	24	.17	-.25	-.36
POSTERIOR	23	.34	.17	.34

Note. All values are PM correlation coefficients.

* $p < .05$ ** $p < .01$ † $p < .001$ †† $p < .0001$

VBR to the Global Deterioration Index ($t_{dr} = 2.00$, $df = 26$, $p < .05$). SPR was not, however, more strongly correlated with the Global Deterioration Index than with PREMORBID ($t_{dr} = .65$, ns). The partial correlation of SPR with the Global Deterioration Index (partialling PREMORBID), however, remained significant ($r_{SPR \text{ Global Deterioration Index.PRE}} = .49$, $df = 26$, $p < .005$, one-tailed).

The only significant inverse relationship between

CT-scan measures and neuropsychological scales were seen between SPR and the MOTOR scale.

Consistency of the Neuropsychological Measures

Intercorrelations between the functional scales are presented in Table 30. The motor and attentional scales

Table 30
Intercorrelations of Neuropsychological Functional Scales

Scale	2	3	4	5	6	7
1. MOTOR	.14	.04	-.15	.24	-.00	.09
2. SOMATOSENSORY	--	.74††	.47*	.29	.53**	.40*
3. PERCEPTUAL		--	.47*	.30	.61**	.39*
4. LANGUAGE			--	.26	.65**	.52*
5. ATTENTIONAL				--	.27	.38
6. MEMORY					--	.64**
7. EXECUTIVE						--

*p<.05 **p<.01 ††p<.0001 (two-tailed)

appeared most distinct from other functional scales (largest r 's with other scales = .24 and .38 respectively). Strong relationships were observed: (a) between SOMATOSENSORY and PERCEPTUAL scales; (b) of PERCEPTUAL and LANGUAGE scales with the MEMORY scale; and (c) between the EXECUTIVE and MEMORY scales (see Table 30).

The intercorrelations of variables within each of the functional scales is provided in Appendix 4. The consistency of each of the functional scales is moderate, with average interitem correlations ranging from .29 to .53. The consistency of certain scales (e.g., MOTOR and SOMATOSENSORY) may be inflated due to the very high

correlations between lateral presentations of the same task. Within the Memory scale, overall interitem correlation is low when both verbal and non-verbal tasks are considered together. The consistency of verbal and visual memory scales considered separately is considerably higher. The SOMATOSENSORY scale appeared to be more heterogeneous than others, with several low interitem correlations. Tests from the SOMATOSENSORY scale correlated highly with the PERCEPTUAL scale, (for one variable, the Right/left Discrimination Test, more highly than with the scale of which it is a part) suggesting that the two scales may be closely related. Among the tests comprising the ATTENTION scale, the two accuracy measures (Trail Making Test, Part B, total errors; and Target Detection Tests, total hits) were only weakly related to other test measures. This is probably due to the fact that there was little variance among subjects (few errors) on these measures.

Correlations between the various regional scales are illustrated in Table 31. Predictably high correlations are seen between left and right ANTERIOR scales, and between left and right POSTERIOR scales, due largely to high correlations between lateralized presentations of identical tasks. The correlation between LEFT ANTERIOR and LEFT POSTERIOR is greater than that of LEFT ANTERIOR and RIGHT POSTERIOR; and the correlation between RIGHT ANTERIOR and RIGHT POSTERIOR is greater than that between RIGHT ANTERIOR

and LEFT POSTERIOR, but neither of the differences between these correlation coefficients is significant.

Table 31
Intercorrelations of the Neuropsychological Regional Scales

Scale	2	3	4	5	6	7	8
1. ANTERIOR LEFT	.65†	.38	.27	.59**	.49*	.89††	.45*
2. ANTERIOR RIGHT	--	.43*	.44*	.53*	.74*	.92††	.40*
3. POSTERIOR LEFT		--	.79††	.80††	.79††	.32	.94††
4. POSTERIOR RIGHT			--	.63**	.76††	.20	.95††
5. LEFT				--	.86††	.56**	.77††
6. RIGHT					--	.70†	.84††
7. ANTERIOR						--	.
8. POSTERIOR							--

*p<.05 **p<.01 †p<.001 ††p<.0001

The neuropsychological indices of global and premorbid functioning as well as the deterioration indices were correlated with each of the functional and regional scales (see Table 32). The GLOBAL scale was highly correlated with all of the functional and regional scales except MOTOR and the anterior regional scales of which motor tests are a part. A similar pattern is seen for PREMORBID, which is highly correlated to GLOBAL ($r = .79$, $df = 28$, $p < .0001$). The Global Deterioration Index was significantly correlated only to the LANGUAGE (directly) and MOTOR (inversely) scales. The Global Deterioration Index was also negatively correlated to ATTENTION ($p < .05$, one-tailed) and there were trends for the Global Deterioration Index to be negatively correlated with each of the anterior regional scales (LEFT ANTERIOR, RIGHT ANTERIOR, ANTERIOR).

Table 32
Correlations of Neuropsychological Indices with Functional and Regional Scales

Neuropsychological Scale	Neuropsychological Index				
	GLO	PI	D1	DL	DR
MOTOR	-.12	-.11	-.41*	-.03	-.06
SOMATOSENSORY	.58**	.50**	.17	.22	.12
PERCEPTUAL	.50*	.53**	.30	.18	.17
LANGUAGE	.65†	.78††	.49*	.42	.28
MEMORY	.60**	.58**	.23	.25	-.02
ATTENTION	.46*	.42*	-.39	-.14	-.02
EXECUTIVE	.66†	.43*	.07	.09	-.23
ANTERIOR LEFT	.33	.38	-.26	-.12	.03
ANTERIOR RIGHT	.28	.11	-.25	-.13	-.25
POSTERIOR LEFT	.60**	.65†	.29	.30	.19
POSTERIOR RIGHT	.56**	.53**	.30	.23	.22
LEFT	.52*	.60**	.08	.32	.12
RIGHT	.50*	.47*	.07	.15	.04
ANTERIOR	.23	.14	-.29	.04	-.16
POSTERIOR	.61**	.63†	.34	.28	.16

Note. All values are PM correlation coefficients. GLO, Global; PI, Premorbid index; D1, Deterioration index (general); DL, Deterioration index (left); DR, Deterioration index (right).

*p < .05 ** p < .01 †p < .001 †† p < .0001

CT-scan Findings

Comparability of CT measures

It was hypothesized that patients would show evidence of brain atrophy relative to published norms, as indicated by measures of VE and CA.

The mean ($\pm$ sd) of measurements for each CT scan index were: for VBR, 6.3 ($\pm$ 3.2); for FHI, 26.4 ($\pm$ 7.1); and for

