Cognitive functioning in familial and nonfamilial groups at high-risk for schizophrenia

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COGNITIVE FUNCTIONING IN FAMILIAL AND NONFAMILIAL GROUPS AT HIGH-RISK FOR SCHIZOPHRENIA

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ABSTRACT

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Differences in the cognitive profiles of schizophrenic individuals who are family history positive and those who are family history negative have been reported throughout the literature. The purpose of this study was to clarify the cognitive deficits that characterize familial and nonfamilial groups at high-risk for schizophrenia. High-risk was defined as 1.) Genetic relatedness to an individual with schizophrenia, or 2.) Extreme scores on a measure of schizotypy (i.e., Chapman Scales of Psychosis Proneness). Twenty-three subjects were administered a battery of neuropsychological tests. ANOVAs revealed a significant interaction effect on a measure of verbal learning and a double dissociation on auditory and visual working memory tasks. It appears that familial risk may be more associated with deficits on tasks that rely upon rapid encoding and organization of visual information, while nonfamilial risk demonstrated a greater association with abnormalities in left hemisphere mediated verbal abilities.
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The aim of the following study is to clarify the cognitive deficits that characterize groups at high-risk for schizophrenia. Towards this end, I will compare the cognitive performance of two groups that differ in their degree of risk for developing the disorder. This study design involves contrasting the cognitive test performance of individuals who are at high-risk (HR) for schizophrenia. The study will include two high-risk groups. Traditionally, high-risk groups have been defined using two criteria: 1) genetic relatedness to an individual with schizophrenia, and 2) extreme scores on measures of schizotypy.

The first group is considered HR because it is widely accepted that schizophrenia has a genetic component (Gottesman & Shields, 1982). Family, twin, and adoption studies have demonstrated that “the risk for developing schizophrenia varies according to the amount of gene sharing and not the amount of environment sharing” (Gottesman, 1991). Therefore, individuals who have a biological relative with schizophrenia are at greater risk for developing the disorder than are those without a family history, because they share the genotype for schizophrenia. Accordingly, one high-risk group will consist of family members of individuals with schizophrenia. However, because not all individuals who develop the disorder have a family history of schizophrenia, a second group will be selected based upon scores on a standard measure of schizotypy. Measures of schizotypy assess symptoms that are consistent with schizophrenia but that
are not great enough in severity to warrant a formal psychiatric diagnosis. The schizotypy group is considered to be at high risk for developing schizophrenia based on their endorsement of deviant or unusual cognitive and perceptual experiences (Chapman & Chapman, 1985; Chapman, Chapman, Kwapił, Eckblad, & Zinser, 1994). In the past, individuals with schizotypy have been identified using self-report measures. The current study will use the Chapman “Psychosis Proneness” Scales (Chapman, Chapman, & Miller, 1982) to measure the schizotypy construct. The Chapman scales cover a number of domains of behavior and experiences that parallel the positive and negative symptoms seen in individuals with schizophrenia. Individuals who obtain significantly elevated scores on these scales demonstrate a notable deviation in their experiences and beliefs regarding themselves and the world, although they do not meet formal diagnostic criteria for schizophrenia. Because of this, the group is thought to be closer to a threshold for psychosis (Chapman & Chapman, 1985; Chapman et al., 1994).

The performance of these two groups will be compared on a battery of cognitive tests previously found to be sensitive to deficits in individuals with schizophrenia and their biological relatives. The cognitive deficits associated with schizophrenia are thought to represent core features of the disorder (Goldberg & Gold, 1995; Goldstein, Allen, & van Kammen, 1998) and as such, possible behavioral markers of the genetic risk for developing the disorder (Kremen, Faraone, Seidman, Peppe, & Tsuang, 1998). However, similar deficits in cognitive functioning have also been found among groups without a family history of schizophrenia (Coursey, Lees, & Siever, 1989; Gooding, Kwapił, & Tallent, 1999; Lenzenweger & Korfine, 1994; Suhr, 1997; Trestman, et al., 1995; Voglmaier, Seidman, Salisbury, & McCarley, 1997) for whom the risk of developing the disorder is based upon being on the lower end of a hypothetical continuum of psychotic disorders (Chapman & Chapman, 1985; Chapman et al., 1994).
Discerning the cognitive profile of these two groups, distinct in their risk for schizophrenia, may help to explicate the pathogenic process or processes behind this debilitating disorder. It is believed that this may be realized by identifying the behavioral correlates of specific regions of CNS dysfunction, including areas of disturbance common to both groups, as well as, and more importantly, the areas which are unique to each risk group. Based upon these findings, purposed explanations regarding the path and origin of the abnormal processes involved in producing the identified cognitive dysfunction in at-risk groups as well as their schizophrenic counterparts, may then be evaluated. Therefore, this investigation is attempting, in part, to address the unresolved issue of etiological heterogeneity in schizophrenia. Differences in the cognitive profile between familial and nonfamilial high-risk groups would suggest potential differences in underlying pathophysiology and hence potential differences in etiology. The study moves towards an understanding of this question by attempting to clarify the biobehavioral signs that mark these separate paths of risk. Before discussing the details of the current study, it is necessary to review several key areas of research that have contributed to the question at hand.
CHAPTER 2

LITERATURE REVIEW

Characteristics of Schizophrenia

Schizophrenia is a chronic disorder in which psychiatric symptoms and deficits in social and cognitive functioning predominate. Typically, the disease is characterized by episodes of florid psychosis, followed by periods of relative quiescence (American Psychiatric Association, 1999). The clinical picture often consists of multiple hospitalizations and in many cases chronic use of antipsychotic medications to control the florid symptoms (Wiersma, Nienhuis, Slooff, & Giel, 1998). Schizophrenia is also associated with both social and vocational impairment as well as a devastating loss in quality of life (Heinrichs, Hanlon, & Carpenter, 1984).

The prevalence rate for schizophrenia in the general population is approximately 1%, with an equal distribution between males and females (American Psychiatric Association, 1999). Typical onset is in the late teens and early 20’s for men, with women tending to manifest clinical symptoms later in their adult lives (i.e., late 20’s) (Häfner, Maurer, Löfler & Riecher-Rössler, 1993). Retrospective studies have shown that an earlier age of onset is associated with more severe symptoms and a worse outcome (Castle & Murray, 1991). Interestingly, a disproportionate number of men are characterized by early onset, poor neuroleptic response, more negative symptoms, and poorer premorbid functioning, indicating that being male may be a risk factor for a more severe form of the disorder (Castle & Murray, 1991).

Several explanations, including differences in socialization (Hall, 1985) and specific
patterns of cerebral lateralization (Hoff et al., 1992), have been put forth over the years to explain these sex differences. Recently, researchers have been looking at the contribution of hormones and specifically the role of estrogen on dopamine turnover in the prefrontal cortex (Häfner et al., 1993), an area previously implicated in schizophrenia (Breier et al., 1992; Weinberger, 1987; Weinberger, Berman, & Zec, 1986). These studies (Todd, 1992) suggest the possibility that dopamine may have a neurotrophic effect on developing structures in the prefrontal cortex (PFC), and specifically the dorsolateral prefrontal region (Weinberger, 1987), leading some to conclude that estrogen may moderate more severe impairment.

The neurotransmitter dopamine has long been implicated in the clinical symptoms of schizophrenia (Karoum, Karson, Bigelow, Lawson, & Wyatt, 1987). The dopamine hypothesis of schizophrenia purports that psychiatric symptoms arise as a result of too much dopamine in certain CNS pathways. This conceptualization led to the development of drug therapies (i.e., dopamine antagonists) which are relatively effective at treating the positive symptoms (e.g., hallucinations, delusions) of schizophrenia. However, schizophrenia is a heterogeneous illness characterized by positive as well as negative (deficit) symptoms. Heterogeneity is reflected within the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). In the DSM-IV, schizophrenia is divided into 5 subtypes; determination of the subtype is based upon which psychiatric symptoms are prominent at the time of hospitalization or diagnosis (American Psychiatric Association, 1999). The DSM-IV symptoms can be divided into those which have positive features and those which have negative features. Positive symptoms represent an excess of normal functioning and include hallucinations and delusions. Negative symptoms are those which represent a deficit in normal functioning and include cognitive deficits, loss of motivation, social isolation, apathy, and flattened affect. Unlike positive psychiatric symptoms, which fluctuate considerably over the
course of the disorder (e.g., due to medication status, life stress, and time) deficit symptoms including cognitive impairment tend to remain relatively stable (Nuechterlein & Dawson, 1984; Sweeney, Haas, Keilp, & Long, 1991) making their presence or absence a better indicator of the underlying disease process and better predictors of long-term outcome (Green, 1998; Kremen et al., 1998). Heterogeneity in cognitive function is also present in schizophrenia with some patients exhibiting severe impairment while others exhibit relatively normal cognitive function (Allen, Goldstein, & Warnick, in press; Goldstein et al., 1998; Kremen, Seidman, Faraone, Toomey, & Tsuang, 1999, Palmer et al., 1997), so that there is not a single prototypic cognitive profile that adequately describes the majority of patients with schizophrenia. However, risk status may be one variable that contributes to the heterogeneity of cognitive function present in schizophrenia, an issue that has yet to be examined but that is investigated in the current study.

Etiology

Genetics of Schizophrenia

While it has been recognized for some time that schizophrenia is consanguineous, the relative contribution of genetic as opposed to environmental factors has not always been clear. Findings in the areas of family, adoption, and twin studies indicate that schizophrenia runs in families due to shared genes rather than shared environment (Gottesman, 1991; Gottesman & Bertelson, 1989; Gottesman & Shields, 1982; Kendler & Diehl, 1993; Kendler & Gruenberg, 1984, Kety, 1988). These studies have demonstrated that the magnitude of risk for developing schizophrenia increases as the amount of shared genetic material increases, while shared environmental factors were not significantly related to increased risk (Gottesman, 1991). In the case of dizygotic twins or other first-degree relatives (who share 50% of their genes), the risk for
developing the disorder is at a concordance rate of approximately 9-17%. Second-
degree relatives (who share 25% of their genes) have a concordance rate of
approximately 3-6%, and monozygotic twins who share 100% of their genes have a
concordance rate of approximately 45-50% (Gottesman, 1991, pp.97-98).

These statistics make it evident that schizophrenia is a disorder with a significant
genetic contribution. However, it can also be seen that the disorder is not fully
determined by an individual's genotype (i.e., underlying genetic structure of the
individual). This fact becomes particularly clear in studies (Gottesman, 1991) examining
concordance rates for monozygotic twins. As previously mentioned, even with an
identical genotype, the concordance rate for schizophrenia between monozygotic twins
is only about 50%. Therefore, the extent to which the genotype is phenotypically
expressed depends on a number of additional environmental factors (Cannon et al,
1993).

Environmental Factors

The role of non-genetic factors in the etiology and expression of schizophrenia has
been extensively investigated. Recently, a focus has been on the role of prenatal and
perinatal risk factors in the development of the disorder. Epidemiological studies
investigating such factors have linked an increased risk for schizophrenia to second
trimester intrauterine exposure to influenza (Barr, Mednick, & Munck-Jorgenson, 1990;
Mednick, Machon, Huttunen, & Bonett, 1988; O'Callaghan, Sham, Takei, Glover, &
Murray, 1991) and severe first trimester malnutrition (Susser & Lin, 1992). Similarly, a
number of retrospective studies have also noted an increased rate of obstetric
complications among individuals who have been diagnosed with schizophrenia (Geddes,
& Lawrie, 1995). However, with respect to this finding, Cannon and Colleagues (1993)
have debated the direction of the connection, suggesting that increased incidence of
obstetric complications in individuals with schizophrenia may be the result of an innate vulnerability rather than the cause of it. They further state that while perinatal events may be capable of pushing an already compromised system over a threshold, it would be unlikely that these events in and of themselves would be enough to cause schizophrenia. In support of this perspective, they point out that such events are known to occur at a high rate in individuals who never develop the disorder, and are likewise absent in a large majority of those who do. Therefore, although we know schizophrenia is a brain disease with a strong genetic component, and one that is also significantly influenced by environmental factors, those specific environmental and genetic factors that cause the disorder continue to remain unclear.

Schizophrenia as a Brain Disorder

The belief that schizophrenia is a brain disorder extends back to Kraepelin, who characterized the illness as an early deterioration of the brain, a condition he referred to as "dementia praecox" (Kraepelin, 1919). However, Kraepelin's (1919) original concept of a degenerative dementia characterized by progressive neuronal death has not been supported. Fortunately, since that time the search for brain mechanisms underlying schizophrenia has benefited from advances in technology and the advent of new brain imaging techniques. Current neuroanatomical studies of schizophrenia, enhanced by the advent of computerized tomography (CT) and magnetic resonance imaging (MRI) techniques, have provided substantial evidence (Bilder, 1992; Cannon, 1991; Nasrallah, 1990; Raz & Raz, 1990) that schizophrenia is associated with a number of structural brain abnormalities, including general indices of brain integrity, such as increased ventricle size (Andreasen et al., 1990; Bilder, 1992; Kelsoe, Cadet, Pickar, & Weinberger, 1988; Raz & Raz, 1990; Suddath et al., 1989; Suddath, Christison, Torrey, Casanova, & Weinberger, 1990), and sulcal widening (Cannon, 1991; Cannon, Mednick,
& Parnas, 1989), as well as more specific findings of reduced hippocampal and prefrontal cortex volumes (Breier, et al., 1992). Although these abnormalities were once thought to represent evidence of atrophy and thus a degenerative process such as dementia, they are now widely believed to be the result of aberrant brain development (Murray, O'Callaghan, Castle, & Lewis, 1992; Nasrallah, 1993; Weinberger, 1987; Weinberger et al., 1986). Consequently, schizophrenia is now considered a neurodevelopmental disorder.

Schizophrenia as a Neurodevelopmental Disorder

Support for an aberrant pathological neurodevelopmental process, as opposed to a degenerative one, as the etiology for brain abnormalities in schizophrenia, stems from three main findings (Keshavan, Anderson, & Pettigrew, 1994; Woods, 1998): 1) a lack of gliosis in the brains of individuals with schizophrenia on autopsy (Bogerts, 1991; Roberts, 1991), 2) neuroimaging evidence indicating the presence of structural brain abnormalities prior to disease onset and lack of brain deterioration after disease onset (Bilder, 1992), and 3) consistent findings of premorbid deficits across social, educational, and cognitive domains (Fish, Marcus, Hans, Auerbach, & Perdue, 1992; Gureje, Aderibigbe, Olley, & Bamidele, 1994; Nasrallah, 1993; Walker, Savoie, & Davis, 1994), suggesting the possibility of an aberrant process present in childhood prior to the onset of the disorder (Murray et al., 1992; Nasrallah, 1993; Weinberger, 1987). The following sections further discuss these three lines of evidence supporting neurodevelopmental theories.

An Absence of Gliosis

Reduction in cortical volume in brain tissue and enlargement of the ventricles in patients with schizophrenia is a robust finding (Bilder, 1992; Cannon, 1991; Raz & Raz,
1990). In response to cell loss or atrophy the ventricles in the brain increase to occupy space left behind as the brain retreats, making ventricular-brain ratio (VBR) a sensitive measure of brain tissue loss (Bilder, 1992). Information obtained from VBR studies, as well as that learned through clinical observation, wherein patients tended to deteriorate after initial diagnosis (Kraepelin, 1919), led many researchers to classify schizophrenia as a neurodegenerative disorder (Bilder, 1992). The problem with this conceptualization is that post mortem studies of the brains of affected individuals have consistently reported an absence of excessive gliosis (Bogerts, 1991; Roberts, 1991; Roberts, Colter, Lofthouse, Johnstone, & Crow, 1987). Gliosis, which is considered a necessary marker of tissue loss and cell death (Oppenheimer, 1984), is the end product of the proliferation of glial astrocytes that amass in reaction to the pathological death of neurons (Vaux, 1993). A lack of gliosis in individuals with schizophrenia has led many researchers to conclude that the structural abnormalities noted in these patients result from an aberrant developmental process (dysplasia), as opposed to a degenerative one, wherein brain tissue is destroyed after normal brain development (Murray et al., 1992; Nasrallah, 1993; Weinberger, 1987; Weinberger et al., 1986).

**Neuroimaging Studies**

Further support for the neurodevelopmental hypothesis comes from neuroimaging studies, which suggest a lack of progressive brain deterioration after onset of the disorder. If schizophrenia were caused by a progressive disease process, brain tissue loss and subsequent increases in the cerebral spinal fluid (CSF) spaces in the brains of schizophrenic patients would be present over time. Early neuroimaging investigations tested the deterioration hypothesis by attempting to correlate ventricular size or total CSF volume with age and chronicity of illness. Most of these cross-sectional studies have been unable to find a relationship between duration of illness and ventricular...
enlargement (Cannon, 1991; Raz & Raz, 1990), although there have been some positive findings (Gur et al., 1991; O'Callaghan et al., 1992). Longitudinal studies that have been able to prospectively evaluate structural changes in schizophrenia using either MRI or CT scans have also had mixed results, with some documenting deterioration after onset of the disorder in a subgroup of chronic patients (Davis et al., 1998; DeLisi et al., 1991; DeLisi et al., 1997; Kemali, Maj, Galderisi, Milici, & Salvati, 1989; Woods & Yurgelun-Todd, 1991), and others not (Hoffman, Ballard, Turner, & Casey, 1991; Nasrallah, Olson, McCalley-Whitters, Chapman, & Jacoby, 1986). Bilder (1992) has suggested that deterioration may be a characteristic of only a small subgroup of cases who have poor outcomes and significant cognitive deficits.