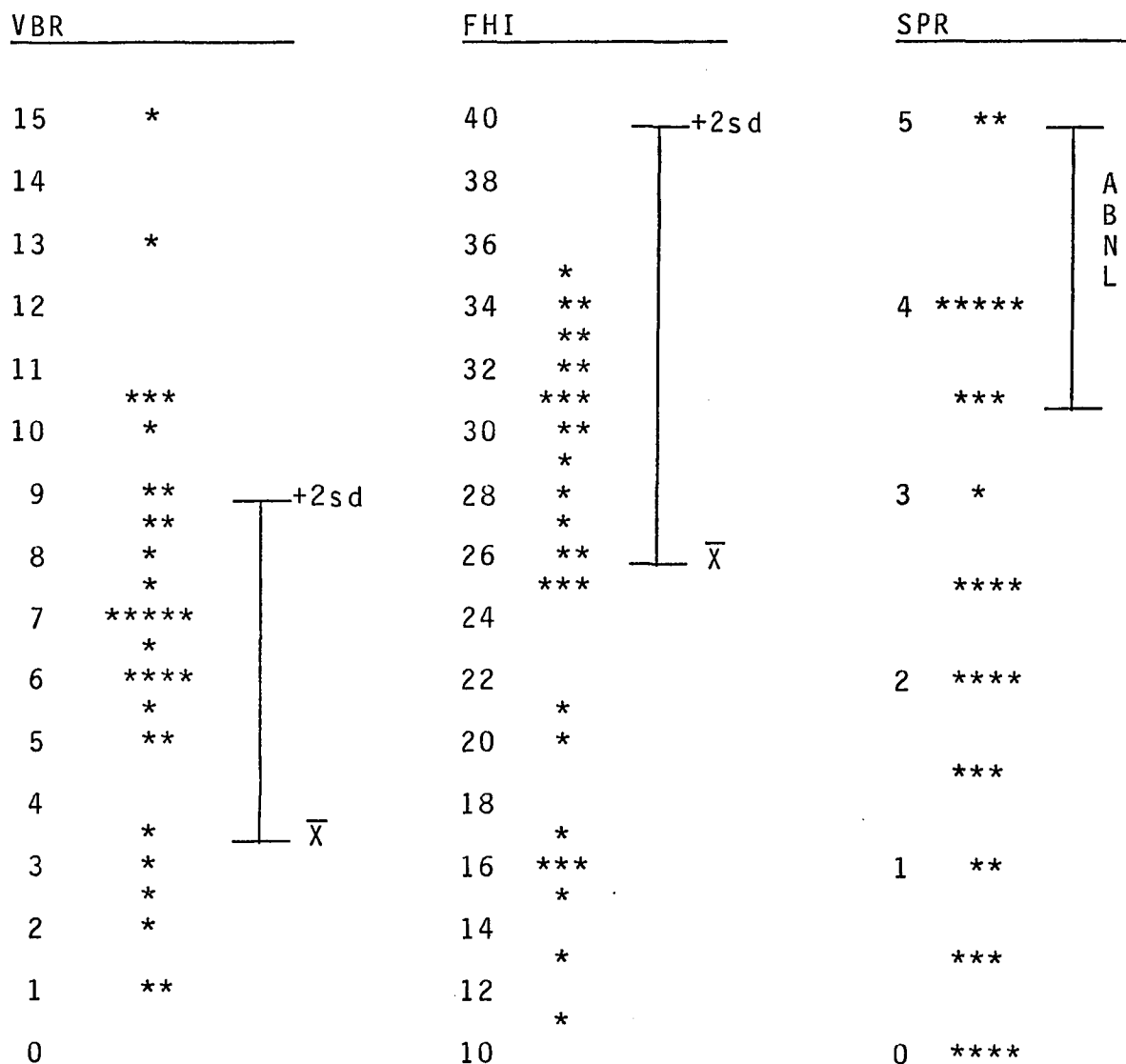
SPR, $2.4 (\pm 1.2)$. The distributions of VBR, FHI, and SPR are presented in Figure 1. To classify scans as "abnormal", normative data for the first two of these measures were taken from published reports. Values of VBR or FHI greater than 2 standard deviations above normal mean scores were classified as abnormal. The normative values for SPR are not well known. In the previous report of Rieder et al. (1979), in which a four-point scale was used (0--3), a value other than 0 was taken to indicate abnormal atrophy. We have selected the value of $SPR \geq 3.5$ as an indication of abnormal atrophy using the revised scale (0--5). Both methods were used to rate the same scans and linear regression indicated this value to be equivalent to that used by Rieder et al. in classification of scans as abnormal.

The percentage of measurements classified as abnormal were: for VBR, 26%; for SPR, 32%. No patient was classified as having abnormal FHI using the 2 sd cutoff.

Correlations of CT-scan Findings with Subject Variables

The correlations of the CT measures with demographic and course variables are presented in Table 33. Only VBR was significantly correlated to age or duration of illness, but these correlations were not significantly greater than those of either FHI or SPR with age or duration of illness.

Figure
Distributions of CT-scan Variables



Note. Means and standard deviations were drawn from: Zatz and Jernigan, 1983 (for VBR); Pandurangi et al., 1984 (for FHI). Abnormality of SPR was determined according to the method of Rieder et al., 1979. See text for explanation.

Table 33
Correlations of CT-scan Measures with Demographic and Course Variables

Demographic & Course Variables	CT-scan Measures		
	VBR	FHI	SPR
Sex (F=0,M=1)	.11	.15	.25
Age	.40*	.28	.34
Education level	.23	.23	.63††
Age at Onset	.07	.11	.24
Duration Ill	.43*	.27	.23

*p < .05 **p < .01 †p < .001 ††p < .0001

Consistent with the unexpected finding that CT abnormalities were correlated with better global intellectual/cognitive functioning, SPR was significantly correlated with education level. SPR was more correlated to education level than were either VBR or FHI (smaller $t_{dr} = 2.36$, $df = 27$, $p < .02$).

PAS average scores were not significantly correlated with any of the CT-scan indices. The correlations of VBR and SPR differed in sign, but the difference between the correlated coefficients of correlation was nonsignificant ($t_{dr} = 1.37$, $df = 26$, $p > .05$).

Review of Correlations of CT-scan Findings with Other Subtyping Measures

CT-scan findings were not correlated significantly to either symptoms or premorbid social adjustment along hypothesized lines. Among the symptom clusters, however, it

appeared that CT-scan abnormalities were least associated with the cognitive disturbance cluster of symptoms; a significant inverse correlation between VBR and Alogia was found, consistent with the findings that CT-abnormalities were positively correlated to better cognitive functioning on neuropsychological tests. A positive correlation of SPR with the Breadth of Psychosis scale was also found, suggesting that this CT-measure might be more associated with core positive symptoms. Nevertheless, each of the CT measures was positively (although nonsignificantly) correlated with all three core negative symptoms.

A consistent pattern of neuropsychological test results, suggesting better premorbid intellectual functioning and better overall functioning (possibly despite greater deterioration), was associated with CT abnormalities.

Consistency of CT-scan Findings

Intercorrelations of the CT measures are shown in Table 34. VBR was significantly correlated with FHI, but not with

Table 34
Intercorrelations of CT-scan Measures

	VBR	FHI	SPR
VBR	--	.42*	.33
FHI		--	.46*
SPR			--

*p < .05 (two-tailed)

SPR. VBR was not, however, more correlated with FHI than with SPR ($t_{dr}=.50$, ns).

Although each of the three CT measures was associated with better estimated premorbid intellectual functioning, there appeared to be differences in their relative associations to symptoms, premorbid adjustment, and neuropsychological functioning. VBR and SPR, which had the lowest intercorrelation among the CT measures, appeared to be the most disparate. VBR, but not SPR, was inversely related to Alogia. Affective flattening, on the other hand, had appeared to relate more to SPR than to VBR. Premorbid adjustment was inversely related to VBR, but directly related to SPR, and this discrepancy was more pronounced when PREMORPID was partialled from these relationships ($r_{VBR \text{ PAST.PREMORPID}} = .44$, $df = 26$, $p < .05$; $r_{SPR \text{ PAST.PREMORPID}} = .01$, ns). Among the neuropsychological scales, there were a number of differences between VBR and SPR. Most conspicuous were differences in the relative associations of VBR and SPR with: (a) the ANTERIOR scale ($t_{dr}=2.69$); (b) the MOTOR scale ($t_{dr}=2.04$); and (c) the Global Deterioration Index ($t_{dr} = 2.00$). It appeared that SPR was more associated than VBR with impairment of "anterior" and "motor" functions, and with deterioration. To illustrate these differences between VBR and SPR with respect to symptoms, premorbid adjustment, and neuropsychological profile, partial canonical correlation

analysis was performed between: (a) the CT variables VBR and SPR, and (b) the best discriminating symptoms (Alogia and Affective Flattening), the Premorbid Adjustment Scale Total Score and the best discriminating neuropsychological scale (ANTERIOR). The index of premorbid intellectual functioning (PREMORBID) was partialled. The two resulting canonical correlations, and the correlations of each of the variables with the canonical variates of their own and the opposite set, are shown in Table 35. Each of the canonical

Table 35
Canonical Correlation Analysis Illustrating Differences
Between VBR and SPR

	<u>1</u>	<u>2</u>
Canonical Correlation	.63	.57
Proportion of Variance	.39	.32
Probability	.05	.08

	<u>Canonical Variates</u>			
	<u>CT1</u>	<u>CT2</u>	<u>CN1</u>	<u>CN2</u>
CT Variables				
VBR	.01	1.00	.00	.57
SPR	.99	.09	.62	.05
CN Variables				
AFF	.45	.23	.72	.40
ALOG	.20	-.22	.31	-.39
PAST	.15	.45	.23	.79
ANTERIOR	-.54	.18	-.86	.32

Note. Values in the body of the main table are correlations between variables and the canonical variates of their own and the opposite set of variables. AFF, Affective Flattening; ALOG, Alogia; PAST, Premorbid Adjustment Scale - Total Score. CN stands for Clinical/Neuropsychological.

correlations was moderate, accounting for 39% and 32% of variance, respectively. The overall significance of the analysis was high (Wilk's Lambda = 0.10; $p < .0001$). As can be seen in Table 35, SPR and VBR each loaded uniquely on the two CT variates. The corresponding neuropsychological variates include one that has strong correlations with Affective Flattening and (inversely) with ANTERIOR, while the other had a primary loading on the Premorbid Adjustment Scale total score, with a moderate negative loading on Alogia.

Discussion

The Positive/Negative Dichotomy

The basic distinction between positive and negative symptoms as proposed by Andreasen & Olsen (1982) was not supported by the results of this study. Using the symptoms proposed by these investigators, it was found that: a) neither the positive nor the negative set of symptoms was internally consistent, b) correlations between positive and negative symptoms were not negative, as would be true if the symptoms represented opposite ends of a continuum; and c) the sets of symptoms did not relate to other subtyping measures in ways that were hypothesized. A different clustering of the symptoms appeared to be appropriate in this sample. These results are discussed below, and possible explanations of the differences between these and previous findings are considered.