Another important finding, suggesting a neurodevelopmental pathogenesis, is the presence of structural abnormalities in unmedicated, first-episode patients (Degreer et al., 1992; Delisi et al., 1991; Nopoulos et al., 1995; Weinberger, DeLisi, Perman, Targum, & Wyatt, 1982) and in unaffected monozygotic twins discordant for schizophrenia. The presence of such structural brain abnormalities and the lack of clear evidence of deterioration over time imply that the pathological process responsible for the damage occurred before the onset of clinical symptoms (Murray et al., 1992; Nasrallah, 1993; Weinberger, 1984). Because of the difficulties involved in identifying individuals who will eventually develop schizophrenia, neuroimaging studies have not been conducted to examine brain structure and function prior to the first episode of psychosis. However, an alternative strategy that has been extensively used is to retrospectively evaluate the premorbid functioning of individuals who already have schizophrenia. If brain abnormalities are thought to be present prior to onset of the disorder, corresponding deficits in cognitive, social, or academic functioning should also be present. Studies of premorbid functioning have consistently demonstrated premorbid deficits in individuals who develop schizophrenia.
Premorbid Functioning in Schizophrenia

Premorbid functioning has been widely investigated in schizophrenia, with the conclusion that a wide range of disturbances exist during infancy, childhood, and adolescence in many individuals who later go on to develop the disorder (Fish; 1987; Fish et al., 1992; Nasrallah, 1993; Walker, et al., 1994). Deficits in social and academic functioning are a common feature of the schizophrenic prodrome and have been noted repeatedly by many investigators (Amminger & Mutschlechner, 1994; Cannon-Spoor, Potkin, & Wyatt, 1982; Gureje et al., 1994). Additional behavioral precursors include: decreased social responsiveness, lack of positive affect, reduced eye contact, and subtle motor and facial expression abnormalities (Fish; 1987; Fish et al., 1992, Jones, Rodgers, Murray, and Marmot, 1994; Walker & Lewine, 1990; Walker, Grimes, Davis, & Smith, 1993; Walker, et al., 1994). Unfortunately, the retrospective nature of this evidence (e.g., many researchers were forced to rely upon school records or the memory of a parent, teacher, or the patient, for information on past functioning) raises concerns about reliability. To circumvent the problems associated with retrospective designs, Walker and Lewine (1990) investigated premorbid neurological soft signs and other behavioral disturbances in schizophrenic patients by using home videos of the patients taken when they were children. Based on blind evaluations, researchers were able to differentiate the healthy sibling from the child who would later develop schizophrenia, including the detection of premorbid cognitive deficits (Walker & Lewine, 1990). Consequently, the identification of premorbid deficits is providing additional evidence supporting neurodevelopmental theories of schizophrenia and early neurodevelopmental models in particular.
Neurodevelopmental Models of Schizophrenia

**Early Developmental Theories**

Early developmental models of schizophrenia posit the existence of a static central nervous system (CNS) lesion, presumably occurring during the prenatal or perinatal period. The term lesion in this context denotes the presence of a disturbance in normal brain development. The effects of the lesion are thought to essentially remain dormant during childhood, but manifest later (adolescence or early adulthood) in response to normal changes (Murray et al., 1992; Weinberger et al., 1986; Weinberger, 1987).

Although the nature of this disturbance remains unclear, the outcome is believed to be a dysgenesis resulting in abnormal brain structure and function.

Weinberger (1987) purposed that cerebral dysgenesis may arise as a result of various independent insults (e.g., genetic, traumatic injury, infection, or toxin exposure) or from a normally distributed trait (e.g., liability) within the population. These factors may also interact to produce different levels of pathology and a heterogeneous clinical presentation. The potential for an insult which has its roots early in life to lie dormant and then manifest as dysfunction in the form of schizophrenia a decade and a half later, requires the supposition of a biological process capable of triggering the CNS scar during the hallmark period of development (i.e., adolescence). According to Weinberger (1987), maturational events (e.g. myelination of axons) taking place later in the course of development may represent just such a process. Hypothetically, a lesion occurring in the perinatal period could remain relatively undetected if it were in an area not considered fully functional until adolescence (Weinberger, 1987). A defect in the neurological substrate controlling certain cognitive abilities could reasonably elude detection until the individual is faced with the developmental challenge (Weinberger, 1987). Weinberger and colleagues (1986, 1988) have hypothesized that this defect may involve the dorsolateral prefrontal cortex (DLPFC), an area implicated in higher order...
cognitive processes and one of the last regions to fully mature. Using the Wisconsin Card Sorting Test (WCST), a putative measure of DLPFC functioning, the authors (Weinberger, Berman, & Illowsky, 1988; Weinberger et al., 1986) demonstrated that regional cerebral blood flow (rCBF) to the DLPFC is hypoactive among individuals with schizophrenia.

The early neurodevelopmental pathogenetic conception of schizophrenia has found support from other areas as well. For instance, the existence of an early static lesion is consistent with the presence of structural abnormalities in unmedicated, first-episode patients (DeLisi et al., 1991); premorbid social, cognitive, and motor dysfunction (Amminger & Mutschlechner, 1994; Jones et al., 1994; Cannon-Spoor et al., 1982; Fish; 1987; Fish et al., 1992; Gureje et al., 1994; Walker, et al., 1994), and epidemiological studies noting increased rates of obstetric complications, second-trimester maternal influenza, and first trimester malnutrition (Barr et al., 1990; Mednick et al., 1988; O'Callaghan et al., 1991; Susser & Lin, 1992) among individuals with schizophrenia. Although there is considerable support for early neurodevelopmental theories, lack of parsimony (i.e., long latency period between the occurrence of the pathogenetic process that renders an individual vulnerable to schizophrenia and the actual onset of clinical symptoms) remains a criticism.

**Late Developmental Theory**

The appeal of a neuropathological process that occurs later in development is its ability to account for the onset of schizophrenia in adolescence and early adulthood. It is well known that the functional development and refinement of a number of neurological processes continues to proceed well into the second (Jernigan & Tallal, 1990; Thompson, Englehart, Hasso, & Hinshaw, 1985) and even third decades of life (Benes, 1994, 1995). Feinberg (1990) purposed that early brain development is
characterized by excessive synaptic proliferation followed by a genetically planned reduction or pruning of these synapses occurring in adolescence. At this time, selective survival of highly competitive connections and the removal of redundant connections takes place in order to increase cognitive efficiency (Feinberg, 1982). This early proliferation and later pruning is thought to be part of a normal developmental process, which is under genetic control (see Keshavan et al., 1994 for a review). Several theorists (Feinberg, 1982; Keshavan et al., 1994) have purposed that schizophrenia results from a malfunction in the pruning process occurring in adolescence, thereby causing the manifestation of clinical symptoms at this characteristic time. Feinberg (1982) left the exact nature of this process (i.e., over-pruning, under-pruning, or pruning of the wrong structure) open to debate and further research. However, Keshavan and colleagues (1994) revisited the issue and set forth a strong argument for the malfunction being one of over-pruning, particularly in the area of the prefrontal cortex. Support for the existence of a "regressive hyper-pruning process" in schizophrenia is bolstered by MRI findings indicating possible loss of cortical tissue in the prefrontal cortex and regional cerebral blood flow (rCBF) studies, which have suggested schizophrenia is associated with hypofrontality (Weinberger et al., 1988; Weinberger et al., 1986).

Although the late model is consistent with research data from a number of areas (see Keshavan et al., 1994 for a review) and is particularly attractive in that it accounts for genetic contributions and requires less speculation regarding a latent process which eventually results in schizophrenia, it too has its faults. Specifically, the late model does not account for certain research findings (e.g., epidemiological and high-risk studies, and reports of premorbid dysfunction in childhood) which are more adequately explained by the early developmental models. As can be seen, neither the early nor the late developmental model explains all the data. Recently, a third model (Woods, 1998) was purposed, challenging the evidence on which deterioration was rejected (Cannon et al.,
1994; Murray et al., 1992; Weinberger, 1987), and essentially reintroducing the
developmental degenerative debate by suggesting that schizophrenia is most
adequately characterized as a developmental and progressive disorder.

Schizophrenia as a Progressive Neurodevelopmental Disorder

Evidence for a progressive process in the development of brain abnormalities and
ultimately the clinical symptoms characteristic of schizophrenia is supported by three
main findings (Keshavan et al., 1994; Woods, 1998): the relationship between abnormal
brain development, cranial size, and the differential distribution of cerebral spinal fluid
within the brains of individuals with schizophrenia (Woods, 1998; Woods et al., 1996),
evidence for an alternative process other than necrosis as a mechanism of continued
cell death in schizophrenia (Woods, 1998), and indication that a genetically planned
pruning process occurs in middle childhood and into adolescence (Feinberg, 1987;
Woods, 1998; Keshavan et al., 1994). The following sections further discuss these three
lines of evidence supporting a progressive neurodevelopmental theory.

Evidence for Progression

In his 1998 paper suggesting that schizophrenia is a neurodevelopmental disorder,
Woods asked the pertinent question, if schizophrenics have smaller brains (i.e.
hypoplasia) as a result of an early static lesion, why don't they have smaller heads?
From the early developmental perspective, evidence of reduced brain tissue volume is
interpreted as an under development of certain brain structures due to a hypothesized
early lesion (Nasrallah, 1993; Murray et al., 1992; Weinberger, 1987; Weinberger et al.,
1986). The problem with this theory, according to Woods (1998), is that intracranial
cavity growth is determined by the size of the brain. In normal development, the brain
grows from the ventricles out, pushing the skull outwards as it develops. This process is
complete by age five, at which time the sutures in the skull are sealed (Woods, 1998; Woods et al., 1996). Therefore, any reduction in brain mass after the sutures are sealed, should result in an increase in space between the interior surface of the skull and the surface of the brain. This space is then filled in by CSF (Woods, 1998; Woods et al., 1996). In contrast, if the brain simply failed to grow sufficiently, as suggested by the early neurodevelopmental theories, the skull would expand in accordance with this reduced brain growth (Woods, 1998; Woods et al., 1996) and affected individuals would have smaller heads (Woods, 1998). Although studies have found evidence for regional intracranial reduction (e.g., prefrontal) suggesting a discrete hypoplastic process (Woods et al., 1996), as opposed to a generalized one, this finding does not account for MRI studies which demonstrate enlargement of the CSF spaces between the brain and skull (Woods, 1998). This pattern of cortical distribution of CSF is consistent with a reduction in brain tissue after the brain has fully developed and not before, however, it is important to note that evidence of later deterioration does not exclude the possibility of regionally reduced brain growth owing to an abnormal early developmental process, and instead suggest a possible role for both (Woods, 1998; Woods et al., 1996).

Death by Apoptosis

In the same paper, Woods (1998) challenges the premise that a lack of gliosis invariably means a lack of degeneration and offers an alternative pathogenetic mechanism to explain brain volume loss in schizophrenia. Within the central nervous system cells die through two processes (Vaux, 1993), necrosis and apoptosis. Necrosis is accompanied by inflammation and is a process in which cells passively react to stress or injury with “loss of membrane integrity, morphological signs of organelle damage, and loss of lysosomal contents”. Apoptosis, also referred to as “programmed cell death”, involves a controlled process in which the cells play an active role in their own demise.
and features a series of events including, "separation from adjacent tissue, preservation of membrane integrity, diminution of cellular volume, plasma membrane bleb formation, morphological preservation of organellar structure, chromatin condensation, nuclear fragmentation, budding off of cellular fragments and retained lysosomal contents" (Bredesen, 1995). It is well documented that with pathological cell death or a necrotic process the brain reacts with gliosis. However, the controlled process of cell death by apoptosis does not involve inflammation or other characteristic changes associated with necrosis and occurs both as a natural developmental process within certain structures (Vaux, 1993) and in response to certain neuropathological conditions (Kerr, Wyllie, & Currie, 1972). In fact, studies have noted that the cellular apoptotic response can be triggered by a subthreshold insult to the CNS not quite capable of inducing necrosis (Bredesen, 1995). Studies in rats have found genes that control apoptosis (Hengartner, Ellis, & Horvitz, 1992) and accumulating evidence suggests that apoptotic processes may be involved in many neuropathological conditions. Although the viability of apoptosis as a contributor to cell loss in schizophrenia remains to be established (Akbarian et al., 1996; Bredesen, 1995), the very possibility of cell or tissue loss without excessive gliosis has revived the old debate of progressive disorder vs. static lesion. Moreover, with regard to gliosis, Woods (1998) points out that the human brain is capable of reacting to damage with gliosis by the twentieth week of gestation (Roessmann & Gambetti, 1986-as cited in Woods, 1998). Consequently, if one subscribes to the belief that insufficient gliosis excludes the possibility of a degenerative process in schizophrenia, then logic dictates that a similar conclusion be reached regarding structural abnormalities resulting from a lesion during the perinatal period (Woods, 1998).
Pathological Pruning

In addition to the lack of gliosis, degeneration in schizophrenia has been dismissed by neurodevelopmental theorists based upon CT and MRI studies which found evidence of abnormalities in unmedicated first episode patients (DeLisi et al., 1991), no correlation between ventricle size and duration of illness (Lim et al., 1996), and contradictory evidence of progressive deterioration on cross-sectional and longitudinal studies (Bilder, 1992; Lim et al., 1996; Nasrallah et al., 1986). As an explanation of these findings, Woods hypothesized a pathological neuronal pruning process in schizophrenia (very much like the one previously suggested by Feinberg and Keshavan) that could account for progressive brain volume loss, while still remaining consistent with the data. According to Woods' (1998) theory, the rate of neuronal pruning in schizophrenia is quantitatively greater than in normal individuals, but continues to follow the usual developmental timeline, which involves a dramatic increase in pruning after age five (Pfefferbaum et al., 1994) and an eventual slowing during adolescence. The result in schizophrenic individuals is an excessive reduction of synapses (beyond a critical threshold) prior to the onset of clinical symptoms and minimal (or undetectable) loss after that point (Woods, 1998). According to Woods, this pattern could produce a condition on MRI that appears to be mostly static. This theory is supported by several longitudinal studies, which have found progressive increases in ventricular size in certain samples (DeLisi et al., 1995; Rapoport et al., 1997). These samples are unique in that they are characterized by young patients, poor outcome patients, or patients who are both. The presence of a subgroup of severe patients who continue to progress after onset of clinical symptoms offers contradictory evidence for the lack of a progressive process in schizophrenia and calls into question whether previous studies (Lim et al., 1996), which did not find this progression, might have been hindered by the use of a cross-sectional design or a heterogeneous sample (Woods, 1998).
Summary

Schizophrenia research has focused on identifying the pathogenesis of schizophrenia by searching for the pathological structural, neurochemical, and cognitive correlates of the disorder. However, accumulated evidence overwhelmingly points to a heterogeneous disorder, possibly with multiple etiologies (Carpenter, Buchanan, Kirkpatrick, Tamminga, & Wood, 1993; Murray et al., 1992; Woods et al., 1996). Consequently, any theory attempting to impose a single etiological process on what appears to be a multifactorial disorder is destined to fall short.

The existence of familial and nonfamilial (or sporadic) forms of schizophrenia highlights the probability that independent pathophysiological processes may be responsible for different symptom aggregations and avenues of risk (Carpenter et al., 1993). Support for separate but similar processes emerged when Cannon and associates (1989) investigated the contribution of genetic as opposed to environmental liability to the distribution of CSF in the brain of patients with schizophrenia. The authors (Cannon et al., 1989) found that enlarged ventricular space was associated with obstetric complications and familial risk, while sulcal enlargement was associated with a family history exclusively. Cannon and colleagues (1989) concluded that "ventricular enlargement might mark a process of environmental insult superimposed on a congenital vulnerability, the double-hit model (Nasrallah, 1993), while sulcal enlargement might mark a more exclusively genetic predisposition". It appears then that a single prototypical schizophrenia profile does not exist. Therefore, although none of the previously proposed etiological models (Feinberg, 1982; Keshavan et al., 1994; Weinberger, 1987; Woods 1998, Woods et al., 1996) is sufficient to explain all the data, they do provide direction for the development of testable hypotheses that allow for the investigation of multiple pathogenetic processes in schizophrenia. Given the numerous disparate findings, this position appears warranted (Carpenter et al., 1993).
Vulnerability Markers

One commonality between the various neurodevelopmental theories is that they all posit a prodrome, i.e., a period of time prior to the onset of schizophrenia that is characterized by subtle yet consistent deficits. Zubin and Spring (1977) describe these deficits as identifiable and stable aspects of functioning that mark vulnerability to developing the disorder. Because of the neurodevelopmental nature of schizophrenia, these behavioral markers are expected to be present prior to the onset of clinical symptoms. As such, a major focus of research has been on the identification of functional abnormalities that indicate the presence of the disease gene (i.e., biobehavioral markers), and in premorbid populations, the potential for future illness (Straube & Hahlweg, 1990).

Cognitive Deficits in Schizophrenia

The recognition of schizophrenia as a brain disease paved the way for the identification of neurocognitive deficits as potential indicators of the schizophrenia pathology (Tsuang, Lyons, & Faraone, 1990). These deficits are so pervasive that many researchers (Goldberg & Gold, 1995; Goldstein et al., 1998) consider them to be fundamental features of the disorder.

Cognitive functioning in schizophrenia is an area that has received a great deal of attention in recent years (for review see Heinrichs, & Zakzanis, 1998). Studies utilizing neuropsychological tests that assess the integrity of the brain have consistently found widespread impairment in basic cognitive and attentional processes in individuals with schizophrenia (Bilder, 1992; Braff, 1993; Heaton et al., 1994). The presence of cognitive impairment among this population is not surprising considering neuroimaging studies have found evidence of abnormal brain development (Breier et al., 1992). However,
despite significant efforts, researchers have been unable to identify a uniform neuropsychological profile (Heaton et al., 1994; Saykin et al., 1991).

The identification of a distinct profile is made difficult by the generalized cognitive impairment that characterizes individuals with the disorder (Chapman & Chapman, 1973). These severe global deficits occurring in individuals with schizophrenia make the identification of neuropathologically specific impairments, termed differential deficits, a more complex endeavor. Studies attempting to find differential deficits have typically compared schizophrenic group scores, on a battery of neuropsychological tests, to those of a control group with the goal of finding a greater performance deficit among the schizophrenia group on certain tests relative to others. Unfortunately, the results of this method can sometimes be misleading, in as much as a greater performance deficit relative to controls on one test and a smaller degree of difference on another may or may not represent a differential deficit in that area; the validity of the finding is largely dependant on the difficulty of the tests (Chapman & Chapman, 1973). Therefore, it is necessary when attempting to identify differential deficits in individuals with schizophrenia that the psychometric properties of tests are taken into consideration.

One of the most consistent findings in schizophrenia research is that of poor performance on neurocognitive tests believed to measure abilities subsumed by the frontal lobes (Levin, Yurgelun-Todd, Craft, 1989). The putative functions subsumed by this region include motor function, attention, problem solving, and concept formation. Analogous to the role of an executive, the frontal lobes determine the allocation of finite resources (e.g. attention and controlled information processing), while acting in an integrative, decision-making capacity within the brain (Levin, 1984).

Specific deficits in attentional functioning are a well-documented observation in patients with schizophrenia (Nuechterlein & Dawson 1984). Aspects of this deficit are believed to be closely related to deficiencies in information processing such that deficient
Selective attention may be linked to: 1) a reduced processing capacity, 2) an inefficient allocation of a limited resource, 3) a deficit in automatic parallel processing (e.g., requiring effortful processing of information that should be unconscious), or 4) a slowed allocation of available processing resources (Nuechterlein & Dawson, 1984).

Nuechterlein & Dawson, (1984) also note that individuals with schizophrenia may experience difficulty filtering out irrelevant information, possibly reflecting a failure of habituation, such that an inability to sufficiently adapt to repeated, trivial stimuli results in sensory overload. Impairment on tests sensitive to these deficits has been noted in numerous studies with schizophrenic patients (Nuechterlein & Dawson, 1984).

In addition to determining what information gets attended to within the environment, the frontal lobes are also believed to play an important role in concept formation, cognitive flexibility, judgment, abstract reasoning, and other higher mental processes. Tests used to measure these executive abilities have found significant impairment of these important processes in schizophrenic populations (Heaton et al., 1994; Yurgelun-Todd, Craft, O'Brien, Kaplan, Levin, 1988). Interestingly, both early and late neurodevelopmental theories of schizophrenia hypothesize a disruptive mechanism operating during the developmental period (childhood or early adolescence) when functional attainment of higher cognitive processes is believed to be taking place. A specific region of the brain that may account for the primary disruption of these cognitive processes, and one that has been the object of much speculation in the schizophrenia literature, is the dorsolateral prefrontal cortex (DLPFC). This area is implicated not only because it is one of the latest brain structures to fully mature (making it a prime suspect for damage during the adolescent years), but also because regional cerebral blood flow (rCBF) studies have shown it to be hypoactive in schizophrenic patients. Relative to normal populations, for which performance on the Wisconsin Card Sorting Test (WCST) has been found to activate the DLPFC, schizophrenic populations show evidence of
decreased activation of this area during performance of the WCST (Weinberger et al., 1988; Weinberger, Berman, Suddath, & Torrey, 1992; Weinberger et al., 1986). These results suggest the possibility of a connection between functional impairment, as measured by the WCST, and an area of pathology potentially unique to schizophrenia.

Another cognitive ability that is influenced by frontal lobe functioning and believed to be impaired in schizophrenia is working memory (Gold, Carpenter, Randolph, Goldberg, & Weinberger, 1997). Working memory has been defined as "transient representations of task-relevant information, which may be related to information that has just been activated from the distant past, linked to the current environment, or based upon something that has recently been experienced, and are used to guide current behavior" (Gazzaniga, Ivry, & Mangun, 2002 pg. G10). Working memory failures in individuals with schizophrenia have often been interpreted as reflecting, in part, a deficit in basic attentional processes (e.g., the inability to selectively attend to an object or stimulus will significantly reduce the chances of it being remembered), a conclusion which based upon the literature is not without merit (Nuechterlein & Dawson, 1984), although possibly premature. Evidence for a primary deficit in working memory capacity in schizophrenia is supported by a recent finding (Gold et al., 1997) in which the WCST, a measure widely believed to be an indication of cognitive flexibility and one schizophrenic individuals routinely perform poorly on, was found to be significantly correlated with performance on the Letter Number Task (LNT), a test of working memory. Gold et al. (1997) found that poor performance by the schizophrenia group on the LNT accounted for a significant amount of the variance between the groups on the WCST. These researchers (Gold et al., 1997) point out that, "intact working memory may be necessary, although not sufficient, for success on the WCST, as well as many other abstract reasoning and concept formation tests," in large part because the ability to solve a problem requires one to remember what was previously said or done and hold that
information in working memory as different hypotheses are tested. Therefore, evidence suggests that poor working memory functioning in schizophrenia may, at least in part, be the result of a primary working memory defect, as opposed to the exclusive product of a failed attentional process.

Studies investigating the involvement of additional cortical regions in the pathophysiology of schizophrenia have most consistently implicated the temporal lobes and more specifically, medial temporal lobe structures including the hippocampus (Suddath et al., 1990). Neuroimaging and neuropathological studies in schizophrenic patients have found evidence of localized cortical changes (DeLisi et al., 1991), including cellular abnormalities and atrophy in these regions (Cannon et al., 1994; Conrad, Abebe, Austin, Forsythe, & Scheibel, 1991).

Evidence for temporal lobe dysfunction has found wide support throughout the neuropsychological literature (Nasrallah, 1993). Characteristic deficits in secondary memory and language comprehension and the presence of some clinical symptoms, such as auditory hallucinations, are all believed to reflect a dysfunction in this region (Bilder, 1992; Flor-Henry, 1976; Harvey et al., 1996; Paulsen et al., 1995; Shenton et al., 1992). Neuropsychological investigations into the role of temporal lobe dysfunction in the pathogenesis of the disorder have been undertaken by comparing the performance profile of individuals with schizophrenia to patients with temporal lobe epilepsy (Gold et al., 1994; Goldstein, Allen, & Weiner, 1999). In some cases these findings have resulted in the identification of a subgroup of individuals with schizophrenia who appear to have a primarily temporal lobe profile on cognitive assessment, a second group that exhibits primarily frontal lobe impairment, and a third group that exhibits both frontal and temporal lobe deficits (Allen, Goldstein, & Weiner, 2001).

Unfortunately, isolating the neural substrates of schizophrenia using neurocognitive measures can be very difficult due to the complex networks of neural circuits that work in
coordination to allow normal performance on even the most simple neurocognitive and motor tests. For example, as with all areas of the brain, the frontal lobes are not a closed system but receive inhibitory and excitatory inputs from other cortical and subcortical regions, including limbic structures and the hippocampus. The frontal lobes also project fibers to various cortical and subcortical regions, thus forming feedback loops that regulate complex cognitive and motor operations, including problem solving and, more generally, executive functions. Therefore, problem solving, which is primarily mediated by the frontal lobes, can be deficient if there is damage to any of the cortical structures that make up the feedback loop.

Findings of brain tissue reduction in periventricular gray matter areas and volume loss in subcortical limbic and paralimbic structures in individuals with schizophrenia (Johnstone et al., 1989) support the involvement of other brain regions as well. These results suggest that the cognitive and clinical symptoms of schizophrenia may be the result of multiple pathological processes active in both fronto-temporal and subcortical structures. Several authors have speculated as to this potential. Weinberger and colleagues (1992) provide evidence for dysfunction involving the pre-frontal limbic network on a number of activities, including performance on cognitive tasks that require working memory. Keshavan and coworkers (1994) have suggested that an essential dysfunction in the connectivity of the prefrontal area with other cortical and subcortical structures might account for the complex pattern of dysfunction in schizophrenia. Although there is no consensus at this time, further research on the nature of the dysfunction experienced by patients with schizophrenia should help investigators to form a more complete picture of the disorder and its causes.

A second issue related to the interpretation of findings is that, in order to attain average performance on neuropsychological tests designed to measure even the most basic cognitive and motor abilities, intact functioning across a number of cognitive and
perceptual domains is required. In essence, even the most basic tests of motor abilities such as the Finger Oscillation Test require multiple abilities and hence the intactness of multiple neural circuits to obtain a normal performance. However, given these considerations, there are extensive neuropsychological, neurological, neuroradiological, and neurophysiological literatures that support the utility of commonly used neuropsychological tests in localizing neuropathology. These tests have provided valuable information regarding normal and abnormal brain function. Within the context of the current study, it is acknowledged that deficient performance on a given test will not provide definitive evidence for localized neuropathology. However, the inclusion of tasks in which component processes can be examined (e.g., recall vs. recognition on memory test performance), the interpretation of patterns of deficit and sparing, as well as the extensive clinical and experimental literature, should provide a substantive basis on which to make predictions regarding neuropathology that can then be quantified using neuroimaging procedures.

Summary

The majority of investigations into cognitive functioning in schizophrenia have attempted to ascertain differential deficits within the global deficits that characterize the disorder. The search for specific deficits carries with it the hope that an identified dysfunction will correspond to a discrete area in the brain, and ultimately a discernible pathological process that can account for the psychiatric and cognitive symptoms of the disorder. The results of neurocognitive testing support the conception of schizophrenia as a heterogeneous disorder, characterized by varied presentations (Seaton, Goldstein, Allen, in press). The most consistent findings point to deficits in executive functioning (Heaton et al., 1994), attentional and information processing (Asarnow & MacCrimmon, 1978; Cornblatt, Lenzenweger, Erlenmeyer-Kimling, 1989; Nuechterlein & Dawson, 1989).
1984), language comprehension (Bilder, 1992), and certain aspects of memory functioning (Harvey et al., 1996; Heaton et al., 1994; Park, Holzman, & Goldman-Rakic, 1995; Paulsen et al., 1995; Saykin et al., 1991; Stone, Gabrieli, Stebbins, & Sullivan, 1998). Because neurocognitive deficits are stable features of the disorder, some have posited that like structural brain abnormalities they are trait markers of schizophrenia, reflecting genetic susceptibility to the disorder. Consequently, differential neurocognitive deficits identified in patients with schizophrenia should also be present in relatives of individuals with the disorder and in those that are at high risk to develop schizophrenia due to other factors. A number of studies have examined this issue by evaluating neurocognitive function in the relatives of individuals with schizophrenia or in individuals who exhibit schizotypy, the latter group being defined as individuals who exhibit symptoms consistent with schizophrenia that are not severe enough to warrant a formal psychiatric diagnosis.

Cognitive Deficits as Markers of Vulnerability

Because of their pervasive nature, Kremen et al. (1998) referred to these deficits as endophenotypes, claiming that their presence was a greater indication of the disease genotype than the schizophrenic phenotype itself, which depending upon a number of other biological and environmental factors, may or may not be expressed. Moreover, because these deficits exist prior to the onset of clinical symptoms (Hoff et al., 1992; Nuechterlein & Dawson, 1984), persist regardless of whether an individual is medicated or hospitalized (Harvey et al., 1990; Nuechterlein & Dawson, 1984; Sweeney et al., 1991), and occur more often in the relatives of individuals with schizophrenia (i.e., heritable) than in normal controls and relatives of other psychiatric disordered individuals (Cannon et al., 1994; Condray, Steinhauer, & Goldstein, 1992; Faraone et al., 1995; Keefe et al., 1994), they are better potential indicators of the enduring biological
susceptibility to schizophrenia than are most clinical symptoms, which are transient and fluctuate overtime (Zubin & Spring, 1977).

More recently the search for vulnerability markers in schizophrenia has expanded to high-risk populations (Cannon et al., 1994; Condray et al., 1992; Cornblatt & Erlenmyer-Kimling, 1985; Faraone et al., 1995; Keefe et al., 1994; Nuechterlein, 1983). Clinically, the use of an at-risk population is advantageous because it provides a unique opportunity for understanding the processes of schizophrenia without the potential confounds that go along with having a mental illness (e.g., neuroleptic exposure, duration of hospitalization, active symptom effects, substance abuse, malnutrition, and the humiliation and degradation associated with severe mental illness) (Cornblatt & Keilp, 1994; Mednick & McNeil, 1968). High-risk research is based on the belief that, discernable indicators (e.g., endophenotypes) of the schizophrenia liability exist in individuals who are at an elevated risk for developing the disorder.

Defining High-Risk

High-risk has been defined according to at least two criteria (Lenzenweger, 1994), family history and personality characteristics (e.g. schizophrenia-like disorders). Family high-risk studies are based on the fact that first-degree relatives are more likely to carry a genetic predisposition to the disorder than is the general population (Gottesman & Shields, 1982). Personality high-risk studies point to the phenomenological overlap between the clinical symptoms of schizophrenia and the schizophrenia-spectrum disorders as indication of an increased liability to psychosis in this population (Chapman & Chapman, 1985).

Schizophrenia Spectrum

Phenotypically the genetic liability for schizophrenia can range from apparent
normality to transient psychosis (Meehl, 1962, 1990). Incomplete expression of the aberrant gene may result in any of several schizophrenia-related personality disorders. These disorders are similar to schizophrenia, but are viewed as less severe variants, characterized by diminished symptomology. Meehl theorized that genetic vulnerability to schizophrenia resulted from a neural integrative defect. He believed that this genetic defect was necessary but not sufficient for schizophrenic breakdown, and that the presence or absence of "unfavorable polygenetic potentiators" (e.g., anxiety) and adverse life events would determine whether a genetically vulnerable individual developed schizophrenia, a schizotypal disorder, or relatively normal functioning.

In line with Meehl's conception is a diathesis-stress model of schizophrenia, which proposes that schizophrenia arises from an interaction between environmental stress and a predisposition. This conceptual model is supported by twin studies which show the concordance rate between monozygotic twins as only 50%, and by studies of the offspring of discordant identical twins which show a similar rate of transmission to their children regardless of whether the schizophrenia genotype was expressed or not (Gottesman & Bertelson, 1989). Additionally, family studies have found a high rate of schizotypal traits among the first order relatives of individuals with schizophrenia, suggesting that schizotypal personality disorder may be the more common manifestation of the genetic vulnerability (Kendler & Gruenberg, 1984; Jacobsen, 1976; Kendler, Gruenberg, & Strauss, 1981; Kety, Rosenthal, Wender, Schulsinger, &; Siever et al., 1990). However, as with actual schizophrenic illness, schizotypal traits are known to occur in individuals with no family history of the disorder as well (Lenzenweger, 1994).

The presence of schizotypal traits is believed to reflect an increased susceptibility to developing a psychotic illness, regardless of whether there is a family history of schizophrenia (Kendler, & Gruenberg, 1984) or not (Chapman et al., 1994). Increased "psychosis proneness" (i.e., a predisposition or diathesis to psychosis) is typically
identified with either a structured clinical interview (e.g., SCID-IP), or a personality inventory such as the Chapman Scales of Psychosis Proneness (Chapman et al., 1982), which are designed to measure schizotypal traits. Recognizing the value of these two apparently separate paths to vulnerability, high-risk studies have attempted to clarify the etiology and nature of schizophrenia by identifying their psychosis prone groups both deductively (family history) and inductively (schizophrenia-like personality characteristic).

Types of High-Risk Studies

Since their inception in the late 1960's and early 1970's, longitudinal high-risk studies have generated valuable information with regard to the neurodevelopmental nature of schizophrenia (Cornblatt, Obuchowski, Roberts, Pollack, & Erlenmeyer-Kimling, 1999; Cornblatt, Obuchowski, Schnur, & O'Brien, 1998; Marcus, Hans, Auerbach, & Auerbach, 1993). In these studies, at-risk children (e.g., children with one or two parents who have schizophrenia) are followed over the course of their development until they have passed the point of greatest risk for psychotic decompensation (e.g., early to late twenties for men and late twenties to early thirties for women). Prospective evaluation of this unique group has helped to confirm the existence of multiple areas (e.g., activity level, alertness, motor coordination, information processing, attentional and social functioning) of premorbid dysfunction in schizophrenia (Cornblatt et al., 1999; Cornblatt et al., 1998; Erlenmeyer-Kimling & Cornblatt, 1987; Fish et al., 1992; Marcus et al., 1993; Nuechterlein, 1983). Information from the repeated assessment of individuals who later went on to develop schizophrenia or schizotypal disorders is being used to help researchers determine which environmental and behavioral variables best predict future illness. The identification of these variables is an important step in the advancement of early intervention programs (Cornblatt et al., 1999; Cornblatt et al., 1998). However, despite the obvious benefits of the prospective method, studies using a longitudinal
design are less common due to the tremendous expense and time commitment.