Consistency of negative and positive symptoms. The pattern of intercorrelations among the SANS subscales suggests that "negative" symptomatology as assessed by this instrument was not homogeneous in the present sample. In fact, two relatively distinct clusters of symptoms appeared

to exist in the SANS, one represented by Attentional Impairment and Alogia, the other represented by Affective Flattening and Avolition/Apathy. Among "positive" symptoms, it was also found that two measures -- Positive Formal Thought Disorder and Bizarre Behavior -- were closely associated, and that these were relatively independent of other measures of the "positive" schizophrenic syndrome -- Delusions and Hallucinations.

Thus, within each group of symptoms --negative and positive-- two apparently dissociable clusters of symptoms emerged. Further, for each group, one of the clusters was a more clearly "cognitive" cluster, while the other appeared to represent the "core" features of negative and positive symptom profiles (for the negative profile -- Affective Flattening, Avolition/Apathy, and Anhedonia; for the positive profile -- Delusions and Hallucinations).

The coherence of these clusters was evident in the pattern of associations seen between variables considered to be indices of negative and positive symptomatology. The relatively strong associations seen between the "cognitive" cluster from each group, (i.e., Alogia and Attentional Impairment from the negative group with Positive Formal Thought Disorder and Bizarre Behavior from the positive group) suggest that a single feature of the illness is being tapped by both sets of measures. The possibility that "positive" and "negative" types of cognitive disturbance are

independent is not supported by these results. Quite to the contrary, the results suggest that cognitive disturbance, whether taking the form of Alogia, Attentional Impairment, Formal Thought Disorder, or Bizarre Behavior, may be part of a relatively unitary construct. The results of factor analysis of the positive and negative symptoms illustrate that this general dimension of cognitive disturbance not only incorporates both "positive" and "negative" constituents, but also that this factor was most prominent in the present sample.

Comparing the results of principal components analysis performed by Andreasen and Olsen (1982) to those obtained in the present study it is apparent that one (or both) of the following may be true: (a) the samples studied differed in presentation of the symptoms; or (b) our rating of the symptoms differed from theirs. In the Andreasen and Olsen study, the most salient principal component (accounting for 42% of variance) was one in which Alogia, Avolition/Apathy, and Anhedonia (positive loadings), and Delusions (negative loading) had the greatest weight. This "bipolar" factor most resembles the second principal component extracted in the present study, which before rotation, had positive loadings on each of the positive, and negative loadings on each of the negative symptoms. In the present study the first principal component (which accounted for 42% of variance) appeared more a severity factor, with

(before rotation) at least moderate loading on all symptoms except Delusions, Hallucinations, and the Breadth of Psychosis Scale. The second factor found by Andreasen and Olsen agrees in some respects with the structure of loadings on Factor 1 found in the present study. Positive Formal Thought Disorder and Bizarre Behavior had similar loadings on this factor, as did Attentional Impairment and Alogia. Considering Andreasen and Olsen's Factor 1 and Factor 2 simultaneously, in fact, suggests that four separable "clusters" of symptoms are present in their data that resemble quite closely the findings of the present study. These clusters are represented by: (a) Positive Formal Thought Disorder and Bizarre Behavior; (b) Affective Flattening, Avolition/Apathy, and Anhedonia; (c) Attentional Impairment and Alogia; and (d) Delusions and Hallucinations. Unlike the results of principal components analysis in the present study, however, Positive Formal Thought Disorder and Bizarre Behavior bore no discernible relationship to Attentional Impairment and Alogia.

Symptom Clusters and Their Correlates

Symptoms and premorbid social adjustment. It was hypothesized that negative symptoms and poor premorbid social adjustment would be related. This relationship was found in comparison of positive and negative symptom groups, but when the mixed group was included, no effect of group

membership on PAS scores was detected. This suggests that premorbid social adjustment differed only between groups with relatively "pure" positive and negative symptomatology. Consistent with this interpretation and most interesting in light of the interrelationships found in analyses of the clinical scales, PAS scores were related selectively to the core cluster of negative symptoms, and bore little relationship to either cognitive disturbance or core positive symptom clusters. These results both support the hypothesized relationship between premorbid adjustment and negative symptomatology, and validate in part the clustering of symptoms.

Relationships between symptoms and neuropsychological performance. The separability of the three clinical symptom clusters or factors extracted in the present study was apparent in their relative association with neuropsychological tests and scales. The symptoms of Alogia, Attentional Impairment, Positive Formal Thought Disorder, and Bizarre Behavior (i.e., the "cognitive cluster of symptoms") were associated with widespread deficits, particularly on tests of language, attentional, and memory functioning. This group of symptoms was also most related to deficiencies in global neuropsychological functioning, and to poorer estimated premorbid intellectual functioning.

The "core negative" cluster of symptoms (Affective Flattening, Avolition/Apathy, Anhedonia) shared with the

cognitive disturbance cluster a relationship to defects of attentional functioning, but did not share the association with disruptions of language and memory functions.

The "core positive" symptom cluster (Delusions, Hallucinations, Breadth of Psychosis) was generally associated with relatively better performance on neuropsychological tests. Only impairment of motor functions was associated slightly more with this cluster of symptoms than with others.

Evidence of deterioration from previously higher levels of intellectual functioning was apparent only for the core negative symptom cluster. Deterioration indices failed to relate to either the cognitive disturbance or the core positive symptom cluster. In fact, it appeared that clinical symptoms of cognitive disturbance were more related to poor premorbid intellectual functioning and continuation of functioning at this low level. In contrast, the core positive symptoms were associated with higher estimates of premorbid ability and relatively sustained functioning at this level. The core negative cluster, however, appeared related to conspicuous deterioration of functioning. It was the only symptom cluster significantly associated with the global deterioration index (D1). Furthermore, the core negative symptom cluster was equal to the core positive cluster in its direct association with the premorbid index,

while the cognitive disturbance cluster was inversely related to the PREMORBID index.

To summarize the associations between neuropsychological functioning and the three clinical symptoms clusters, it appeared that:

1. The cognitive disturbance cluster of symptoms was most associated with significant impairments of language and memory functions, however overall levels of functioning, and evidence of low premorbid ability.

2. The core negative cluster of symptoms was associated as strongly as the cognitive disturbance cluster with impairments of attentional functioning, but not with language, memory, or estimated premorbid levels of functioning. The core negative cluster appeared more related to deterioration of functioning than other symptom clusters.

3. The core positive cluster of symptoms was associated less with impairments of neuropsychological functioning and was not associated (as was the cognitive disturbance cluster) with evidence of poor premorbid ability, nor was it associated (as was the core negative cluster) with evidence of intellectual deterioration.

Relationships between symptoms and CT-scan measures.

Patients classified into positive and negative symptom groups according to the criteria of Andreasen and Olsen (1982) did not differ significantly on any of the CT

measures. Only for SPR was even a trend noticed for groups to follow the hypothesized relationship between negative symptom profile and increased CT-scan abnormality.

Among the individual measures of negative and positive symptoms, only two significant relationships to CT-scan measures were obtained. VBR was inversely related to Alogia, while SPR was directly related to the Breadth of Psychosis Scale. Each of these findings contradicts the hypothesized relationship between negative symptomatology and CT-scan abnormality. The pattern of relationships between the CT-scan findings and individual negative symptoms suggests, however, that the heterogeneity of SANS subscales may have obscured a direct association of some negative symptoms with VE and CA. For each of the CT measures, correlations were positive for the three SANS subscales comprising the core negative symptom cluster (Affective Flattening, Avolition/Apathy, Anhedonia), while correlations with the two SANS subscales that contribute to the cognitive disturbance cluster (Alogia and Attentional Impairment) were either negative or lower in magnitude. If one simultaneously considers, for example, the relationships of CT indices to Affective Flattening and Alogia, Alogia can be seen as a suppressor variable. The correlations of either VBR or SPR with Affective Flattening were significant if Alogia was partialled.

These analyses provide support for an association between CT-scan abnormalities and negative symptoms, but only if negative symptoms are considered in the more narrow sense that was advocated earlier in discussing the interrelationships among the clinical symptoms and the relationships between symptoms and neuropsychological test performance.

In a similar way, the set of "positive" symptoms considered as a homogeneous group was largely unrelated to CT-scan findings. It was found, however, that CT-abnormality was inversely related to the two positive symptoms contributing to the cognitive disturbance cluster of symptoms (Bizarre Behavior and Positive Formal Thought Disorder), while positive relationships were found between the CT-measures and two of the measures comprising the core cluster of positive symptoms (Hallucinations and the Breadth of Psychosis Scale). These results are consistent with those obtained in comparison of CT-scan measures and negative symptoms; suggesting again that CT-scan abnormality was least associated with the cognitive disturbance cluster of symptoms.