Most high-risk studies employ a between-subjects design, which involves comparing a control group to individuals with schizophrenia and their relatives who, although carry the schizophrenia genotype (e.g., they have a biological family member with schizophrenia), have successfully surpassed the critical period for developing the disorder. These studies are designed to psychometrically isolate the behavioral deficits (i.e., vulnerability markers) that exist at a higher rate in individuals with schizophrenia and their genetically vulnerable, although unaffected relatives. Deficits in cognitive and attentional functioning have been previously identified as behavioral markers of the disease genotype (Kremen et al., 1998) and as such would be expected to exist at an increased rate in individuals with a family history of the disorder.

Cognitive Deficits in Family High-Risk Studies

Many studies (Cannon et al., 1994; Condray et al., 1992; Cornblatt & Obuchowski, 1997; Faraone et al., 1995; Green, Nuechterlein, & Breitmeyer, 1997; Harris et al., 1996; Keefe et al., 1994; Mirsky, Yardley, Jones, Walsh, & Kendler, 1995; Steinhauer et al., 1991) comparing the cognitive functioning of schizophrenic patients, their relatives, and a normal control group, have found a pattern of deficits in which the schizophrenic patients do the worst, then the relatives, then controls. This pattern of deficit has been noted in multiple domains including attention, learning efficiency, memory, perceptual-motor functioning, language comprehension, verbal fluency, and abstraction. Like their schizophrenic probands, relatives have generally been found to demonstrate a similar, although more subtle profile of impairment, with deficits in the aforementioned areas and relative sparing of simple spatial abilities and sensory motor functions (Cannon et al., 1994; Faraone, et al., 1995; Kremen et al., 1994; Steinhauer et al., 1991).

On tests of abstraction, verbal memory, auditory attention, mental control-encoding,
and verbal ability, Faraone and his team (1995) found that relatives performed worse than controls and that the differences were not related to psychopathology or general intellectual ability. Kremen et al. (1994) had similar findings, however they also identified poorer performance relative to controls on measures of learning, motor, and complex visual-spatial tasks. A number of studies (Keefe et al., 1994; Kinney, Yurgelun-Todd, Waternaux, & Matthysse, 1994) have also reported worse performance in the relatives of schizophrenic patients compared to controls on tests of perceptual motor speed such as Trail Making Test, Digit Symbol/Coding Test, and Purdue Peg Board. While there have been negative findings (Condray et al., 1992; Goldberg et al., 1990; Keefe et al., 1994) with regard to the evaluation of certain cognitive abilities using specific tests such as the Wisconsin Card Sorting Test, the majority of these same studies have found impairment in other areas, such as language comprehension (Condray et al., 1992), and most studies noted scores that were generally in the direction of worse performance by the relatives of schizophrenic probands. So while the majority of data seems to support a pattern of intermediate impairment among the relatives, there have been inconsistent findings with regard to the measurement of specific cognitive deficits that reliably characterize the genetic vulnerability to schizophrenia.

By contrast, attentional dysfunction, specifically sustained attention measured using one of the more difficult versions of the CPT, has demonstrated consistent findings and may be considered the strongest neuropsychological risk indicator (Garver, 1987). Studies of attention utilizing either the Degraded Stimulus (DS CPT; Nuechterlein, 1983) or the Identical Pairs version of the CPT (CPT-IP; Cornblatt, Risch, Faris, Friedman, & Erlenmeyer-Kimling, 1988), have consistently found d' values (d' is a measure of sensitivity or the ability to discriminate the target (signal) stimuli from the nontarget (noise) stimuli) for relatives that were at an intermediate level, with the schizophrenic probands doing the worst and the controls the best (Cornblatt et al., 1988; Cornblatt &
Keilp, 1994; Nuechterlein, 1985). Mirskey, Lochhead, Jones, Kugelmass, Walsh, & Kendler, (1992) used a group of factor-analyzed tests to measure four different aspects of attentional processing in two separate high-risk groups (i.e., Israeli high-risk study and Ireland high-risk study). They found that the attentional elements of sustain and focus/execute measured respectively by the CPT-IP, Digit Symbol, Trail Making Test and Letter Cancellation, were more discriminatory than those tests measuring the encode (WAIS-R: Digit Span, Arithmetic) and shift elements (WCST), although all the elements differentiated between the high-risk groups and normal controls (Mirskey et al., 1992). Global attentional deficits have also been noted in longitudinal high-risk studies as possible childhood markers of the liability of at-risk individuals to develop either a schizophrenia related disorder or the full clinical syndrome (Cornblatt & Erlenmeyer-Kimling, 1985; Cornblatt et al., 1999). Because attentional abilities appear to be heritable (Harris et al., 1996), and deficits in attention are a stable and consistent finding among both schizophrenic and family high-risk populations, these deficits may reflect possible features or traits of the schizophrenia genotype (Cornblatt et al., 1999; Nuechterlein et al., 1994).

Further evidence that neuropsychological impairment may be a valid indicator of the schizophrenia vulnerability comes from studies comparing the performance of schizophrenic relatives to the relatives of individuals with other psychiatric disorders. In a study conducted by Nuechterlein (1983), poorer performance on the CPT d' factor was achieved by significantly more children of mothers with schizophrenia than the children of normal control mothers and mothers with nonpsychotic psychiatric disorders. A similar study by Cornblatt & Erlenmeyer-Kimling (1985) found that a global attentional measure taken in childhood was predictive of behavioral disturbances in adolescence in at-risk children of schizophrenic mothers but not the children of mothers with affective disorders or those of normal controls. In another study, (Kremen et al., 1998) the
Performance of the adult relatives of schizophrenic probands was compared to relatives of bipolar disordered individuals and normal controls, with results indicating that the schizophrenic relatives performed the worst on measures of memory and attention. These studies indicate that the identified cognitive deficits demonstrate some specificity to the schizophrenia pathology (Kremen et al., 1998). Taken together these findings suggest there is potential value in the identification and use of cognitive and attentional deficits as biobehavioral markers of the genetic vulnerability to schizophrenia.

Cognitive Deficits in Schizotypy Studies

Similar to family investigations, high-risk studies exploring cognitive deficits in schizotypy or hypothetically psychosis prone groups, have generally found a pattern of results in which the schizotypy group performs better than the schizophrenics, but worse than normal controls. Deficits have been noted on tests of attention, abstraction, memory, visuoperceptual processing, and verbal learning (Bergman et al., 1998; Cadenhead, Perry, Schafer, & Braff, 1999; Coursey et al., 1989; Gooding et al., 1999; Lenzenweger & Korfine, 1994; Suhr, 1997; Trestman et al., 1995; Voglmaier et al., 1997).

Schizotypy studies select individuals based on extreme scores on measures of schizotypy (e.g., Chapman Scales of Psychosis Proneness) or personality characteristics assessed by a structured clinical interview (SCID-IP). Schizotypy groups may include individuals with a positive family history of schizophrenia as well as those with no family history, as the basis for inclusion is personality characteristics not genetic relatedness to a schizophrenic proband (Chapman & Chapman, 1985). This may be a significant distinction because genetic factors are important in the etiology of schizophrenia and appear to play a role in schizophrenia-related disorders such as schizotypal personality disorder (SPD) (Kety et al., 1976). Studies which have noted
differences between familial and nonfamilial schizotypes (Condray & Steinhauer, 1992; Thaker, Moran, Adami, & Cassady, 1993) on a measure of smooth pursuit eye tracking and comprehension of grammatical constructions, provide further support for this subtyping among SPD groups. Additionally, there is evidence to suggest that the negative dimension of schizotypy is a better indication of the familial vulnerability to schizophrenia than is the positive dimension of schizotypy (Gunderson, Siever, & Spaulding, 1983; Kendler, McGuire, Gruenberg, & Walsh, 1995). Franke, Maier, Mardt, Hain, & Cornblatt (1994) reported that family members with a schizophrenic proband performed significantly worse than normal controls on the CPT-IP and reportedly admitted to experiencing significantly more physical anhedonia, but had similar ratings of self reported perceptual aberrations as controls.

**Familial Versus Nonfamilial Schizophrenia**

Differences in familial and nonfamilial schizotypes might be expected considering individuals with familial and nonfamilial forms of schizophrenia demonstrate significant differences in a number of areas (Cannon et al., 1994; Lyons, Kremen, Tsuang, & Faraone, 1989; Schwartz, O'Brien, Evans, Sautter, & Winstead, 1995; Tsuang et al., 1990). Griffiths et al. (1998) found that neurological signs of focal damage more often characterized nonfamilial or sporadic cases of schizophrenia, while a more distributed pattern of signs was found in the familial schizophrenics and their relatives. Furthermore, familial schizophrenia is associated with abnormalities in visual and motor development in infancy (Fish et al., 1992), disrupted smooth pursuit eye movements (Schwartz et al., 1995), cortical and ventricular abnormalities (Cannon, Mednick, & Parnas, 1989), lateral ventricular asymmetry (Roy, Flaum, Arndt, Crowe, & Andreasen, 1994), and longer latencies of P300 auditory evoked potentials (Roxborough, Muir, Blackwood, Walker, & Blackburn, 1993). Nonfamilial schizophrenia is associated with
ventricular enlargement on both sides (Roy et al., 1994), a more generalized deficit, and an increased number of perinatal complications (Reveley & Reveley, 1986).

Evidence also exists indicating that patients with familial forms of schizophrenia perform worse than nonfamilial patients in certain areas of neurophysiological and neuropsychological functioning (Asarnow & MacCrimmon, 1978; Lyons et al., 1989; Sautter et al., 1994; Sautter et al., 1995; Schwarzkopf et al., 1988). Using the evoked potential paradigm, Schwarzkopf et al., (1988) observed that familial and sporadic schizophrenics both deviated from normal controls, but in the opposite directions from one another. Walker and Shaye (1982) found that schizophrenics with a family history of the disorder performed worse on the AX CPT than those without a family history, which is consistent with Lyons et al.'s (1989) review indicating decreased sustained attention in family history positive patients. In addition to attentional differences, Sautter et al. (1994) found a significant distinction in the cognitive profiles of familial and nonfamilial schizophrenics when they factor analyzed the neuropsychological patterns of deficit within the two groups. The familial schizophrenics in their study were two standard deviations below the mean on all eight of the cognitive measures. Their profile was characterized by specific focal difficulties in the areas of fine motor control and abstraction and problem solving abilities (which could reflect working memory problems), while the nonfamilial group demonstrated a generalized cognitive deficit with a performance on seven of the eight tests that was two standard deviations below the mean (this latter profile is consistent with an old impairment). The authors concluded that familial schizophrenia might be associated with more severe "specific central nervous system deficits" and the nonfamilial form with a less severe generalized profile (Sautter et., al 1994).

In another study, Sautter and colleagues, (1997) compared the neuropsychological performance of four groups that varied in their familial loading for schizophrenia; a
normal control group, a nonfamilial schizophrenia group, a familial schizophrenia group with only one other psychotic relative, and a familial schizophrenia group with multiply affected relatives. The results demonstrated a pattern of performance in which the group with multiply affected family members performed worse than the familial group with only one other schizophrenic proband on measures of abstract concept formation, visuomotor-coordination, and attention. These "low-density" families in turn performed worse than the nonfamilial schizophrenics on measures of fine motor-control. The authors concluded that level of family loading for schizophrenia may mediate the degree of brain abnormalities in those frontal systems controlling abstract concept formation and fine motor performance (Sautter et al., 1997). Interestingly, it has also been noted that among family high-risk groups those individuals with the greatest neuropsychological impairment are also those with a greater number of SPD traits (Cannon et al., 1994; Keefe et al., 1994; Condray et al., 1992). In a study of schizophrenics and their brothers, Condray and colleagues (1992) noted that the probands performed the worst, then the brothers with schizophrenia spectrum disorders (e.g., SPD), then the healthy brothers, and then controls. Accumulated evidence suggests a differential degree and pattern of cognitive deficits among individuals with schizophrenia depending upon whether the etiology is familial or nonfamilial. Based on the results of these investigations, it seems a comparison between familial and nonfamilial high-risk groups may be the next important step in delineating the deficits that characterize these two potentially separate paths of risk.

Proposed Study

Cognitive functioning in familial high-risk groups and in schizotypy groups has been compared to control groups and individuals with schizophrenia, however, there have been no studies comparing the cognitive characteristics of these specific high-risk
groups to each other. This is an important comparison because research suggests that there are differences in the cognitive profiles of schizophrenic individuals with a family history of schizophrenia and those who have no family history of schizophrenia (Asarnow, Cromwell, & Rennick, 1978; Sautter et al., 1994, Sautter et al., 1995; Walker and Shaye, 1982). Therefore, a comparison of neurocognitive functioning in these high-risk groups may be a useful way of investigating the role etiological origin of liability plays in the schizophrenia phenotype. Additionally, because high-risk groups lack the potential confounds associated with schizophrenia (e.g., neuroleptic exposure, duration of hospitalization, active symptom effects, substance abuse, malnutrition, and the humiliation and degradation associated with severe mental illness) this approach has the benefit of making the data more interpretable.

This study will compare the cognitive profiles of a family history negative (FH-) high-risk group and a family history positive (FH+) high-risk group. The FH- group will be a psychometrically defined schizotypy group, while the FH+ group will include only individuals who have a positive family history of schizophrenia. Based on previous high-risk investigations and studies on familial and nonfamilial schizophrenia and schizotypy, I have made several a priori hypotheses.

Hypothesis 1: the family history positive (FH+) high-risk group will score worse than the nonfamilial (FH-) schizotypy high-risk group on a measure of attention (DS-CPT), abstract reasoning (WCST, Stroop), perceptual motor speed (Purdue Peg Board) and working memory (LNS; Digits and Spatial Span Backward), as these are the areas demonstrating a differential pattern of deficit between familial and nonfamilial schizophrenics.

Hypothesis 2: Of the family history positive individuals, those with greater elevations on the schizotypy scales are predicted to score worse than the other members of the family history positive, and the nonfamilial schizotypy group on the previously mentioned
measures of attention, abstract reasoning, auditory working memory, and perceptual motor speed.

Hypothesis 3: The negative dimension of schizotypy will be more highly associated with family liability, as well as poorer performance on tests requiring sustained attention.
CHAPTER 3

METHODOLOGY

Subjects

Approval for Use of Human Subjects

The experimental process used in the University of Nevada current investigation was authorized by the Social/Behavioral Committee of the University of Nevada, Las Vegas Institutional Review Board for Psychological Research. The OSP number is 113s1000-135. Copies of the approved consent forms are included in Appendices A and B.

Population From Which Sample Was Drawn

The data utilized in the current investigation was collected over the course of approximately one year (2001-2002) at the University of Nevada Las Vegas. The individuals who participated in the study were recruited based upon their participation in an initial screening process. The individuals who participated in the screening process were Psychology 101 and Psychology 240 students at the University of Nevada Las Vegas. For participation in this portion of the study, students received extra credit or research credit, which went toward fulfilling a class requirement.

The number of individuals who were sampled as part of the screening phase of the study was 1,165; the sample was reduced to 1,147 due to substantial missing data for 18 subjects. Of the remaining subjects, 893 agreed to participate in the second stage if selected and 254 said no to further participation. Scores on the Chapman Scales and

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family history data for the remaining subjects were continually evaluated as new groups were screened in order to systematically identify individuals for inclusion in the second portion of the study. Screening procedures described in the Measures section were used to determine the presence of a family history of schizophrenia and/or threshold schizotypy symptoms on the Chapman Scales. Individuals who met inclusion criteria and who gave written permission for further contact (n =133) were then recruited over the phone and scheduled for further testing. Attempts were made to contact all subjects who met study criteria.

In addition to the primary selection criteria, several exclusion criteria were also utilized. At the same time subjects were contacted for participation in the second phase of the study it was also decided whether individuals had conditions predetermined as warranting exclusion. Individuals were excluded from the study if they: (a) were older than 45 years of age or younger than 18 years of age; (b) had a history of head injury or an incident involving a loss of consciousness; (c) had a serious medical illness or major physiological disturbance as indicated by the need for prescription medication; (d) were not free of over-the-counter medications with potential CNS effects (e.g., antihistamines) for at least 14 days before testing; (e) were unable to provide informed consent; or (f) spoke a language other than English as their first language. These criteria effectively excluded most individuals who may have had cognitive dysfunction resulting from extraneous factors or may have had a testing disadvantage at baseline.

Subjects Participating in the Cognitive Assessment

From the sample of 133 individuals who met criteria for participation in the second portion of the study, 26 participated in the cognitive testing. It is the data from these 26 that was utilized in the current investigation. Of these individuals, 10 had a family history positive for schizophrenia and 16 had elevated scores on the Chapman scales.
Procedures

Data Collection Procedures for Initial Screening

Individuals provided informed consent for participation in the initial screening process during which, family history, Chapman scores, and demographic information were collected. Table 1 presents a schedule of evaluation procedures (all tables are contained in Appendix D). As part of the screening process, individuals answered a question asking whether it would be acceptable to contact them for participation in the second portion of the experiment at some point in the future. Subjects were given a brief description of what the second phase of the experiment would involve and were informed that they would be paid $8 an hour for any further participation. Care was taken to ensure that all subjects were aware of their right to refuse participation at any time, even after having given written permission for further contact. Subject anonymity was maintained at all times by coding the evaluation results and storing these results in locked files.