More surprising were the significant association of SPR with the breadth of psychosis scale (the Breadth of Psychosis Scale), and the correlational trend ($p < .10$; two-tailed) of VBR with Hallucinations. The popular hypotheses that positive symptoms are inversely related to

CT-scan abnormality are at odds with these findings. At best, the results suggest that the "thought disorder" and "bizarre behavior" aspects of positive symptomatology may be inversely related to CT-scan abnormalities in the present sample.

The relationships between symptoms and CT-scan measures in the present sample point to a general association of structural atrophy and the core clusters of either negative or positive symptoms, although this association was more consistent with respect to the negative symptoms. The cognitive disturbance cluster of symptoms was less, or inversely related to CT-indices of structural degeneration.

It is possible that associations of CT-abnormality with negative symptoms found by other investigators have been related more to the core cluster of negative symptoms, and that decreased incidence of positive symptomatology in CT-positive patients found previously was due to the thought disorder and bizarre behavior components of the cognitive disturbance cluster. It is possible also to conclude simply that patients in the present sample who manifested greater evidence of CT-abnormality tended to be "higher functioning", be better educated, and manifest less severe illness in global terms. The cognitive disturbance cluster of symptoms, which in factor analysis was found to account for more variance than either of the other principal components, may be most representative of global severity of

illness, and this was found least associated with CT-scan abnormality. That an inverse relationship between severity of illness and CT-scan abnormality might exist is directly opposed to the Type I/Type II distinction. Such a conclusion would also be difficult to support given previous findings.

It seems most likely that in our sample the symptoms of cognitive disturbance were more prevalent than found in other investigations and that this cluster of symptoms is largely independent of CT-scan status. The present results did favor an association of CT abnormality with the core negative cluster of symptoms, in agreement with the Type I/Type II distinction. The direct association of SPR with the Breadth of Psychosis Scale and the trend for VBR to relate directly to severity of hallucinations, may be due to the absence of such symptoms in the cognitive disturbance cluster, which tended to be inversely related to CT scan abnormalities. In other words, patients with least CT abnormality may have manifested primarily cognitive disturbance symptoms. The remaining patients, with relatively greater indices of structural degeneration, manifested more of the symptoms least associated with cognitive disturbance, including hallucinations and the breadth of psychosis measures.

Premorbid Social Adjustment

The results tended to support the hypothesized association of poor premorbid social adjustment and increased negative symptomatology. In the comparison of positive and negative groups defined according to the criteria of Andreasen and Olsen (1982), the negative group had significantly higher PAS scores. Support for the association of individual negative symptoms and poor premorbid social adjustment was also provided by the significant correlations of PAS scores with the sum of SANS subscale scores and the SANS Global Total Score. It was found, however, that poor premorbid social adjustment was more directly related to measures from the core group of negative symptoms (Affective Flattening, Avolition/Apathy). The hypothesis that PAS scores would be inversely related to positive symptoms was not supported. Premorbid adjustment appeared to bear little relationship to either the negative or positive components of the cognitive disturbance cluster of symptoms. Thus, while the hypothesis that poor premorbid social adjustment and negative symptoms was supported, it is likely that this relationship was due only to the more circumscribed cluster of core negative symptoms.

The hypothesis that PAS scores would be related to neuropsychological impairment was weakly supported. Only three individual neuropsychological tests were related

significantly to PAS scores: a verbal memory task (Wechsler Memory Scale, Logical Memory Subtest), a receptive language test (Syntactic Comprehension) and the Digit Symbol subtest of the WAIS-R. In each case, poorer performance was related to higher PAS scores (poorer premorbid adjustment). Higher PAS scores were not significantly related to better performance on any neuropsychological test. Thus it is not probable that these correlations were merely chance occurrences. There were, however, no significant neuropsychological scale correlates of the PAS, suggesting that neuropsychological deficits associated with poor premorbid social adjustment were neither specific nor widespread in this sample.

None of the CT measures was significantly related to PAS scores for the total sample. There was a difference, however, between VBR and SPR, with VBR positively, and SPR negatively related to PAS scores. Furthermore, when the index of premorbid intellectual functioning was partialled, VBR was significantly correlated with PAS scores, but SPR was not. Such findings may be relevant to the possibility that VBR and SPR are distinguishable, but fail to support the hypothesized association between premorbid adjustment and CT abnormalities.

It was hypothesized that poor premorbid social adjustment would be related to earlier age at onset and lower levels of educational attainment, but only the latter

association was substantiated. Given that scores on the PAS reflect in part success in school before the onset of the illness, along with the problem (discussed in the Introduction) of distinguishing "early morbid" or prodromal symptoms from "premorbid" adjustment, this finding should probably not be interpreted too strongly.

In summary, higher PAS scores were associated with negative-symptom-group classification, with more negative symptoms (especially core negative symptoms) and with some neuropsychological impairment. PAS scores were largely unrelated to CT measures, although there was a statistical effect for higher PAS scores to be more related to VBR than to SPR. While PAS scores were related to educational level, as was hypothesized, a clear association of premorbid adjustment with course (earlier onset) was not found.

As was discussed in the section on Positive and Negative Symptoms, the role of premorbid social adjustment appeared prominent in this sample only given the revised clustering of symptoms.

Neuropsychological and Structural Indices of
Degeneration

Association of Neuropsychological Performance and CT-scan
Findings

A most unanticipated result of this study was the strong association of CT-abnormality with better performance on many neuropsychological tests. This effect appeared to depend primarily on an association of CT-scan abnormality with measures usually associated with premorbid intellectual functioning, and the premorbid index was related significantly to all three CT-scan measures. Further, among the significant neuropsychological test correlates of the CT-scan measures, most were "hold" measures, (i.e., Information and Vocabulary subtests of the WAIS-R, as well as certain language and memory tests). Given the relatively strong relationships observed between measures of premorbid intellectual functioning and increased evidence of structural deterioration, it is not surprising that only those neuropsychological measures least dependent on general intellectual and premorbid abilities were found to correlate negatively with CT-scan abnormalities. Thus, tests of motor and attentional functions were the only neuropsychological variables for which poorer performance tended to be associated with CT-scan abnormalities.

The association of estimated premorbid intellectual functioning with the CT-measures makes the relationship of deterioration and neuropsychological impairment with CT abnormality difficult to assess. It might be argued that the significant associations of FHI and SPR with the index of global deterioration (D1) were due to premorbid differences alone. Neither FHI nor SPR was significantly more strongly correlated with deterioration indices than with the PREMORBID index. Statistically controlling for the premorbid index (by partialling it from the CT X D1 correlations) also resulted in attenuation of these relationships, although they remained significant.

Regardless of the strength of the relationship between indices of deterioration and CT-scan abnormality, it is striking that the patients evidencing brain atrophy showed considerably better functioning selectively on neuropsychological tests considered resistant to brain damage, while they performed other tasks at levels similar to the rest of the sample.

This pattern resembles that found by Rieder et al. (1979) in their comparison of patients with and without sulcal prominence. In that study, the two groups were equal in Verbal IQ, but the group with sulcal prominence had lower Performance IQ. The discrepancy between Verbal and Performance IQ is similar to that found in the present sample. It should be remembered also that the two groups

studied by Rieder et al. (1979) were matched in level of adaptive functioning, which was considerable higher than that observed in the present sample. Moreover, overall intellectual functioning (Full Scale IQ) in their sample was average, while that of the present sample was in the low-average to borderline range.

The sample studied by Donnelly et al. (1982) also had significantly less impaired intellectual functioning than the present sample, with mean FSIQ for their total sample in the average range. The mean IQ of patients in their CT-normal group was, in fact, in the high average range. These data clearly indicate a difference in sample composition, and suggest an explanation for the apparently discordant findings between this study and that of Donnelly et al. (1982).

Given that assessed levels of intellectual and neuropsychological functioning reflect both premorbid abilities and cerebral compromise, one can picture four "types" of patient defined according to these two dimensions. The type with highest assessed functioning would be that with high premorbid ability and low degree of cerebral compromise. The type with lowest functioning would be that with poor premorbid ability and a high degree of cerebral compromise. Intermediate levels of functioning would be expected for the two groups characterized by either low premorbid ability and low degree of cerebral compromise,

or high premorbid ability and high degree of cerebral compromise. The differences in performance of these two intermediate types should be related to the relative dependence of tasks on premorbid abilities, and the relative sensitivity of the tasks to cerebral compromise.