This initial screening information allowed for a determination of whether an individual was eligible to participate in the second phase of the experiment. Two methods were used to identify individuals who may be at high-risk for schizophrenia. The inclusion criteria were, (1) a positive family history of schizophrenia or, (2) significantly elevated scores on the Chapman Scales. Summing of the scale scores of the Social and Physical Anhedonia scales (Soc/Phy) and the Perceptual Aberration and Magical Ideation scales (Per/Mag) derived the two Chapman variables used in the current investigation. The family group was selected from individuals who reported, on the Family History Questionnaire (FH+), having a first or second order relative with schizophrenia. Individuals were recruited for the nonfamilial schizotypy group if they reported a negative family history of schizophrenia, and scored 2 standard deviations higher than the UNLV sample mean on either combined Chapman index (i.e., the
Physical/Social Anhedonia index or the Perceptual Aberration/Magical Ideation index), or if they scored 2 standard deviations higher than the UNLV sample mean on any one of the individual scales (i.e., Physical Anhedonia, Social Anhedonia, Magical Ideation, and Perceptual Aberration) and at least 1.5 standard deviations above the UNLV sample mean on either of the two Chapman indices (i.e., Phy/Soc and Per/Mag).

After an individual had been identified as meeting the inclusion criteria, the individual was then contacted via the telephone, at that time a more in depth description of the project was provided by a research assistant, after which the individual was asked if they would be willing to participate in the cognitive assessment phase. The description of the project corresponded with the information presented in the informed consent form (see appendix B), including a summarization of the study and a brief description of the tasks involved. The research assistant who conducted phone screening never administered neuropsychological evaluations. This step was taken in order to ensure that the individual administering the neuropsychological evaluations was blind to group membership.

Individuals who agreed to participate in cognitive testing were then evaluated for exclusionary conditions. Those who met the criteria for participation were scheduled appointments for cognitive testing. Those individuals who agreed to participate and showed up for their appointments were requested to provide their informed consent by signing the aforementioned informed consent form (see Appendix B). In order to protect subjects’ anonymity and to minimize experimenter expectation effects, subjects and testers were blind to group membership. Additionally, all evaluation results were stored in secure locked files.

Individuals who participated in the cognitive assessment portion of the study completed the following tests: (1) the Lateral Dominance Test; (2) the California Verbal Learning Test; (3) Finger Tapping Test; (4) Trail Making Tests Parts A and B; (5) Purdue
Pegboard; (6) WAIS-III Vocabulary subtest; (7) WAIS-III Digit Symbol subtest; (8) WAIS-III Information subtest; (11) WAIS-III Digit Span Forward and Backward subtest; (12) WAIS-III Letter-Number Sequencing subtest; (13) WMS-III Corsi Block Forward and Backward subtest; (14) Controlled Oral Word Association (FAS); (15) Verbal Fluency Category; (16) Stroop Color-Word; (17) Wisconsin Card Sorting Test; and (18) the Continuous Performance Test. These measures were administered in a fixed order (as specified above) by either the primary investigator (Erin Warnick), who has extensive neuropsychological testing experience, or Kelly Smith, a graduate student who was trained by the principal investigator in standardized administration techniques. The tests were administered in a single evaluation session, which lasted approximately 3.5 hours. Breaks were given as needed with a scheduled break occurring for all subjects after the administration of the WCST and prior to participation in the DS-CPT.

Exclusion of Individuals with a History of Psychosis

Because the focus of the current study was on individuals at high-risk for schizophrenia and not individuals with an actual diagnosis of schizophrenia, it was important to ensure that individuals with psychotic disorders were excluded from the investigation. Administration of the psychotic disorders module of the Structured Clinical Interview for DSM IV (SCID), along with several of the inclusionary and exclusionary criteria employed in the investigation, made it highly unlikely that individuals who met criteria for a lifetime diagnosis of schizophrenia or schizoaffective disorder would be included in the final analyses.

First, individuals who participated were asked whether they had ever received treatment from a mental health provider or whether they took any prescription medications on a regular basis. If they answered affirmatively to either of these questions, they were excluded from the study. Second, individuals who participated in
the study had to be able to provide informed consent and had to be enrolled in college classes at the University of Nevada Las Vegas. This criterion excluded the majority of seriously psychotic individuals, as they are often unable to function at such high levels without medication.

As a third and final criteria to ensure that no individuals with diagnosable psychotic disorders were included in the experimental sample, all individuals were given the psychotic disorders module from the SCID. This was administered after all neuropsychological assessment was complete to ensure that the interview experience did not taint the testing. All individuals with SCID scores greater than 2 (threshold) on any single question were excluded. This cutoff criterion was stricter than is customary; as such, disqualification should not be interpreted as being synonymous with a diagnosis of schizophrenia. A more rigid threshold was employed in the current investigation in order to meet the goal of having no individuals with psychotic disorders in the sample.

Measures

The measures used in the current investigation include the Chapman Scales of Psychosis Proneness (Chapman, & Chapman, 1987), a family history questionnaire, and a battery of neuropsychological tests including: (1) the Lateral Dominance Test; (2) the California Verbal Learning Test; (3) Finger Tapping Test; (4) Trail Making Tests Parts A subtest; (8) WAIS-III Information subtest; (11) WAIS-III Digit Span Forward and Backward subtest; (12) WAIS-III Letter-Number Sequencing subtest; (13) WMS-III Corsi Block Forward and Backward subtest; (14) Controlled Oral Word Association (FAS); (15) Verbal Fluency Category; (16) Stroop Color-Word; (17) Wisconsin Card Sorting Test; and (18) the Continuous Performance Test. In addition, a number of demographic (i.e., age, gender, race, and education) and clinical (laterality, visual acuity, and alcohol consumption) variables were also measured. A description of the format of the
Chapman Scales is provided here, along with information regarding their validity and reliability. A brief review of the neuropsychological measures employed in this investigation is presented as well.

**Chapman Scales of Psychosis Proneness**

Rationale for Use of the Chapman Scales

There are a number of tests that have been used to psychometrically identify psychosis proneness (e.g., MMPI, The Eysenck Psychoticism Scale). The Chapman scales were selected for this study because of their prominence, theoretical approach, and adequate psychometric properties (Lenzenweger, 1994; Chapman & Chapman, 1985, 1987; Chapman et al., 1994). The development of the scales was based on the assumption that schizophrenia is a heterogeneous disorder with varied symptom clusters. Therefore, the authors sought to design scales that would distinguish separate varieties or forms of the disorder (Chapman et al., 1985). Schizophrenia is associated with both positive and negative symptom clusters. Positive symptoms represent an excess of normal functioning and are typically characterized by hallucinations and delusions. Negative symptoms are those which represent a deficit in normal functioning and include loss of motivation, social isolation, apathy, and flattened affect. The scales were designed to represent the different phenomenologic manifestations of the schizophrenia psychopathology. This theoretical approach is particularly relevant to the current study, as it has been predicted that separate etiologies of risk (i.e., family history of schizophrenia as opposed to "nonfamilial" schizotypal personality characteristics) will be characterized by different patterns of cognitive impairment and potentially schizotypal traits.
Format of the Chapman Scales

There are seven separate scales that make up the Chapman Scales of Psychosis Proneness; the Perceptual Aberration Scale (Chapman & Chapman, 1978), the Magical Ideation Scale (Eckblad & Chapman, 1983), the Revised Physical Anhedonia Scale (Chapman, Chapman, & Raulin, 1976), the Revised Social Anhedonia Scale (Eckblad, Chapman, Chapman, & Mishlove, 1982), the Impulsive Nonconformity Scale (Chapman et al., 1984), the Hypomanic Personality Scale (Eckblad, & Chapman, 1986), and the Infrequency Scale (Chapman, unpublished). "All of the scales have been carefully constructed to minimize correlations with social desirability and acquiescence factors while ensuring internal consistency (e.g., the coefficient alpha consistency reliabilities of all the scales were in the .80's, test-retest reliabilities ran between .75 and .85), content validity and construct validity" (Chapman & Chapman, 1985, 1987). Items on each scale are presented in a true-false format with aberrant responses keyed in both directions to reduce biased responding.

The 35-item Perceptual Aberration Scale (PAS) (Chapman, Chapman, & Raulin, 1976) was constructed to measure "grossly deviant perceptions, feelings, and beliefs about one's own body". The test also includes 7 items that sample symptoms for other perceptual distortions. The PAS includes items such as, "sometimes when I look at things like tables and chairs they seem strange" (true). The 30-item Magical Ideation Scale (MIS) (Eckblad & Chapman, 1983) measures "belief in forms of causation that, by conventional standards of the dominant culture, are regarded as invalid and magical". The MIS includes items such as, "I have occasionally had the silly feeling that a TV or radio broadcaster knew I was listening to him" (true). These two scales have been found to correlate highly and are often combined into a single measure of the positive dimension of schizotypy (Eckbald & Chapman, 1983). A combination of the two
measures was used in the current study. A score of 2 SD's above the mean was set as the cutting point.

The 61-item Revised Physical Anhedonia Scale (Chapman, Chapman, & Raulin, 1976) is designed to measure the lowered ability to experience pleasure. The PAS-R includes items such as, "there just are not many things that I have ever really enjoyed doing" (true). The Revised (40-item) Social Anhedonia Scale (Eckblad et al., 1982) is designed to assess schizoid indifference to other people, but it is not a measure of social anxiety (Mishlove & Chapman, 1985). The SAS-R includes items such as, "I have always enjoyed looking at photographs of friends" (false). Because these two scales (the Physical & Social Anhedonia Scales) have been found to correlate highly, they too are often combined. In the present study, the Social and Physical Anhedonia scales were summed to create a single variable (Phy/Soc), which has been found to reliably index the negative dimension of schizotypy. Although research suggests that the negative dimension may be more associated with a genetic or family risk (Gunderson et al., 1983; Kendler et al., 1995), predictive validity for poor social outcome has been demonstrated in both familial and nonfamilial high-risk groups (Freedman, Rock, Roberts, Cornblatt, & Erlenmeyer-Kimling, 1998).

The 51-item Impulsive Nonconformity Scale (Chapman et al., 1984) is an index of "failure to incorporate societal norms, a lack of empathy for the pain of others, and an unrestrained yielding to impulse and self gratification." The INS scale includes items such as, "I almost always do what makes me happy now, even at the expense of some distant goal" (true). The 48-item Hypomanic Personality Scale (Eckblad, & Chapman, 1986) is designed to measure subthreshold manifestations of mania. The scale includes items such as, "when I feel very excited and happy, I almost always know the reason why" (false). There is also an Infrequency Scale (Chapman, & Chapman, unpublished), that contains 13 items and is an indicator of aberrant and invalid responding. The
Infrequency scale includes items such as, "At times when I was ill or tired, I have felt like going to bed early" (false). The authors note that, "protocols with more than two of the infrequency items endorsed are considered invalid." This cutoff score was used in the current study. Items from all the scales were intermixed in a random order because the authors found that scores on the Perceptual Aberration and Magical Ideation Scales tended to be lower when they were administered together uninterrupted (Chapman, Chapman, Kwapił, & Zinser, 1994).

**Family History Questionnaire**

The family history questionnaire used in this study is not a validated measure for determining the psychiatric history of an individual's family. The standardized form was created with two goals in mind, 1) to elicit an accurate family mental health history, and 2) ensure the privacy of the individual and their family members. The form asks participants to, "please indicate whether any individuals in your immediate biological family have ever been treated for a psychiatric or psychological condition with medication or individual counseling." Directly below the form reads in bold, "PLEASE DO NOT INDICATE WHICH FAMILY MEMBER (for this portion include only biological MOTHER, FATHER, SISTERS, BROTHERS, and CHILDREN in your considerations)."

After this instruction, an inquiry is then made as to the degree of certainty the individual experiences with regard to knowledge of their family's psychiatric history (i.e., very certain, somewhat certain, or do not know). Any conditions for which individuals believe their family member was treated are then elicited. A list of conditions are presented (Schizophrenia, Bipolar Affective Disorder, Anxiety, Depression and other), with the instruction to "please check all that apply". A second and identical inquiry is then made regarding their extended biological family, which states, "for this portion include only
biological AUNTS, UNCLEs, NEPHEWS, NEICES, GRANDFATHERS, GRANDMOTHERS, & GRANDCHILDREN in your considerations”.

The family history questionnaire was used to screen for a family history of schizophrenia in the first and second order relatives of the subject. When at all possible, individuals with a first-order relative were sought. However, the use of second order relatives was necessary in order to obtain an adequate N in the family high-risk sample. It has previously been reported that the use of second-order relatives is acceptable as long as the proportion of shared genes greatly exceeds the frequency of the disorder among the general population (Hunt, Williams, & Barlow, 1986).

**Neuropsychological Tests**

All subjects received the same group of neuropsychological tests which included; the Lateral Dominance test, the California Verbal Learning Test, Finger Tapping Test, Trail Making Tests Parts A and B, Purdue Pegboard, WAIS-III Vocabulary, Digit Symbol, Information, Digit Span Forward and Backward, Letter-Number Sequencing subtest, Corsi Block Test Forward and Backward, Controlled Oral Word Association (FAS), Verbal Fluency Category, Stroop Color-Word, Wisconsin Card Sorting Test; and the Continuous Performance Test. Each test was administered in accordance with standardized procedures.

The goal of neuropsychological assessment is to "describe and delineate the independent variables which reflect the biological condition of the brain and thereby permit correlation of dependant (behavioral and/ or psychological) variables with brain status" (Reitan, 1993). The imagining techniques of magnetic resonance imaging (MRI) and computerized tomography (CT scan) are very good at diagnosis of conditions such as brain tumors and cerebral aneurysms. However, unlike behavioral measures, they do not reveal the functional capacity of the brain, or the individual’s ability to think logically.
The neurocognitive measures included in the current investigation are behavioral tests, which have been widely used to detect cognitive deficits in individuals with schizophrenia. These tests exhibit adequate psychometric properties, including test-retest reliability and construct validity. They have been found to be sensitive to cognitive deficits in individuals with schizophrenia and high-risk groups (Kremen et al., 1994).

Many of the tests included in the battery are believed to be subserved primarily by frontal or temporal lobe structures, and were selected given the extensive literature suggesting neuropathology in these structures in schizophrenia (Bilder, 1996). Frontal lobe tests include those assessing attention, working memory, abstraction and problem solving, and motor control. The neuropsychological test battery was supplemented with tests assessing verbal and visual memory given the potential importance of temporal lobe structures in the pathogenesis of schizophrenia. Table 2 contains the names of all the tests and the areas they measure.

Attention

Tests of attention include: the Continuous Performance Test (CPT), Digit Span Forward, Corsi Block Test Forward (from the Wechsler Memory Scale – III; WMS-III) and the Stroop Color-word Association Test. Efficiency of attention or "passive span of apprehension" (Kaufman, McLean, Reynolds, 1991; Hayslip & Kennelly, 1980, from Lezak, 1995) will be assessed using the Digit Span subtest for auditory information and it's visual analog, the Corsi Block Test – forward for visual information (WMS-III; Wechsler, 1997a). The Stroop Color-word Association Test will be used to assess interference effects (Stroop, 1935; Golden, 1978). Sustained attention was assessed utilizing the Degraded Stimulus version of the Continuous Performance Test (Nuechterlein; 1983), as has been used in similar high-risk studies (Nuechterlein; 1983, 1991; Nestor, Faux, McCarley, Shenton, & Sands, 1990).

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The Degraded Stimulus Continuous Performance Test (DS-CPT) takes approximately 16 - 20 minutes to complete. The CPT is a visual vigilance performance task that is administered via computer. Fifty percent degraded stimuli (0-9) are presented on a computer terminal at irregular intervals (mean=1000ms) with a stimuli duration of 200ms. Targets, the number "0," compose 25% of the 480 total trials. Subjects are directed to respond to targets by pressing a mouse key immediately after the target appears on the computer screen. This version of the CPT has been used extensively and found to differentiate high-risk subjects from controls and individuals with schizophrenia (Nuechterlein, 1991). The most common indices calculated for the CPT are sensitivity (CPT d'), and response criterion (CPT β). Sensitivity (CPT d') refers to the ability to discriminate the target (signal) stimuli from the nontarget (noise) stimuli. CPT d' is obtained by evaluating the hit rate and false alarm rate, a CPTd' of 0.0 represents a chance discrimination level. Response criterion (CPT β) measures the amount of perceptual evidence that the person requires to decide that a stimulus is a target.

The version of the Stroop Color-Word Association Test (Stroop, 1935; Golden, 1978) used in the current study consists of three pieces of paper each containing 5 rows of 20 items. There are three parts to the test. In Part 1, the subject reads randomized color names printed in black type. In Part 2, the subject has to name the color of X's (blue, red, and green). In Part 3, the subject reads the color names (blue, red, green) printed in colored ink (blue, red, and green), ignoring the color of the print (the print color never corresponds to the color name). The score for each task is the time taken to complete the task. Of primary interest is the subjects score on the interference (Part 3) trial. The Stroop test measures the ease with which a person can shift his or her perceptual set to conform to changing demands and suppress a habitual response in favor of an unusual one.
Memory

Working memory has been divided according to modality specific short-term memory stores that include the phonological loop and the visuospatial scratchpad (Baddeley, 1986, 1992). Auditory working memory was assessed in the current study with the Letter-Number Sequencing task and Digit Span Backwards (Wechsler, 1997b). Visual working memory was assessed with the backward condition of the Corsi Blocks from the WMS-III (Wechsler, 1997a).

Digit Span Forward & Backward is a subtest from the Wechsler Adult Intelligence Scale (Wechsler, 1997b). A sequence of digits is presented aurally to the examinee. The examinee is then asked to repeat the same digits in the same sequence. The backward version is exactly the same except following the presentation of the number series examinees are asked to repeat the number series in the reverse order. Each item consists of two trials, with different number combinations for each. Scores are the number of items correct for all trials.

The Spatial Span Forward & Backward is a subtest form the Wechsler Memory Scale III (Wechsler, 1997a) and is the visual analog to the Digit Span subtest from the WAIS-III. For visual Memory Span, individuals are asked to tap sequences of raised squares in the same order as the examiner. The number of squares tapped by the examiner increases as the test progresses. The test is discontinued when two failures occur at any one level. For Tapping Forward, subjects are asked to tap the squares in the same order as the examiner. For Tapping Backwards, examinees are asked to tap the squares in reverse sequence. Scores are the number of trials successfully completed.

Letter Number Sequencing is a subtest from the Wechsler Adult Intelligence Scale (Wechsler, 1997b). A combination of numbers and letters is presented aurally to the examinee. Immediately following the presentation, the examinee is asked to repeat back the series of numbers and letters starting with the numbers in sequential order.
followed by the letters in alphabetical order. Each item consists of three trials, with different number combinations for each. Scores are the number of items correct for all trials.

Learning & Long-term Memory

The California Verbal Learning Test (CVLT; Delis et al., 1987) was used to assess recent memory for verbal information that is presented auditorily. The CVLT is a list learning task that has been widely used to assess the varied aspects of how verbal learning occurs as well as the amount of verbal material learned (As cited in Spreen & Strauss, 1998). The recognition component of the CVLT allows for evaluation of interference effects and retrieval. The CVLT measures recall, recognition, and list learning over multiple trials. Examinees are presented a grocery list (List A) 5 times and asked to recall the list immediately after each presentation. A second grocery list (List B) is then presented and recalled as a distracter list, after which subjects are again asked to recall items from grocery list A. Following the free recall of grocery list A, subjects are cued with the categories fruit, clothing, tools, and spices and asked to name all the items from list A that belong to each semantic category. After a 20 minute delay, during which nonverbal testing (i.e., Finger Tapping, Purdue Peg Board, and Trails A & B) is given, subjects are again asked to recall items from list A. Following the free recall task cued recall and recognition of list A is assessed. There are a variety of scores derived from the CVLT, however for the purpose of this study the only scores calculated were: immediate recall on lists 1-5, recall of list b, immediate free and cued recall, delayed free and cued recall, discriminability, and recognition.
Verbal IQ

The Vocabulary subtest from the Wechsler Adult Intelligence Scale III (Wechsler, 1997b) consists of 33 items that require the subject to provide definitions for words of varying degrees of difficulty. Item scores can range from 0-2, with a two point score indicating a full credit response, one point indicates a partial credit response, and 0 points represent an incorrect response or lack of a response.

The Information subtest from the Wechsler Adult Intelligence Scale III (Wechsler, 1997b) consists of 28 items that require a general knowledge of current and historical events. Items are scored as either correct or incorrect and the total number of correct items serves as the raw score. The Information and Vocabulary subtests are highly correlated with Verbal IQ scores and are included in this study as estimates of Verbal IQ.

Frontal/Executive Abilities

Frontal/Executive abilities were examined via a standard administration of the Wisconsin Card Sorting Test (WCST; Grant & Berg, 1948; Heaton, Chelune, Talley, Kay, & Curtiss, 1993), Trailmaking Test, Parts A & B (Reitan, Wolfson, 1993), Controlled Oral Word Association (FAS), and Verbal Fluency Category (VFCAT), and the Digit Symbol subtest from the WAIS-III (Wechsler, 1997b). All five tests have been extensively used in the evaluation of patients with schizophrenia and groups at high-risk for the disorder.

For the Wisconsin Card Sorting Test (WCST) four stimulus cards are placed in front of the subject, the first with a red triangle, the second with two green stars, the third with three yellow crosses, the fourth with four blue circles on them. The subject is then given two packs of cards, with response cards in each. On the cards are designs similar to those on the stimulus cards, varying in color, geometric form, and number. The subject is told to match each of the cards in the decks to one of the four key cards and is given feedback each time as to whether he or she is right or wrong according to a
predetermined principal. There is no time limit to this test. Adequate performance on the WCST requires abstract concept formation, the ability to modulate impulsive responding, the ability to develop and maintain a cognitive strategy, and the ability to shift strategy as feedback is given. The dependant measures used in this study were the number of perseverative errors, expressed as a T-score, and the number of categories achieved.

The Trail Making Test Part A & B (Reitan & Wolfson, 1985) is a test for visual search, attention, mental flexibility, and motor function. Part A consists of 25 circles; each contains a number from 1 to 25. The subject has to connect the circles by drawing lines with a pencil as quickly as possible beginning with 1 and proceeding in numerical order to number 25.

Trail Making Test Part B consists of circles numbered from 1 to 13 and lettered from A to L. The task in part B is to connect the circles in sequence, alternating between numbers and letters. The Trail Making Test B requires immediate recognition of the symbolic significance of numbers and letters, ability to scan the page continuously to identify the next number or letter in sequence, flexibility in integrating the numerical and alphabetical series, and completion of these requirements under the pressure of time (Reitan & Wolfson, 1985). Time required to complete the tasks was used as a measure of performance.

Controlled Oral Word Association (COWA) is a phonetic fluency measure designed to assess spontaneous verbal production of words in a limited period of time. Subjects are given 60 seconds to produce orally as many words as they can beginning with the letter specified by the examiner. The most commonly used letters for this test and the ones used in the current study are F, A, and S. Scoring involves summing the number of valid words for each letter. Invalid words include: proper nouns, wrong words, and repeated words or ones in which only the ending is changed (e.g., eat, eating). Test-
retest reliability estimates vary depending upon the population and the amount of time between testings, however in normal adults retest reliability after 19 -42 days was .88 (des Rosiers & Kavanagh, 1987 - as cited in Spreen & Strauss, 1998).

Verbal Fluency -Category (VFCAT) is a measure of semantic fluency and is designed to assess spontaneous production of words belonging to a given category or group such as "food". Subjects are given 60 seconds to produce as many words as they can that belong to the stated category. A common category and the one used in the current study is "Animals". Scoring involves calculating the number of valid responses given during the 1 minute time period.

Neuropsychological studies investigating the COWA and the VFCAT have repeatedly noted the demands placed on executive abilities during the performance of these tasks (Spreen & Strauss, 1998). Both tests are thought of as measures of frontal lobe impairment however, phonetic fluency is believed to be a more sensitive measure of left hemisphere involvement as compared to right (Loring et al., 1994 - as cited in Spreen & Strauss, 1998) while category fluency, which makes more demands on semantic cognitive abilities, is thought to incorporate right frontal dysfunction as well.

The Digit symbol substitution task is a subtest from the WAIS-III (Wechsler, 1997b) which consists of rows of blank squares; each has a randomly assigned number (1-9) printed above. A key is printed above these rows showing each number paired with a different nonsense symbol. The subject’s task is to fill the blanks with the corresponding symbols as rapidly as possible. Subjects are given 2 minutes to finish as much as possible. Total number of blanks filled correctly is the final score.

Lateral Dominance

The Lateral Dominance Examination (Reitan & Wolfson, 1985), consists of a series of performances used to determine an individuals preference for using the left or right
hand on a unimanual task and the left or right foot on a unipedal task. This information is important for establishing handedness in order to administer and interpret some of the tests.

Motor

Finally, the Purdue Pegboard Test (Purdue Research Foundation, 1948) and the Finger Tapping Test (Reitan & Wolfson, 1993) were administered to assess motor abilities. The Pegboard test is a measure of timed motor speed and coordination that is sensitive to subtle motor dysfunction. The finger-tapping test is a widely used measure of manual dexterity and laterality.

The Purdue Pegboard is a test of manual dexterity originally developed for selecting factory workers. The board contains two parallel columns of 25 holes. Three trays located at the top of the board, are filled with metal pegs. Subjects are instructed to select one peg at a time with the preferred hand (e.g., right) and place it as quickly as possible into the right column. Subjects are given 30 seconds to place as many pegs as they can into the holes beginning at the top and moving down without skipping any holes. Three trials are performed on the dominant hand after which the same procedure is repeated with the nondominant hand and then with both hands simultaneously. Scores are derived by counting the number of pins inserted in the time period for each hand. A mean score for each hand and both hands is then calculated.

The Finger tapping test is an index of finger-tapping speed. Subjects are instructed to tap as quickly as possible with the index finger of the preferred hand after which they are instructed to perform the same task with their nonpreferred hand. Ideally, five consecutive 10 second trials are given for each hand. However, too much variation in performance (i.e., a score five taps slower or faster is considered to be an outlier) within the five 10-second trials necessitates the administration of more trials, the maximum
number being 10 for each hand. Final scores are calculated by taking the mean of the valid trials, five trials within 5 points of each other, or if this criterion is not met, the mean of 10 trials.

Finger Tapping is primarily dependent upon motor speed and the integrity of the motor cortex for the contralateral side of the brain as the hand used (Reitan & Wolfson, 1985). Results are interpreted primarily in relation to a disparity in measurement on the two sides of the body, which are hypothesized to have significance for the biological status of the contralateral cerebral hemisphere (Reitan & Wolfson, 1985).

Data Analysis

The data collected in this study was subjected to several phases of statistical analyses. In the first phase, the data was examined to detect the presence of missing variables or outliers. Next, analyses were performed to determine the comparability, on clinical and demographic variables, of the initial sample and subsequent samples created by attrition and/or the employment of the inclusion criteria (i.e., Infrequency score less than 3; agreement to be contacted for further participation; qualification for participation in the second portion of the study based upon family history or Chapman Scale scores; and participation in the second portion of the study). Preliminary analyses of the Chapman Scales and family history data were also accomplished to determine whether the strategy for dividing groups was successful. After the preliminary analyses were complete, descriptive statistics were calculated for major demographic and clinical variables in the current investigation.

Following description of the data, comparisons were made between experimental groups on major variables (i.e., DS-CPT, WCST, Stroop, Purdue Peg Board, LNS; and Digits and Spatial Span Backward) to determine the presence or absence of predicted differences; post hoc comparisons were performed on the remaining cognitive variables.
Because the design of the current study involved contrasting the performances of the at-risk groups on the neurocognitive measures, Univariate F tests were utilized to make between group comparisons with the following exceptions. For paired lateralizing tests, such as pegboard performance for the right and left hands, a repeated measures design was employed in which the right and left hand performances were treated as repeated measures, and group membership was used as the between subjects variable.

Similarly, analyses of the component processes of specific abilities were subjected to repeated measures. For example, on the California Verbal Learning Test, the recall and recognition scores were considered repeated measures with group membership utilized as the between subjects factor. Additionally, the repeated measures design with group membership as the between subjects factor, was also employed to evaluate paired modality specific tests, such as verbal and visual working memory performance. The repeated measures analytic strategy was used in these cases because it allowed for the examination of double dissociations which, if present, would provide strong evidence supporting neurocognitive profiles that are unique to each of the high-risk groups. An example of a double dissociation would be if the right hand pegboard performance of the FH+ group was better than that of the FH− group, but the left hand performance of the FH+ group was worse than that of the FH− group. In this situation, one could infer right hemisphere impairment in the FH+ group and left hemisphere impairment in the FH− group, a finding supporting unique pathophysiology associated with each type of risk.

The last phase of data analysis involved examining the relationship between the major cognitive variables and the Chapman indices in order to clarify the relationship between neuropsychological test performance and the positive and negative dimensions of schizotypy. For all analyses, an alpha level of .05 was used to determine the significance of findings, unless otherwise noted.
CHAPTER 4

RESULTS

Data Screening

Missing scores for the entire sample of 1,165 subjects that completed the screening procedures were dealt with in the first step of data screening. It was determined that 90 subjects had some missing data on the Chapman scales due to a lack of responding or an omission. Frequency counts indicated that no individual scale exhibited a greater tendency to have questions omitted. The largest contributor to incidence of missing data occurred as a result of the final page of the Chapman Scales (10 questions) being overlooked. For these cases the mean score was substituted for the missing data, as this procedure does not increase the variance of the sample, but does retain statistical power (Tabachnick and Fidell, 1989). Only in situations where a case had a large number of missing values was that case deleted (n = 18). The substitution of means for Chapman Scale questions was not necessary for any member of the experimental sample.

In order to detect out of range values, frequency counts were performed for each of the Chapman variables under consideration. Also, the means and standard deviations were examined to determine if these variables were plausible. Individual scores that appeared extreme or were out of range were examined and corrections were made if there were data entry errors.

In the second step of data screening, neurocognitive test scores and demographic measures for the individuals completing these assessments were dealt with in the same
manner previously discussed. Of those individuals completing the neuropsychological evaluations (N= 26), five had missing data for level of education. Because all students were recruited from Psychology 101 and 240 courses, suggesting relative homogeneity in education, and the mean number of years of education of the remaining sample was 13.1, a mean of 13.1 was used to replace those cases with missing education data.

In order to detect out of range values, the ranges, means, and standard deviations were examined to determine if all data points were plausible. Neuropsychological tests scores that appeared extreme or were determined to be out of range due to data entry errors were corrected. In order to evaluate whether cognitive variables were normally distributed, skewness and kurtosis were calculated for each of the variables used in the analyses. As can be seen from Table 3, most variables were relatively normally distributed with skewness and kurtosis values of |1| or less. A notable exception was the Stroop word condition, which had skewness and kurtosis of 3.32 and 13.61, respectively.

Inspection of the raw data indicated that the distribution was skewed and kurtotic because of a single outlier; one individual exhibited very poor performance scoring almost three standard deviations above the mean. Two methods were used to attempt to normalize the distribution prior to further analyses. First, log transformation was utilized in an attempt to normalize the distribution. Second, the outlier raw score was converted so that it was one unit greater than the next highest scores in the distribution in order to decrease its effects on the distribution. Both methods substantially decreased the skewness and kurtosis estimates, although the second method was more satisfactory. The transformed scores are also presented in Table 3. Analyses were conducted using transformed scores and the raw scores to determine the effect that transformation had on the results.
Sample Selection

Of the 1,147 subjects that completed the Chapman scales and the family history questionnaire 254 said "no" to further contact. An additional 130 subjects had an infrequency score higher than 2, indicating aberrant responding and unreliable reporting of symptoms, and were thus eliminated from further participation. After excluding these individuals, 811 subjects were available for further evaluation on the Chapman Scales and the Family History Questionnaire. A comparison of included subjects (n = 1017) and excluded subjects (n = 130) (i.e., aberrant responders) from the initial sample indicated no significant difference between groups on the demographic variable age (F (1,1145) = 2.67, p>.05). However, chi-square analyses indicated significant differences between the "included" and "excluded" groups on gender (\(\chi^2 (1, 1) = 27.51, p<.001\)), race (\(\chi^2 (1, 5) = 11.04, p=.051\)), family history of schizophrenia (\(\chi^2 (1, 5) = 11.04, p=.051\)), and willingness to be contacted (\(\chi^2 (1, 1) = 18.57, p<.001\)). A significantly greater number of males invalidated the Chapman Scales and a significantly greater number of those who invalidated the Chapman Scales said no to further contact. Additionally, a family history of schizophrenia was associated with significantly fewer invalid profiles overall, while African American students were generally found to have a significantly greater number of invalid infrequency profiles. Descriptive statistics are presented in Table 4.

A second comparison, in which the "valid responding" group was divided according to those who said "yes" to further contact and those who said "no", was accomplished on the demographic variables and the Chapman Scales. Similar to the previous finding, results indicated a significant difference on the demographic variable gender \(\chi^2 (1,1) = 8.50, p<.01\), with males declining participation more frequently than females. No differences were noted between the groups on the variables race \(\chi^2 (1, 5) = 8.40,\)
Analyses of the Chapman Scales indicated significant differences between those who said "yes" and those who said "no" to further participation. Perceptual Aberration and Hypomanic Personality scores along with the Per/Mag index were significantly higher for those who said "yes" as compared to those who said "no", while the Physical Anhedonia scale, as well as the Phy/Soc index, were significantly higher for individuals who said "no" compared to those who said "yes". Descriptive statistics and F-test results are presented in Table 6.

An evaluation comparing the individuals that met study criteria (n = 167) (i.e. family history of schizophrenia or significant elevation on the Chapman Scales) and agreed to participate (n=133) to those that met study criteria but did not agree to participate (n=35), indicated findings similar to those noted in the previous section. Significant differences were present between the groups on the Physical Anhedonia scale and the negative symptom indicator (i.e., Phy/Soc). The same three scales that were significant in the last analyses approached significance in the current analyses (i.e., Perceptual Aberration, Hypomaniac Personality, and Per/Mag). Descriptive statistics and F-test results are presented in Table 7.