It seems likely that of these four types of patients, the present sample includes few of those patients that would be expected to fall in the "highest" functioning category (i.e., patients with high premorbid ability and minimal cerebral compromise). This was apparent in the findings of overall intellectual and neuropsychological impairment of this sample compared to others. If it is true that our sample preferentially included only patients of the "intermediate" and "lowest" expected levels of functioning, then the association of cerebral compromise and premorbid ability should be expected.

While these sampling considerations may help to explain the results of the present work, it seems unlikely that they alone could account for the strength of the association between premorbid ability (or educational achievement) and CT-scan findings. While the fourfold model would predict lowest functioning among patients with both CT-scan and premorbid deficits, the results suggest that among patients manifesting the lowest levels of functioning many were patients without CT-scan abnormalities. These patients might be characterized in clinical neuropsychological terms

as having static cerebral dysfunction of long duration; a picture more akin to that of borderline intelligence or mild mental retardation due to congenital or perinatal compromise.

These two considerations taken together would account for the apparent contradiction between our results and those of other investigators:

1. that the sample preferentially excluded patients at the highest levels of functioning, and
2. that there was an overrepresentation of those patients manifesting low premorbid abilities due to factors that are not reflected by CT-scan abnormalities.

The second of these sampling considerations is supported by the difference in symptom presentation between the present sample and that of Andreasen and Olsen, which was discussed earlier. In their sample, relatively "pure" clusters of positive and negative symptoms appeared prominently. In the present sample, the most salient symptomatology was that which I have described as the symptoms of cognitive disturbance. Differentiation of the "purer" positive and negative symptoms was observed in our sample secondarily. Moreover, it was the symptoms of cognitive disturbance that were most clearly related to neuropsychological impairment. Each of the core symptom clusters was less associated with neuropsychological compromise.

Differentiation of VE and CA

Previous findings that indices of VE and CA were not highly correlated, and suggestions that independent processes might be represented by these two measures (Nasrallah, 1982; Dewan et al., 1984) led to exploration of the differences between these variables.

It was found in this study, as in previous ones, that VBR and SPR were not significantly correlated. Significant ($p < .05$, two-tailed) differences in the relative associations of each CT-measure with other measures were found. Higher SPR was found more related than VBR to higher education level, the global deterioration index (DI), and lower scores on the MOTOR, ANTERIOR LEFT, and ANTERIOR scales. There were also trends for differences to appear in the relative associations of VBR and SPR with clinical measures, with VBR (more than SPR) negatively correlated to Alogia, and positively associated with PAS scores. These statistically selected measures were not surprisingly able to define canonical variates on which VBR and SPR were well separated. This statistical representation was intended simply to condense the results of univariate findings. Indeed, finding five "significant" ($p < .05$) differences in 30 comparisons is not in itself a highly improbable event, particularly given the fact that three of the neuropsychological variables are strongly interdependent.

Taking a more justifiably conservative statistical approach (e.g., choosing an alpha level of .001, or less than .05 / 30), the hypothesis that VBR and SPR differ in their associations with demographic, clinical, or neuropsychological variables would be rejected.

It is intuitively appealing to speculate that CA may be more associated with intellectual deterioration and more anterior dysfunction consistent with dorsolateral cortical compromise, while VBR might relate more to defects in sociosexual adjustment (premorbid asociality) linked to periventricular atrophy. Nevertheless, such speculations are at best marginally supported by the results of this investigation.

Generalizability of Findings

Sampling Considerations

The results of the present investigation differ from previous ones in several critical respects, and some of these differences have been attributed to sampling considerations. How could such differences occur? The sample investigated in the present study was similar in a number of basic respects to those employed in previous investigations. The mean and distribution of age was close to most other samples that have been studied with similar

methods (e.g., Jeste et al, 1982; Andreasen & Olsen, 1982; Donnelly et al., 1980; Cannon-Spoor et al., 1982; Nasrallah et al., 1983; Dewan et al., 1983).

The sex composition of the present sample, with almost equal representation of males and females, is similar only to that of Andreasen and Olsen (1982). Most other investigations have included primarily, or exclusively, males.

Age at onset tends to be relatively uniform in any sample of chronic schizophrenics, and that found in the present sample (mean = 19.8 years) is fairly representative. Patients with very early onset were less represented than, for example, was found in the Cannon-Spoor et al. (1982) study, where 65% of patients had onset age at 18 years or younger. Although not many of our patients had very early onset, the present sample tended to manifest illness somewhat earlier than in several other studies (e.g., Andreasen et al., 1982; Nasrallah et al., 1982, 1983). As is true for onset age, range of education differs little from sample to sample. Most patients tend to complete the 10th or 11th grade, many complete high school, and a smaller number go on to complete part or all of college. Our sample is representative in these respects.

The duration of illness in the present sample (mean = 12.5 years) compares only to that found in the Jeste et al. (1982) or Weinberger et al. (1979) studies. Most

other studies have included patients ill for only four to seven years. An exception is the series of studies by Johnstone, Owens, and their colleagues, in which much older patients were subjects.

It is most difficult to compare "absolute" levels of psychopathology in different samples. GAS scores, for example, may provide a reasonable index of overall functioning for comparisons of subgroups within a sample. It is less clear, however, that such values enable reasonable comparisons across samples. For example, mean GAS score for the present sample was 34.2, somewhat higher than that found by Andreasen and Olsen (1982). This difference is discordant with the fact that our sample had been ill longer, and more strikingly, included virtually no employable patients, while over half of their sample were able to work after discharge. On the other hand, their sample probably included more patients with acute exacerbations of chronic illness while the present sample included many patients who were relatively "stable." Thus, although our patients probably represent a more adaptively impaired group when considered over time, the impairments seen in the Andreasen and Olsen sample may have been greater at the time these patients were evaluated.

An important feature of the present sample is that it selectively includes patients for whom prognosis is poor. Similar to patients who are admitted to St. Elizabeth's

Hospital for participation in NIMH research projects, our patients all tended to have shown poor response to standard treatments. Further, while CPC does receive acute admissions, such patients were not included in the sample. Only patients for whom discharge was not imminent were even considered for transfer to the IPCU and admission to the protocol. Thus, those patients with more favorable prognosis, good response to treatment, and relatively good functioning between episodes (i.e., those able to live outside the hospital) were probably particularly underrepresented in the present sample.

Comparability of Experimental Measures

The frequency of patients classified into positive, negative, or mixed groups does not differ from that reported by Andreasen and Olsen (1982). SANS scores also appeared to follow a similar distribution. PAS total scores are somewhat higher than those reported by Cannon-Spoor et al. (1982) for their total schizophrenic sample, but are comparable to the scores obtained by that group in an inpatient sample.

The level of intellectual functioning of the present sample was quite low. The other relevant published reports in which IQ was specified, indicated significantly better performance (e.g., Rieder et al., 1979; Donnelly et al., 1980). In these studies, Full Scale IQ's were largely

average; in the present study, FSIQ's were generally in the borderline range. Similarly, while Donnelly et al. (1980) found approximately half of the their sample to score below "cutoff" levels on tasks used for the identification of "organicity", most patients in the present sample were in the "brain damaged" range on similar measures.

The prevalence of CT-scan abnormalities in this sample is comparable to previous reports with respect to VE (approximately 30% abnormal as measured by VBR). The failure to classify any patients as having "abnormal" FHI may reflect an overly strict criterion. If it were assumed that the proportion of abnormal FHI's should approximate the proportion of abnormal VBR's, then a cutoff in the range of 31-32 (or about 1 sd above previously reported control means) would be more appropriate. Unlike Weinberger and his colleagues, who found VE more prevalent than CA, we found equal frequency of VE and CA. It may be that the absence of a control group in the present study explains this difference (i.e., that our VBR ratings were overly conservative). The similarities in distributions of measurements for VBR argues against this interpretation. It is also possible that our cutoff for CA was too lenient. This too seems unlikely given that a neuroradiologist who independently viewed the scans judged a similar proportion as manifesting mild to moderate atrophy. Given the number of patients in this sample it is impossible to generalize

about population parameters of VE and CA, but it does appear that this sample may manifest relatively more CA than others.

Mean ratings of VBR, FHI, and SPR are quite similar to those found by other investigators. The number of patients showing extreme values of VBR, however, is somewhat lower than was reported by Weinberger et al. in their original (1979) study. The mean FHI found in the present sample was actually higher than that found in the Dewan et al. (1983) study. As was the case for VBR, however, our sample appeared to have fewer extreme values of FHI.

None of the distributions of CT measures appeared to reflect bimodality. The distribution of VBR was roughly normal, that of FHI negatively skewed, and that of SPR roughly rectangular (see Figure 1). Given the sample size of the present study, the hypothesis that the schizophrenic population distribution of VBR (or of other measures) is bimodal cannot be rejected. Unlike the data of Andreasen, Olsen, Dennert, and Smith (1982), however, the present results do not support such an hypothesis.