Further analyses indicated significant differences between groups with regard to gender $\chi^2 (1, 1) = 4.90, p < .05$, and race $\chi^2 (1, 5) = 16.09, p < .01$, as well. Males refused participation more frequently than females and a greater number of Caucasian and African American students agreed to participate as compared to individuals of Hispanic and Asian origin. No significant differences were present for age $F (1, 166) = 1.36, p > .05$ or family history of schizophrenia $\chi^2 (1, 1) = .13, p < .01$. Descriptive statistics are presented in Table 8.

From the 133 eligible subjects (i.e. those who met study criteria, had valid profiles,
and agreed to further contact), 26 individuals completed the neuropsychological evaluations. Of these 26, one was later excluded after it was determined that he had prior exposure to some of the neuropsychological tests and that he had borderline scores on the Chapman scales. For this individual, Chapman scores were considered borderline after comparing his scores to those for the total UNLV sample. In general, the UNLV sample obtained relatively higher scores on some of the Chapman scales (Social and Physical Anhedonia and Impulsive Nonconformity) when compared to the University of Wisconsin norms, that were provided with the Chapman scales by the authors. All other individuals included in the sample exceeded the UNLV cutoff scores for Per/Mag and Phy/Soc indexes. Two additional subjects were excluded due to left hand dominance. Left handers were excluded because of the increased possibility of mixed or reverse hemisphere dominance, which would have confounded comparisons between groups based on laterality measures. Eligible subjects who did not participate in the neuropsychological evaluations either refused to participate after filling out the initial questionnaires, could not be reached, or failed to show up for their scheduled neuropsychological evaluation (68 subjects were scheduled but did not show for their appointments). ANOVA and chi-square analyses indicated no significant demographic (i.e., age $F(1, 131) = 9.26, p > .05$, gender $\chi^2(1, 1) = 1.16, p > .05$, race $\chi^2(1, 4) = 2.65, p > .05$, and family history of schizophrenia $\chi^2(1, 1) = 1.89, p > .05$) differences between these groups. Descriptive statistics are presented in Table 9. Analyses of the Chapman Scales indicated no significant differences on any individual scale or on the composite indices Per/Mag, and Phy/Soc. These results suggest that the final sample of 26 individuals was similar to the larger sample in terms of symptom severity and presentation, and could therefore be considered representative of the larger sample of individuals. Descriptive statistics and F-test results are presented in Table 10.
Preliminary Analyses

Chapman Scales and Family History Questionnaire

One hundred and thirty three individuals met criteria for inclusion in the current study based on significantly elevated scores on an individual Chapman scale (n = 9) or on one of the two Chapman indices, social/physical Anhedonia (n = 40), magical/perceptual aberration (n = 45), or by having a family history that was positive for schizophrenia (n = 38). Analyses were accomplished that compared the sample of FH+ (n = 38), FH- (n = 94), and valid controls (n = 679) on demographic variables, the Chapman scales, and the two Chapman indices. Descriptive statistics for demographic variables are presented in Table 11. Descriptive statistics, F test results, and post hoc comparisons for the Chapman variables are presented in Table 12.

There were no significant differences between the three groups on the demographic variables of gender $\chi^2 (1, 2) = 5.50, p > .05$, race $\chi^2 (1, 10) = 13.37, p > .05$, and age $F (2, 810) = .26, p > .05$. ANOVA indicated that the FH- group scored significantly higher than the normal comparison group on six of the Chapman scales and the indices physical/social anhedonia (Phy/Soc) and perceptual aberration/magical ideation (Per/Mag). Compared to the FH+ group, the FH- group scored significantly higher ($p < .05$) on the indices Phy/Soc and Per/Mag and all of Chapman scales not including the Hypomanic Personality Scale. The FH+ group scored higher than the NC group on all seven scales, and significantly so on the Magical Ideation Scale, and the Per/Mag index. Differences on the other scales and index were not significant. Results of these initial analyses of the Chapman scales indicate that the selection method was successful in obtaining a FH- sample that exhibited sub-threshold symptoms of schizophrenia.

Comparisons of Demographic & Clinical Variables

For the 23 subjects included in the high-risk groups, preliminary analyses indicated
no significant differences between the FH+ (n = 10) and FH- (n = 13) groups on any of the demographic variables including race ($\chi^2 (1,3) = 4.95, p > .05$, education ($F (1,21) = .85, p > .05$, gender ($\chi^2 (1, 21) = .67, p > .05$, age ($F (1,21) = 1.22, p > .05$, and visual acuity ($F (1,21) = .22, p > .05$. The group scores on the alcohol measure were also similar, with no significant differences between the groups on this variable ($F (1,21) = 6.46, p > .05$). Also, none of the individuals included in the study exceeded the cutoff score that would indicate risk for alcohol abuse or dependence. None of the subjects met criteria for schizophrenia as indicated by the SCID. Additionally, there were no differences between the groups on the Vocabulary ($F (1,21) = .002, p > .05$, or Information ($F (1,21) = .0003, p > .05$ subtests of the WAIS-III indicating comparable levels of verbal intelligence for the groups. Lack of significant differences between groups assured they were equal with respect to these important variables. Descriptive statistics are presented in Table 13. Compared to the normative sample both the FH+ and the FH- groups had clinically elevated Chapman Scales. However, although none of the differences were significant, the FH- group scored worse than the FH+ group on four of the six clinical scales and both the positive and negative symptom indices. Results of these analyses are also presented in Table 14.

Evaluation of Major Hypotheses

Table 15 contains descriptive statistics of the experimental groups on the major cognitive variables assessed. In addition, means and standard deviations of normative samples taken from various sources have been included for comparison purposes on the majority of neuropsychological measures included in the study. These variables were used to test the major hypotheses of the current study.
Hypothesis I: Evaluation of Cognitive Variables

It was predicted that the FH+ group would score worse than the FH- schizotypy group on a measure of attention (CPT d' and beta, Stroop), abstract reasoning (WCST % perseverative errors), perceptual motor speed (Purdue Peg Board) and working memory (LNS; Digit Span and Spatial Span). No differences were hypothesized to be present on a test of verbal secondary memory (CVLT). The results of the ANOVAs evaluating these hypotheses are presented in Table 16. Descriptive statistics for the FH+ and FH- groups on the neurocognitive tests were previously presented in Table 15. Results of the ANOVAs indicated that the hypothesis was partially supported.

With regard to the California Verbal Learning Test (CVLT), the interaction effect and the within subjects quadratic contrast was significant when the initial list learning trial was compared to the fifth trial and the delayed free recall trial. This interaction effect is presented in Figure 1. As can be seen from the Figure, the FH- group demonstrated a pattern of performance characterized by better recall (more words) on the first trial, fewer words on the fifth trial, and about the same number of words as the FH+ group on the delayed recall trial. In contrast, the FH+ group had poorer initial recall (first trial), and better recall performance on the fifth trial, followed by performance on the delayed recall trial that was approximately equal to the FH- group. These interaction effects represent statistically as well as clinically significant differences between the groups with respect to verbal learning and recall. No significant interaction effects were present for the CVLT analyses examining interference effects (trial 5 compared to list A) or long delayed recall vs. recognition differences, although significant main effects for evaluation were present for both analyses. The main effect for interference indicated an expected decrease in recall following presentation of list B. Similarly, the main effect for recall vs. recognition reflected the expected increased number of words recalled during the recognition task. Significant interaction effects were also present when repeated measures analysis was
Figure 1.

Interaction effect for CVLT recall 1, recall 5, and delayed recall for FH+ and FH- Groups.
used to compare the performance of the FH+ and FH- groups on the Digit Span Test and the Visual Span Test. Figure 2 indicates that, contrary to what was hypothesized, the FH+ group performed better on Digit Span than the FH- group. However, the reverse pattern was present for Visual Span, which accounts for the lack of significant main effects and the significant interaction effect.

Because Digit Span and Visual Span are each composed of a forward condition and backward condition, further analyses were accomplished to determine if the overall interaction effect could be better accounted for by performance on these individual conditions. Significant interaction effects were again present for these analyses and the results are presented in Table 16. The interaction effect for the Digit Span forward and Visual Span forward comparison are presented in Figure 3, while the Digit Span backward and Visual Span backward interaction appears in Figure 4. Both Figures indicate the same pattern of performance previously noted, i.e., the FH+ group performed better on Digit Span tests and worse on the Visual Span test when compared to the FH- group.

Repeated measures analysis indicated a significant effect for test (i.e., performance over time) was present for CPT d' although no between subject or interaction effects were present. A significant decrease in d' scores across the 6 blocks of the CPT accounted for the significant test effect, indicating a decrease in vigilance over time. No significant effects were present for CPT beta.

A significant main effect for test indicated the expected differences in performance between Stroop conditions. The Stroop word and color versions are relatively simple tasks, which most subjects are able to complete without difficulty in a relatively short period of time. In contrast, the interference version is substantially more demanding and as such is expected to take longer to complete. Analyses were run for raw scores and transformed scores, with no difference in the pattern of main effects or interaction.
Figure 2.

Interaction for FH+ and FH- groups on Digit Span and Visual Span tests.
effects. Analyses conducted with raw scores are presented for ease of interpretation. Means and standard deviations are presented in Table 15.

A significant main effect for test on the Purdue Peg Board indicated the expected differences in performance between right and left hands for right hand dominant individuals. Performance with the dominant hand is approximately 10% faster than with the nondominant hand, which was reflected in the scores of the two groups. Means and standard deviations are presented in Table 14.

It was hypothesized that the FH+ group would perform worse, relative to the FH- group, on the WCST index percentage of perseverative errors and the WAIS subtest LNS. However, F-tests indicated no significant differences were present between the groups on these measures. Means and standard deviations are presented in Table 15.

Hypothesis 2: Schizotypy and Cognitive Function

Of the FH+ individuals, those with greater elevations on the schizotypy scales were predicted to 1) score worse than the other members of the family history positive group, and 2) score worse than the nonfamilial schizotypy group on the previously mentioned measures of attention (DS-CPT d') abstract reasoning (WCST), working memory (Digit Span, Visual Span, and LNS) and perceptual motor speed (Purdue Peg Board).

In order to evaluate the first part of Hypothesis 2, a composite score was developed that represented the sum of the Physical Anhedonia, Social Anhedonia, Perceptual Aberration, and Magical Ideation scales. Preliminary comparison of the composite scores indicated a significant difference between the groups ($F (1, 21) = 8.49, p < .01$). The FH+ group had significantly lower scores (mean = 50.9, sd = 10.0) than the FH- group (mean = 61.5, sd = 7.4). Correlations were calculated between the composite score and the neurocognitive variables of interest. Only the FH+ group was included in

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these analyses ($n = 10$). The results of the correlations are presented in Table 17. A significant correlation was present between the Chapman Scale composite score and CVLT list 1-5 recall ($r = -.62$, $p < .05$), which indicates that, for the family history group, as schizotypy symptoms increase learning decreases across the five trials of the CVLT. In order to evaluate if this effect was specific to the FH+ group or was a more general finding that was also present in the FH- group, a correlation was calculated between the FH- group’s composite score and CVLT list 1-5. As with the FH+ group, the correlation for the FH- group was also significant ($r = -.48$, $p < .05$, $n = 13$) and indicated that as schizotypy symptoms increased, learning decreased. When both groups were included in the analysis, as is presented in Figure 5, the correlation remained significant ($r = -.52$, $p < .05$, $n = 23$).

The second part of Hypothesis 2 was evaluated by dividing the FH+ group into high and low schizotypy subgroups using the composite score. The sample was divided evenly so that the 5 subjects with the highest composite scores were in the high schizotypy group (mean composite score = 57.4, $sd = 5.8$) and the 5 subjects with the lowest composite scores were in the low schizotypy group (mean composite score = 44.4, $sd = 9.2$). A t-test indicated that high and low groups differed significantly on the schizotypy composite score ($t = 2.7$, $df = 8$, $p < .05$). Univariate tests were performed that compared the FH-, FH+ (high), and FH+ (low) groups on the neurocognitive variables of interest. Descriptive statistics and F-test results are presented in Table 18. No significant differences emerged between the groups on any of the measures, although the Digit Span Test approached significance ($p = .083$).

**Hypothesis 3: Negative Schizotypy and Attention**

It was hypothesized that the negative dimension of schizotypy would 1) be more highly associated with family liability as well as 2) be associated with poorer
Figure 5.

Correlation between Chapman composite score and CVLT Recall trials 1-5 for the entire sample.
performance on a test requiring sustained attention (DS-CPT). To evaluate the first part of the third hypothesis, a correlation was calculated between the negative dimension of schizotypy (Phys/Soc Anhedonia) and family history of schizophrenia. In this correlational analysis, family history of schizophrenia was coded as 1 (FH-) or 2 (FH+) and was then correlated with scores from the Phy/Soc Anhedonia scale. Analysis indicated no significant correlation (one-tailed) was present for family liability and the negative dimension of schizotypy ($p > .05$).

The second part of hypothesis 3 was evaluated by calculating a correlation between the negative dimension of schizotypy and select variables from the CPT (CPT $d'$, CPT hit rate, and CPT Beta). The results of these correlations are presented in Table 19. A significant negative correlation was present between the negative schizotypy dimension score and CPT Beta. The correlation is presented in Figure 6 and indicates that, as negative schizotypy symptoms increase response bias decreases (becomes more liberal).

To determine if this finding is specific to the negative dimension of schizotypy further analyses were accomplished which calculated the relationship between this measure and the positive dimension of schizotypy (Per/Mag). These correlations are presented in Table 19. A significant positive correlation was present between the positive dimension of schizotypy and the CPT response criterion score (CPT Beta). Figure 7 indicates that, as scores on the positive dimension of schizotypy increase willingness to respond becomes more conservative (Beta increases).
CHAPTER 5

DISCUSSION

Although some missing data was present for the Chapman scales, all of the individuals in the experimental groups (FH+ and FH-) completed the Chapman scale items. Additionally, all subjects in the experimental conditions obtained scores on the Infrequency scale of less than 3, suggesting that they responded in a consistent manner to the Chapman scale questions. It appears then, that their scores on the Chapman scales were a valid reflection of their current subjective experiences and could be accurately used to select individuals for the schizotypy group.

For the total sample, female subjects and those with a family history of schizophrenia were more likely to complete the Chapman scales accurately when compared to the rest of the sample. Males in general were less likely to agree to further participation after completing the Chapman scales, as were individuals who were of Asian and Hispanic ancestry. Also, individuals exhibiting increased social and physical anhedonia were more likely to decline further contact. This finding may reflect the nature of negative symptoms, which often include social isolation and withdrawal. In contrast, individuals who agreed to participate were more likely to have elevations on the positive symptoms, which are not typically associated with interpersonal disturbance or avoidant behavior.

There was a high no-show rate for neuropsychological evaluations. Of the 94 individuals scheduled for evaluation, 26 completed neuropsychological testing. This rate of attrition was not anticipated and may have been due to a number of factors. One
consideration is that all of the individuals were by definition within the schizophrenia spectrum and as such, may have exhibited poor motivation and noncompliance as a feature of the disorder. If this were the case, the individuals included in the study may have had less severe interpersonal and cognitive deficits when compared to those who volunteered to participate but then in the end did not participate. For the entire sample, (N = 1147) individuals who declined further contact (n = 254) after completing the Chapman scales also exhibited more severe negative symptoms, and negative symptoms are most consistently associated with cognitive deficit and social impairment (Roy & Crowe, 1994). However, the group that agreed to participate in neuropsychological testing but then did not follow through did not exhibit more severe negative symptoms when compared to the group that did complete neuropsychological evaluation.

An alternate explanation for the high attrition rate may be the somewhat extensive time allowed to lapse between completion of the Chapman Scales and actual phone contact. In some instances, this interval reached two months or more. These delays were not typical and occurred for various reasons including summer and winter break, time needed for data entry and scoring procedures, and scheduling difficulties. Another possibility for the poor follow through may have been that the incentives offered for participation were not great enough to convince the majority of students to contribute three-and-a-half hours of their valuable study and free time. If this were the case, it might explain why such a large number of students were originally open to scheduling an appointment but then when it came to meeting the commitment, did not show.

Preliminary Analyses

When all individuals who qualified for inclusion in the FH+ (n = 38) and FH- (n = 94) groups were compared to the remainder of the sample (n = 679), significant differences
in symptomatology were present. The FH- group exhibited both positive and negative symptoms, while the FH+ group exhibited primarily positive symptoms. The FH- group also exhibited more severe positive and negative symptoms relative to the FH+ group. Selection of the sample at least partially accounted for these differences in that all of the FH- group members had to have elevations 2 sds above the mean on either the positive or negative symptom domains in order to be included in the study, while no such requirement was made for the FH+ group. In contrast, the FH+ and FH- groups who completed neuropsychological testing (n = 23) did not differ on the positive and negative schizotypy dimensions when these dimensions were analyzed separately. Also, there were no significant differences between the groups on other variables that could have affected neuropsychological test performance, including years of education, verbal IQ, age, and alcohol use. Similar visual acuity and CPT "lookaway" scores were also obtained by the groups, which helped ensure that performance measures on the CPT were valid.

Evaluation of Major Hypotheses

In comparison to published norms for the individual tests, both groups performed average to above average on most measures in the battery. These findings are inconsistent with many of the previously reported studies, which have noted a pattern wherein both family and psychometrically defined high-risk groups do poorer than normal control groups on measures of neuropsychological functioning. Because the average subject in the current study had completed at least 1 year of college, individuals with earlier age of onset and a potentially more severe course were excluded. Also, the years of education undoubtedly contributed to the average performance of these subjects on the neuropsychological measures. Thus, individuals included in the current
study represent select samples that were probably at the higher end of functioning for these at-risk groups.