Influence of Demographic and Course Variables

Considering clinical classifications (into positive, negative, and mixed groups), clinical symptoms, and historical measures, only the PAS and one "negative" symptom (the Avolition/Apathy subscale of the SANS) bore significant

relationships to either demographic or course variables. The finding that PAS scores were inversely related to education level might be interpreted as indirectly suggesting earlier onset of symptoms and interference with school performance. This interpretation is difficult to support, given that there was no significant overall relationship between age at onset and PAS scores, along with the fact that PAS scores are based in part on academic functioning.

In the Cannon-Spoor et al. (1982) study, the significant association between early onset and PAS scores was due almost exclusively to the nine (of 40) patients in their sample with onset age of 15 years or less. Thus, the present findings (or absence thereof) may be related to the fact that a restricted range of onset age was observed.

The relationship of neuropsychological performance to demographic and course variables tended to bear out the major hypotheses. As was hypothesized, education level and the index of premorbid intellectual functioning were significantly related. Education level was also associated with the GLOBAL and LANGUAGE scales.

While age at onset was not significantly related to the PREMORBID index, it was positively correlated to this index and to every other neuropsychological scale, significantly so in the cases of ANTERIOR RIGHT and ANTERIOR scales. These results tend to support the association of

later onset with better cognitive functioning.

The indices of deterioration from previous levels of functioning were generally associated with age, education, and duration of illness, as was hypothesized. Interpretation of these relationships is clouded, however, by the unexpected finding that older patients (and thus patients who had been ill longer) showed higher estimated levels of premorbid functioning. When the premorbid index was partialled, none of the deterioration indices was significantly related to age, education, or duration of illness. Therefore, no direct support for an association between the length of illness and intellectual deterioration is provided.

Sex differences in neuropsychological test performance were limited to uncorrected motor tests, the "Closure" test, and the test for finger gnosis (right hand administration). The sex differences in raw motor test scores were expected, and fell within the range of sex differences found for normal subjects on the same tasks (Fromm-Auch & Yeudall, 1983; Gardner, 1979). Sex differences on closure and finger gnosis tests were not predicted, but are not surprising given theoretical differences in the degree of lateralization in each sex. The fact that males performed better on the closure test is consistent both with theories of male superiority in visuospatial processing, and with the hypothesis of greater hemisphere specialization in males.

The sex difference in finger gnosis is also in accord with the theory of greater hemisphere specialization in males. The fact that differences were apparent only for the right hand presentations is further interesting in light of Semmes' (1969) work demonstrating finer somatotopic tuning of left post-central regions.

No general conclusions regarding sex differences or hemisphere specialization are meant to be made on the basis of these observation on a small, neurobehaviorally abnormal sample. Certainly, the presence of "sex differences" on two of fifty comparisons is not an unlikely event by chance. The point is rather that the sex differences observed in the present sample are not unusual in light of brain-behavior theory and are unlikely to have had significant impact on other results.

No significant sex effects were noted on measures of VBR, FHI, or SPR. Each of the CT indices was directly associated with age and duration of illness, but these effects were only significant for VBR. As was the case in previous investigations, data from the present study do not enable assessment of differences between age and duration of illness in their associations with CT-measures. Until either very large samples or samples selectively including patients with early and late onset are studied, effects specific to duration of illness (and not age) will be impossible to address.

While age at onset was not significantly related to any of the CT-measures, each of the CT-measures was positively correlated to age at onset, in opposition to hypotheses that CT-abnormalities may be associated with early onset of illness.

Most unexpected was the highly significant direct relationship between education level and sulcal prominence. This finding, which certainly conflicts with theories relating CT-scan abnormalities to premorbid deficits and earlier onset of pathology, may be significant in interpreting the relationships between neuropsychological test results and CT-scan findings. The fact that education level was more associated with SPR than either VBR or FHI may also be significant in interpreting possible differences between the behavioral concomitants of VE and CA. It is of course impossible to determine whether chance differences in educational attainment, or premorbid intellectual differences resulting in longer success at school, have greater relevance to interpreting the correlations between CT abnormalities and better neuropsychological functioning. It is clear, however, that a consistent profile of better cognitive/intellectual/academic functioning was associated with evidence of structural atrophy.

Conclusion

Many of the findings presented here were not predictable in the framework of the hypothetical dichotomy between degenerative and non-degenerative forms of schizophrenia. It is likely that the differences between the results of this study and others are largely due to differences in sample selection. In effect, the present study involved primarily those patients who would be called "Type II" schizophrenics in the sense used by Crow (1980). All patients had relatively poor prognosis according to standard clinical indications; most had "irreversible" syndromes, refractory to neuroleptic treatment, otherwise they would not have been present in the hospital for extended intervals or included in the study. Furthermore, almost all patients had moderate-to-severe neuropsychological compromise. In fact, it was only the absence of structural abnormalities, and the presence of florid psychotic symptoms in some patients, that would prevent the entire sample from being classified "Type II".

If the nature of the sample is taken into account, then some of the present findings are in fact consistent with the Type I/Type II dichotomy. Positive symptomatology was not associated with CT-scan abnormalities or poor premorbid social adjustment, nor were the "core" positive symptoms

(Delusions, Hallucinations) related to neuropsychological impairment. Moreover, the "core" group of negative symptoms was related to poor premorbid social functioning, to at least some neuropsychological deficits, and (more than other symptom clusters) with CT-scan abnormalities. Those findings that are not consistent with the positive/negative or Type I/Type II distinctions (i.e., the association of symptomatic and neuropsychological defects independent of premorbid social adjustment and CT-scan findings) may be most important for future research.

The concordance of symptomatic and neuropsychological dysfunction in patients without CT-scan abnormalities has at least one potentially significant implication. It appeared from the results that a process largely independent of the positive/negative dichotomy, premorbid social adjustment, and CT-scan findings, may contribute significantly to clinical psychiatric and neuropsychological impairment. This process would be characterized clinically as one in which a primary disturbance of thought and language is manifest. This process might stand in contrast to processes involving a defect of affect, volition, and hedonic approach behavior; or processes in which delusional behavior and hallucinatory experiences predominate.

It would certainly be premature to speculate on the basis of this small sample that a "Type III" syndrome in schizophrenia exists. In fact, the validity of Type I and

Type II syndromes has not been adequately demonstrated. Rather, the results demonstrate that severe clinical and neuropsychological impairments are not necessarily related to the neuropathology reflected in CT scans, and that the "defect state" is not necessarily a monothetic construct. The appeal of a dualistic model in which "functional" and "organic" types occupy opposite poles has been apparent in researchers' responses to the introduction of the Type I/Type II distinction. Findings of CT-scan abnormalities stimulated, and have continued to fuel, expressions of such a dichotomy. The results presented here suggest that the CT-scan may not serve as a rosetta stone for the identification of "organicity" in schizophrenia.

It might be argued that the concordance of severe clinical and neuropsychological impairments unrelated to CT-scan findings demonstrate the impact that "functional" forms of thought disorder may have on neuropsychological test results. In other words, staunch advocates of a Type I/Type II distinction might suggest that these impairments are representative of a particularly severe form of Type I disorder that renders neuropsychological inference invalid. Such an argument is impossible to refute, but is reminiscent of those advanced before the appearance in 1978 of the articles by Heaton et al., Malec, and Goldstein, each of which suggested that neuropsychological methods were indeed serving to identify "organicity" in schizophrenia.

I suggest that both clinical and neuropsychological methods are agreeing in the identification of neurobehavioral dysfunction that is not apparent in CT-scans. Such dysfunction might represent cellular loss in regions beneath the resolution of current CT-methods, potentially reversible neurometabolic disturbance, or atypical development of cerebral systems. The last of these is superficially most consistent with the neuropsychological findings suggesting impaired premorbid intellectual functioning and absence of deterioration from that level, but does not exclude (and might critically depend on) cellular loss and/or metabolic dysfunction occurring early in the life span.

A salient difficulty in interpretation of neuropsychological estimates of "premorbid" ability and "deterioration" is that such estimates are almost invariably linked to assessment of language function. To take an extreme example, if a patient suffering from acute expressive aphasia (without hemiparesis) were evaluated blindly using only the "premorbid index" and the "global deterioration index" designed for the present study, that patient (unable to respond to questions but able to comprehend and execute a visuomotor task), would be said to have poor premorbid ability and no deterioration from that level. It could be the case that specific involvement of left hemisphere functions accounts for the

neuropsychological impairments associated with the cognitive disturbance cluster of symptoms found in the present study.

On the other hand, developmental compromise affecting the normal course of cerebral lateralization and the acquisition of language may result in a similar pattern. In this case, however, it is not that specific impairment of localized cerebral functions has occurred, but rather that expected patterns of localized cerebral functions have never developed. It is conceivable that some of the evidence supporting hypotheses of lateralized dysfunction reflect not impairment of lateralized cerebral systems, but instead the absence of expected patterns of lateralization. Given that the expected functions of the dominant left hemisphere are better known, and that this hemisphere is probably more "specialized" both functionally and anatomically (Goldberg & Costa, 1981), lack of such specialization would lead to predictions of relative left hemisphere impairment in cases of developmental compromise.

Such questions may only be answered by more direct methods than those employed in the present study. Longitudinal assessments in high-risk samples or more thorough retrospective investigations of developmental history are required to address these issues. It seems justified, based on the results of the present study, for future investigations to consider seriously the role of premorbid intellectual abilities and the development of

cognitive skills in the assessment of current neuropsychological functioning.

Appendix 1

Subject Characteristics

Subj. No.	Age	Sex	Hand	Dx	Type	Years Ill	CPZEQ	FSIQ
1	23	M	R	1	POS	5	1000	76
2	26	M	R	2	NEG	5	220	81
3	29	M	R	1	NEG	9	210	84
4	33	M	R	1	MIX	12	280	82
5	38	F	R	2	NEG	21	1200	na
6	26	F	R	1	NEG	8	1800	80
7	20	M	R	5	NEG	6	380	70
8	45	F	L	1	NEG	22	500	104
9	38	M	R	3	POS	14	0	91
10	28	F	R	4	MIX	12	1000	na
11	45	M	R	4	MIX	25	1000	71
12	35	F	R	4	POS	na	na	na
13	40	F	R	2	MIX	15	5000	71
14	28	F	R	4	POS	10	1800	71
15	40	F	R	1	MIX	26	1600	na
16	29	M	R	4	NEG	8	600	69
17	29	F	R	2	MIX	8	600	76
18	21	M	L	1	NEG	4	1200	69
19	34	F	R	1	POS	6	1200	93
20	40	M	L	1	NEG	17	500	76
21	34	F	R	3	NEG	5	400	82
22	29	M	R	4	POS	12	315	77
23	35	F	R	4	POS	17	380	78
24	29	F	R	4	MIX	5	5000	77
25	25	M	R	2	MIX	5	1500	67
26	32	M	R	2	MIX	16	1500	88
27	20	F	R	4	NEG	3	2000	72
28	35	M	R	1	MIX	18	150	87
29	33	M	R	1	NEG	13	6500	97
30	48	F	R	4	POS	27	4000	112
31	33	M	R	1	POS	18	1000	79
32	47	F	R	5	POS	24	1600	94

Note. Hand, handedness. Dx, RDC diagnostic subtype: 1=Paranoid, 2=Disorganized, 3=Catatonic, 4=Undifferentiated, 5=Schizoaffective, mainly schizophrenic. Type, classification of Andreasen and Olsen (1982): POS, positive; NEG, negative; MIX, mixed. CPZEQ, dosage of medication at time of evaluation in chlorpromazine equivalents (from "The Initiation of Long Term Pharmacotherapy in Schizophrenia: Dosage and Side Effect Comparison Between Oral and Depot Fluphenazine" by N. R. Schooler, 1976, Pharmako. Psych., 9, 159-169.). FSIQ, Full Scale IQ, WAIS-R.

Appendix 2

Consent Forms

In the following four pages, photoduplications of the actual consent forms used in the study protocols are shown. The consent forms have been reduced in size (to 64% of original) to fit the margins. The first form is for the protocol "Brain-Behavior Relationships in Schizophrenia," which incorporates the clinical psychiatric and neuropsychological procedures. The second form is for the study "Neuroradiographic Evaluations of Schizophrenic and Affective Disorder Patients: Clinical, Biologic, and Genetic Correlates," which incorporates the CT-scanning procedures. The protocol procedures and these consent forms were approved by the Institutional Review Boards at both the New York State Psychiatric Institute & Hospital, and Creedmoor Psychiatric Center (where this study was conducted).

CREEDMOOR PSYCHIATRIC CENTER

INFORMED CONSENT FORM

Name of Principal Investigator Ronald O. Rieder M.D.

Affiliation of Principal Investigator Columbia University, Dept. of Psychiatry

Title of Study: Brain-Behavior Relationships in Schizophrenia

Purpose of Study: To gather systematic information about psychiatric history and mental functioning. To determine the reasons why people with severe psychiatric symptoms have difficulty with some tasks.

Procedure to be Used: Standard clinical questionnaires and tests. Neurological examination to check hearing, vision, reflexes and motor skills.

Description of Study including types and dosages of medication to be administered, if any; description of physical examinations, if any; expected benefits to be derived from this Study:

You will be interviewed on the ward by a member of the research team to complete a number of clinical questionnaires. You will also have a neurological examination by a physician from the research team. The interviews and test sessions will last approximately 2-3 hours each. There will be 4 such sessions. The neurological examination will last about 30 minutes.

Possible benefits include detecting any medical or neurological illness that might be contributing to your psychiatric problems. The clinical tests will also help assess your strengths and weaknesses and are often useful in making plans for you after your discharge. At a private hospital these exams would cost \$500-\$1000, but as a participant in this study you would receive this evaluation free of any charge.

A description of alternative services that might prove equally as advantageous:

The routine clinical examination that you will receive on the ward could be considered an alternative, but is not as thorough as the one you will receive as a participant in this research. Also, the clinical tests are not a part of the ward's routine clinical examination.

Projected duration of Study:

The 4 sessions are expected to be completed in 7-10 days time.

INFORMED CONSENT FORM**Possible adverse effects or side effects:**

There are no side effects. Some fatigue, from interviews or testing, is possible, but unlikely. You will not be graded on any of the tests. We will ask you that you do your best.

The nature of this Study and possible side effects (if any) have been clearly explained to me both in writing and verbally. I understand that the Creedmoor Psychiatric Center Institutional Review Board has approved the recruitment of subjects for this study. I understand that my participation in this Study is strictly voluntary. I may refuse to participate in this Study without my treatment being withheld or change in any form. I have the right to withdraw from this experiment any time if I do choose to participate. I understand that my right to privacy will be safeguarded, and if research papers are written I will not be mentioned by name.

I understand that should I have any questions about my participation in this program or any other relevant matter, I may call the Project Director or Director of the Unit, whose numbers are included in this Consent, and I will be given an opportunity to discuss in confidence any questions I may have with them, or with a member of the Institutional Review Board, if they are not available.

I further understand that in the event of physical injury resulting from the research procedures, medical treatment for injuries or illness is available, but financial compensation is not provided.

I have read the above, and I am presently willing to participate in this Study.

Project Director Ronald Rieder, M.D. Telephone Number 960-5553

Director of Unit Sukdeb Mukherjee, M.D. Telephone Number 212 464-7500, Ext. 2700

Signature of Participant _____ Date _____

Signature of Next-of-Kin or CPC Director's designee _____
(when applicable)

Date: _____

Mr./Ms. _____ is able to make a decision.
Name of Patient

regarding his/her participation in this Study. Participation in this study is in no way contraindicated for this patient.

Signature of Treating Psychiatrist _____

Date: _____

Original - Patient's Chart
Copy - Chairman, IRB

CREEDMOOR PSYCHIATRIC CENTER

INFORMED CONSENT FORMName of Principal Investigator Ronald Eder, M.D.Affiliation of Principal Investigator Columbia University, Department of PsychiatryTitle of Study: Neuroradiographic Evaluation of Schizophrenic and Affective DisorderPatients: Clinical, Biologic and Genetic Correlations

Purpose of Study:

To determine whether the anatomy of the brain has any relationship to serious psychiatric problems.

Procedure to be Used:

CT scan of the head.

This is a sophisticated type of x-ray that allows us to obtain a detailed picture of the different parts of the brain.

Description of Study including types and dosages of medication to be administered, if any; description of physical examinations, if any; expected benefits to be derived from this Study:

An appointment will be scheduled for you at the New York State Institute for Basic Research on Staten Island. Accompanied by a staff member from the ward you will go there in a car. The total amount of driving time and waiting would be approximately 3 hours, though the x-ray itself will take only 15 minutes. You will be asked to relax and lie still for 15 minutes on the x-ray couch while the picture is taken.

Possible benefits are that we might find something on the x-rays which would help us give you better medical care.

A description of alternative services that might prove equally as advantageous:

There is no real alternative to the CT scan. Simple x-rays of the head do not reveal the brain or its parts.

Projected duration of Study:

The day of the x-ray will be the only day of study for you.

INFORMED CONSENT FORM

(continued)

Possible adverse effects or side effects:

As with any other x-ray there is some amount of radiation used in making the picture. Large amounts of radiation have been related to cancer. However, the amount of radiation for this CT scan is actually less than the amount of radiation that is administered when a patient has a regular set of x-rays of the head.

The nature of this Study and possible side effects (if any) have been clearly explained to me both in writing and verbally. I understand that the Creedmoor Psychiatric Center Institutional Review Board has approved the recruitment of subjects for this study. I understand that my participation in this Study is strictly voluntary. I may refuse to participate in this Study without my treatment being withheld or changed in any form. I have the right to withdraw from this experiment any time if I do choose to participate. I understand that my right to privacy and the confidentiality of my participation in this project should I choose to participate will be safeguarded, and if research papers are written I will not be mentioned by name.

I understand that should I have any questions about my participation in this program, or any other relevant matter, I may call the Project Director or Director of the Unit, whose numbers are included in this Consent, and I will be given an opportunity to discuss in confidence any questions I may have with them, or with a number of the Institutional Review Board, if they are not available.

I further understand that in the event of physical injury resulting from the research procedures, medical treatment for injuries or illness is available, but financial compensation is not provided, and additional medical treatment is not covered.

I have read the above, and I am presently willing to participate in this Study.

Project Director Ronald Rieder, M.D. Telephone Number 960-5553

Director of Unit Sukdeb Mukherjee, M.D. Telephone Number (212) 464-7500 Ext.2700

Signature of Participant _____ Date: _____

Signature of Next-of-Kin or CPC Director's designee _____
(when applicable)

Date _____

Mr/Ms. _____ is able to make a decision.
Name of Patient

regarding his/her participation in this Study. Participation in this Study is in no way contraindicated for this patient.

Signature of Treating Psychiatrist _____

Date: _____

Original - Patient's Chart
Copy - Chairman, IRB

Appendix 3

Neuropsychological Test ReferencesMotor Tests

Hand Grip Strength. Reitan & Davison, 1974; Newman et al., 1984

Finger Oscillation. Reitan & Davison, 1974; Fromm-Auch & Yeudall, 1983

Motor Performance Battery. Denckla, 1974; Quitkin, Rifkin, & Klein, 1976

Bimanual Coordination & Dynamic Praxis. Luria, 1980; Christensen, 1975

Verbal Tests

Controlled Word Association. Benton & Hamsher, 1978; Goodglass & Kaplan, 1972; Borod et al., 1980

Auditory Discrimination. Wepman, 1958; Reitan & Davison, 1974; Caudrey & Kirk, 1979

Syntactic Comprehension. Menyuk, 1973

Picture Naming. Newcombe et al. 1971

Sentence Reading. Goodglass & Kaplan, 1972; Borod et al., 1980

Word Reading. Goodglass & Kaplan, 1972; Borod et al., 1980

Sentence Repetition. Spreen & Benton, 1968

continued

Verbal Tests (continued)

Complex Ideational Material. Goodglass & Kaplan, 1972;
Borod et al., 1980

Visuospatial/Somesthetic Tests

Popplereuter Figure Analysis. Christensen, 1975;
Luria, 1980

Spatial Block Span & Learning. Milner, 1971; DeRenzi
et al., 1977

Facial Recognition. Benton et al., 1975

Drawing Test. Piercy et al, 1960; Rosen, 1984

Closure. Wasserstein, 1980

Finger Gnosis. Kinsbourne & Warrington, 1962

Graphesthesia. Reitan & Davison, 1974; Reitan, 1969;
Matthews & Klove, 1964

Right-left Orientation. Reitan & Davison, 1974; Spreen
& Benton, 1968

Tests of Attention, Executive Functions & Behavioral
Programming

Target Detection. Rudel et al., 1978; Diller et al.,
1974

Trail Making Test [A; B]. Reitan & Davison, 1974;
Lilliston, 1970

Competing Programs. Christensen, 1979; Luria, 1980

Wisconsin Card Sorting Test. Berg, 1948; Drewe, 1974;
Nelson, 1976; Milner, 1963

continued

Tests of Learning & Memory

List Learning (Forms 1,2). Buschke, 1973; Buschke & Fuld, 1974

Recurring Figures Test. Kimura, 1963; Brooks, 1974; Milner, 1971

Associative Memory -Visual-. Unpublished test, available from Department of Biological Psychiatry, New York State Psychiatric Institute, New York

Wechsler Memory Scale. Wechsler, 1945; Prigitano, 1978; Logue & Wyrick, 1979; Power et al., 1979

Additional Tests

W.A.I.S.-R. Wechsler, 1945, 1981; Mattarazzo, 1978; DeWolfe, 1971

Raven Standard Progressive Matrices. Raven, 1960; Peck, 1970

Mini Mental State Exam. Folstein, Folstein, & McHugh, 1975; DePaulo et al., 1980

Purdue Pegboard. Goldberg & Smith, 1976; Costa et al, 1963

Appendix 4

Intercorrelations within Neuropsychological
Functional Scales

Intercorrelations of Neuropsychological Variables in the
Motor Scale

Variable	2	3	4	5	6
1. Hand Grip Strength (right)	.96	.57	.47	.31	.38
2. Hand Grip Strength (left)	--	.62	.56	.39	.45
3. Finger Oscillation (right)		--	.80	.40	.34
4. Finger Oscillation (left)			--	.45	.33
5. Motor Perf. Battery (right)				--	.94
6. Motor Perf. Battery (left)					--

Intercorrelations of Neuropsychological Variables in the
Verbal Scale

Variable	2	3	4	5	6	7	8
1. CWAT	.37	.71	.59	.29	.23	.15	.44
2. Auditory Discrim.	--	.26	.45	.19	.53	.25	.53
3. Sentence Repetition		--	.59	.30	.26	.21	-.32
4. Syntactic Comprehen.			--	.17	.55	.31	.32
5. Picture Naming				--	.10	.57	.40
6. Responsive Naming					--	.36	.34
7. Cx. Ideational Mater.						--	.29
8. Similarities, WAIS-R							--

Note. Signs for the correlations of the Auditory Discrimination Test (error score) with other variables were reversed. CWAT, Controlled Word Association Test.

Intercorrelations of Neuropsychological Variables in the
Perceptual Scale

Variable	2	3	4	PERCEP
1. Spatial Block Span (learning)	.47	.33	.48	.79
2. Facial Recognition Test	--	.54	.32	.81
3. Closure Test (total score)		--	.20	.68
4. Poppelreuter Figure Analysis			--	.69

Note. PERCEP is the Perceptual scale.

continued

Intercorrelations of Neuropsychological Variables in the Memory Scale

Variable	2	3	4	5	6	7	8
1. WMS-Logical Memory	.29	.44	-.17	-.15	.35	.23	.27
2. WMS-Visual Reprod'n.	--	.06	.46	.26	.56	.20	.39
3. WMS-Associate Lrng.		--	.01	-.03	.28	.45	.50
4. ALVS1			--	.37	.22	-.02	.28
5. ALVS2				--	.13	.05	-.04
6. Recurring Figs. net					--	.45	.21
7. BSRT total hits						--	.35
8. BSRT consistent LTR							--

	Variable							
	1	2	3	4	5	6	7	8
r with MEMORY scale	.40	.71	.53	.65	.34	.69	.57	.52

Note. WMS, Wechsler Memory Scale; ALVS1 and ALVS2, Associate learning, visual, forms 1 and 2 respectively; BSRT, Buschke Selective Reminding Test; LTR, long-term retrieval.

Intercorrelations of Neuropsychological Variables in the Somatosensory Scale; and Correlations with both the Somatosensory and Perceptual Scales

Variable	2	3	4	5	SOMAT	PERCEP
1. Graphesthesia (right)	.74	.12	-.09	.03	.56	.46
2. Graphesthesia (left)	--	.47	.36	.06	.81	.45
3. Finger Gnosis (right)		--	.84	.13	.78	.49
4. Finger Gnosis (left)			--	.22	.71	.55
5. Right-left Discrim.				--	.44	.46

Note. SOMAT, Somatosensory scale; PERCEP, Perceptual scale.

Intercorrelations of Neuropsychological Variables in the Attentional Scale

Variable	2	3	4	5	6	ATTENT
1. Digit Symbol, WAIS-R	.49	.23	.62	.43	.69	.81
2. Digit Span, WAIS-R	--	.28	.23	.46	.23	.72
3. Trails B (errors)		--	.22	.02	.10	.49
4. Trails B (time)			--	.10	.59	.62
5. Target Detection (errors)				--	.00	.43
6. Target Detection (time)					--	.69

Note. ATTENT, Attentional scale.

Intercorrelations of Neuropsychological Variables in the
Executive Scale

Variable	2	3	4	EXEC
1. Competing Programs	.10	.22	.29	.63
2. WCST, Categories achieved	--	.53	.23	.66
3. WCST, Perseverative errors		--	.34	.72
4. Picture Arrangement, WAIS-R			--	.70
Note. WCST, Wisconsin Card Sorting Test.				

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