**Hypothesis 1**

Significant differences in neuropsychological test performance between the FH+ and FH- groups were noted in a number of areas including verbal learning and verbal and visual working memory. The FH- group was slower to learn a list of words than the FH+ group, which suggested a problem with initial encoding of verbal information. However, retention of information over time was also different between the groups and favored the FH- group as indicated by equal performances on long delayed recall and recognition tests. Essentially, the learning advantage exhibited by the FH+ group after five exposures to the word list had disappeared when they were asked to recall the same list 20 minutes later. Because there were no differences present between the groups on the delayed recognition trial of the CVLT, the decrease in long delayed free recall was not the result of retrieval deficits. Rather, the decrease in word recall emerged after the presentation of List B and persisted until delayed recall approximately 20 minutes later. Therefore, the decline is more likely due to susceptibility to interference effects on the part of the FH+ group, or decay of information from the long-term store over time.

Verbal learning deficits similar to, although not as severe as those seen in schizophrenia, have previously been noted in schizotypy individuals relative to personality disordered individuals (Bergman et al., 1998) and community controls (Volgemier et al., 1994). Interestingly, the current findings replicate the pattern of CVLT performance noted in the two prior studies (Bergman, 1998; Volgemier et al., 1994). In all three studies schizotypy subjects demonstrated worse performance on the first trial of the CVLT but equivalent rates of retention as compared to normal controls at delayed recall. These findings may suggest a deficit in the initial focusing and encoding of verbal
information for both schizophrenic and schizotypal individuals.

Learning of verbal information is associated with left hippocampal function, a site that has been repeatedly implicated in the pathogenesis of schizophrenia. Some studies have found that a reduction in hippocampal volume in schizophrenic probands corresponds to reductions in this structure in their first-order relatives (Gold et al., 1997). In contrast, Suddath and coworkers (1990) found that monozygotic twins discordant for schizophrenia were also discordant for hippocampal volume. They concluded that hippocampal pathology might be a critical pathogenic element unrelated to genetic factors.

A relative dissociation between verbal learning deficits and genetic risk has also been found for familial and nonfamilial schizophrenics. Sautter (1997) reported that the familial schizophrenic group in his study scored worse than the control group on all eight neuropsychological measures, except a test of verbal learning (Rey Auditory Verbal Learning Test). In contrast, the nonfamilial schizophrenia group scored significantly worse than controls on only three measures in the battery, one of which was the verbal learning test. Because the finding presented in the current study reflects the unique risk of schizotypy without a family history of schizophrenia, the current results may be taken as support for the contention that verbal learning deficits are a unique feature of the schizotypy phenotype.

The second finding with respect to verbal memory, related to differences in retention ability between the FH+ and FH- groups, which indicated that FH+ individuals maybe more susceptible to interference effects or rapid forgetting of verbal information than FH- individuals. This finding is consistent with the decrement in performance exhibited by the FH+ group after the second list of words (List B) were introduced and recalled, and may be indicative of either a greater susceptibility to interference effects on the part of FH+ individuals or increased forgetting in the FH+ group. Although a tendency for rapid
forgetting in schizophrenia has been previously noted (Calev, Venables, & Monk, 1983), it is difficult to draw conclusions based upon the current data, as the CVLT does not have a measure of forgetting, in the absence of interference. This distinction may be better evaluated through the use of tests that measure verbal delayed recall without the interference condition.

In addition to learning and memory differences, a double dissociation was present for the auditory/verbal (Digit Span) and visual/spatial (Visual Span) working memory tasks. The FH+ group’s better performance on the test of auditory working memory for verbal information is consistent with the findings on the CVLT, where the FH+ group also exhibited accelerated learning of a word list compared to the FH- group. The relative deficit in the area of auditory working memory in the FH- group may be the basis for the decreased learning effects noted on the CVLT when compared to the FH+ group. Auditory working memory deficits are a common finding among schizophrenic individuals (both FH+ and FH-) and high-risk groups (both biological relatives and SPDs) relative to controls, suggesting a shared pathology in the structures that mediate working memory processes. The current finding that family high-risk individuals exhibit an advantage over nonfamilials on an auditory working memory task (Digit Span) is noteworthy but not without precedent.

In a prior study, comparing sporadic and familial forms of schizophrenia, Alm, Lindstrohm, Ost, & Ohman (1984) also demonstrated that family history of schizophrenia was associated with better performance on the WAIS Digit Span subtest. The current study replicated that finding and extended it to familial and nonfamilial high-risk groups. With respect to the current findings, it is important to note that the familial schizophrenia group in the previous study was still impaired relative to controls on the Digit Span test. In the current study, the FH+ group was not impaired relative to a normative sample; however, other studies have found this group to be impaired on auditory working
memory measures when compared to controls. Therefore, these results suggest a 
shared deficit associated with schizophrenia-like disorders, but one which may be 
mediated by disease factors.

The double dissociation between spatial and auditory working memory processes for 
FH+ and FH- high-risk groups is a unique finding; potentially because these two groups 
have never been compared before. However, no such dissociation has been reported 
among sporadic and familial schizophrenia groups either. Neuroimaging studies of 
auditory and visual working memory with normals suggest that these cognitive 
processes are lateralized to some degree (visual right, auditory left/right). Intact working 
memory ability is dependant upon complex neural networks and the bilateral integrity of 
the prefrontal cortex. The dorsal lateral prefrontal cortex (DLPFC) and ventral lateral 
prefrontal cortex (VLPFC) have consistently been identified as neural sites for working 
memory. Working memory deficits in schizophrenia have been specifically associated 
with reduced rCBF to the dorsolateral prefrontal cortex. The dorsolateral prefrontal 
circuitry includes aspects of the dorsolateral prefrontal and parietal cortices. The double 
dissociation between visual spatial working memory tasks relative to auditory working 
memory tasks suggest lateralized dysfunction, with greater left hemisphere impairment 
in FH- and, greater right hemisphere impairment in FH+. Because deficits in auditory 
working memory may represent a generalized deficit in schizophrenia and those at risk 
for schizophrenia, clarifying the current results might be best accomplished by focusing 
on right hemisphere differences in familial and nonfamilial high-risk and schizophrenic 
groups.

In a review of the literature on laterality, Walker & McGuire (1982) concluded that 
there was evidence of a slow down in the processing of stimuli presented to the right 
sensory field in individuals with schizophrenia. Visual processing deficits in 
schizophrenia were also noted in a review by Knight (1984), in which he attributed poor
performance to a perceptual organization deficit, which he also associated with a
processing slowdown. Knight further suggested that this processing deficit was more
caracteristic of individuals who had poor premorbid status and greater negative
symptoms. Studies using the Backward Masking Task, a test designed to tap speed of
early-stage information processing, have generally found that patients with
schizophrenia require a longer interstimulus on interval to recognize the mask, this delay
is believed to be due to a disruption in the initial encoding and schematization of visual
information. A localization of this deficit to the right hemisphere was noted in a
backward masking study conducted by Green and Walker (1986), in which they
presented the targets to either the right or the left visual field. Additionally, the authors
found that negative symptom ratings were a significant predictor of increasing
interstimulus interval for the right visual field. Interestingly, the positive symptom scores
showed a trend towards an inverse relation with right visual field intervals, with greater
positive symptoms corresponding to shorter critical intervals. These findings lend
support to the current finding of right hemisphere dysfunction in at-risk groups but they
do not provide direct support for the familial-nonfamilial dissociation that was found here,
as Green and Walker did not differentiate between familial and nonfamilial
schizophrenia. Two additional studies comparing familial and nonfamilial forms of
schizophrenia provide further clarification.

In the first, Schwartz et al, (1995) reported that schizophrenics with a positive family
history demonstrated impairment in right smooth pursuit gain as compared to controls
and nonfamilial schizophrenics on an measure of eye tracking, suggesting right
hemisphere dysfunction in familial schizophrenia. Even more interesting is a study by
Harris et al, (1996) which compared schizophrenic probands, their parents, and controls
on a battery of neurocognitive test. The authors found a significant difference between
probands with a family history on tests of attention/working memory and verbal efficiency
when they were compared to their own parents. Specifically, the schizophrenic patients scored significantly different than the negative-history parent on the attention measure but not the positive history parent. On the learning efficiency measure probands differed from both the negative history parent and the positive history parent, suggesting that attentional dysfunction may be related to the familial schizophrenia genotype and that the verbal learning deficits may reflect the actual disease process.

**Hypothesis 2**

It was also predicted that increased severity of schizotypy symptoms in the FH+ group would be predictive of poorer neurocognitive test performance. Severity of schizotypy symptoms was reflected in a composite score that combined Per/Mag and Phy/Soc index scores. Correlations indicated a relationship between severity of symptoms and a neuropsychological measure that assessed verbal learning (CVLT). However, the finding was not specific to the FH+ group, as the same relationship was noted in the FH- group. Greater severity of symptoms (higher composite scores) was significantly correlated with poorer CVLT recall 1-5 performance in the sample as a whole. When the composite score was used as a covariate in secondary analyses, the significant interaction effects for CVLT learning were substantially diminished.

An examination of the individual Chapman scales to determine the source of the group differences with regard to severity of symptomology, indicated that the composite score differentiated the groups primarily due to positive symptoms reflected by the Perceptual Aberration and Magical Ideation scales or more specifically the Per/Mag index. Liddle (1996) has discussed three symptom syndromes in schizophrenia including psychomotor poverty (negative symptoms), disorganization (thought disorder), and reality distortion (hallucinations and delusions). Each syndrome is associated with a distinct area of cortical dysfunction. The negative dimension, represented in the current
study by the Phy/Soc index, was related to the circuitry of the DLPFC, which has previously been implicated in reasoning and abstraction. The Per/Mag index is most like Liddle's syndrome of reality distortion. Reality distortion is associated with left parahippocampal dysfunction, which is related to poor verbal memory ability. Therefore, it may be that the CVLT finding in the current study is due to positive symptom differences between groups. Using the Per/Mag index as a covariate does reduce the significance of the CVLT findings, which may indicate that increased memory impairment is associated with greater severity of positive symptoms. A similar finding was reported by Calev et al. (1983) in which, encoding deficits (associated with early stages of processing involved in entering of information prior to memory consolidation) were present for both acute and chronic schizophrenic patients, but an additional deficit in postencoding (associated with later stages of processing such as memory loss and retrieval deficits) was found in chronic patients only.

Interestingly, when the Phy/Soc and Per/Mag indexes are treated as separate domains of schizotypy (not as a composite score), no significant correlations were present between them and any of the neuropsychological measures, and no significant differences were present between the FH+ and FH- groups on the domain scores. Furthermore, the Phy/Soc and Per/Mag indexes were strongly negatively correlated in the current sample ($r = -.71$, $p < .001$, $n = 23$). Some individuals in the sample had primarily positive symptoms in the absence of negative symptoms, while others had primarily negative symptoms in the absence of positive symptoms. Still others had about equal levels of positive and negative symptoms. These patterns are common in schizophrenia, and are particularly prominent in the current sample based on the selection criteria. The results are generally consistent with prior research indicating that positive and negative symptoms represent distinct symptom syndromes that can occur with equal severity or, alternatively, can predominate in the relative absence of the other.
Based on these considerations, it may be inappropriate to combine them into one composite score and to use the composite as an index of severity. Future studies could examine the relationships between positive symptoms and cognitive functioning by evaluating groups matched on positive symptom severity. Importantly, the digit span findings were unaffected by the use of Per/Mag as a covariate suggesting that the differences in working memory and frontal lobe function are independent of symptoms and may represent differential trait markers for the risk groups.

Contrary to a previous finding (Condray & Steinhauer, 1992) in which schizotypal relatives demonstrated greater cognitive deficits relative to their own unaffected brothers, in the current study no differences were found between FH+ individuals who had higher schizotypy symptoms and those with lower schizotypy symptoms. Given the previous findings and the relationship between schizotypy symptom severity and verbal learning in the current study, this finding is somewhat surprising, and suggests that this result may have been a consequence of inadequate power. This possibility seems likely, as in the Condray and Steinhauer (1992) study, comparisons were made between schizophrenic probands and their own brothers (high schizotypy and low schizotypy). It may be that genetic homogeneity afforded by comparing high and low relatives to each other decreased the amount of irrelevant variation in the data making it possible to find subtle differences with a relatively small sample.

**Hypothesis 3**

For hypothesis 3, there was no significant relationship between family history of schizophrenia and presence of negative symptoms. In other words, the FH+ and FH- groups had about the same severity of negative symptoms. This finding is contrary to a large number of studies (see Roy, & Crowe, 1994 for review) that have found familial risk to be more strongly associated with the negative symptom dimension. As well as those
findings indicating that the paranoid form of schizophrenia, which is comprised mostly of positive symptoms (e.g., hallucinations and delusions) and has a characteristically later age of onset (lower genetic load), is the most common subtype seen in response to environmental insult (head injury, temporal lobe epilepsy). However, the current result may be consistent with those studies (Nuechterlein, Edell, Norris, & Dawson, 1986) that have indicated a unique association between family risk and symptoms of formal thought disorder (derailment, disorganized speech), which is considered a positive symptom. Therefore, the current finding may reflect that familial schizophrenia is more accurately characterized as having a mixed presentation, with formal thought disorder being the primary feature manifesting from the positive symptom dimension. Another possibility is that the selection criteria biased the FH- group to have more subjects with negative symptoms. It was noted previously that in general individuals with higher negative symptoms were less likely to agree to further participation. While this difficulty could be corrected to some degree among the larger FH- group (n = 94) by using negative symptoms as a selection criteria, the FH+ pool was much smaller (n = 38) and there was no such criteria for selecting the group. Because selection criteria for schizotypy samples necessarily bias the sample for having high levels of either positive or negative symptoms, the relationship between negative symptoms and family history of schizophrenia may best be studied in individuals who already have the disorder.

For the second part of Hypothesis 3, correlational analyses indicated no relationship between a measure of CPT sensitivity (d') and negative symptomatology. Again, this negative finding may be due to the fewer number of subjects in the study with elevations on the negative dimension scales. However, in general, CPT performance for this group was characteristic. Specifically, this group exhibited approximately the same levels of decline in d' over trials as that noted in previous studies of normal individuals, indicating that vigilance decreases over time. For patients with schizophrenia, an accelerated
decrease in vigilance occurs across consecutive CPT trials. However, in the current study, the rate of decline noted in the FH+ and FH- groups was not substantially different than what is found in normal individuals and was not significantly different between the groups.

In contrast to d', CPT beta was found to be significantly negatively correlated with negative schizotypy and positively correlated with positive schizotypy, suggesting that as negative schizotypy increases, responding become less conservative. Beta is affected by commission errors so that individuals with more false alarms will have lower beta scores, and those with fewer commission errors will have higher (more conservative) beta scores. Secondary analyses correlating negative and positive schizotypy with CPT false alarm rates indicated a significant correlation with negative schizotypy ($r = .38, p < .05$) and a nonsignificant correlation with positive schizotypy ($r = .26, p > .05$). This suggests that errors of commission were a significant factor in accounting for the liberal response bias associated with negative schizotypy. In the case of negative schizotypy, commission errors may reflect an inability to discriminate between target stimuli and distracters, which suggests deficits in the early stages of visual information processing. Therefore, this finding replicates other studies (Green & Walker, 1986; Finkelstein, Cannon, Gur, Gur & Moberg, 1997) which have found evidence of early processing deficits in patients with schizophrenia who have prominent negative symptoms.

**Negative Findings**

It is difficult to make statements about negative findings in the current study as failure to find significant differences between groups may have been the result of several factors including 1) sample size, 2) homogeneity in education, 3) symptom heterogeneity in FH- and FH+ high-risk groups, 4) biased selection of higher functioning FH+ subjects, or 5) unreliability in the family history measure. Alternatively, it may be that these results
represent a valid finding and no differences exist between groups on these cognitive variables. A brief review of each of these possibilities follows.

As previously mentioned, the sample is smaller than was originally planned. Power analyses, performed with samples of 25 subjects in each group, indicated sufficient power to find differences. However, the final sample had 10 subjects in the family history high-risk group and 13 in the psychometrically defined high-risk group. Thus, the study may have lacked sufficient power to detect differences between groups. It is possible that differences other than those reported in the current study might have emerged given a larger sample. However, inspection of means for the neuropsychological tests indicated only small differences between the FH+ and FH- groups on test scores, indicating that even with increased sample size, significant differences between groups probably would not have been present.

All participants in the current study were college students, which may have caused a significant restriction of range. There was some evidence that this may have occurred as both groups performed average to above average on the majority of cognitive measures. However, in groups that perform average to above average in general, relative areas of weakness stand out. So, although deficits may be harder to detect given the reduced variability in college samples, when findings are present they are relatively unambiguous and thus can be more readily interpreted.

The family history positive and family history negative groups both manifested significant variability in symptom presentation. Specifically, both groups contained individuals with significant elevations on the positive dimension index (Per/Mag), and the negative dimension index (Phy/Soc). Given the negative correlation between these two symptom domains, it may be that combining individuals who had primarily negative symptoms with those who had positive symptoms created too much variability in the groups which served to mask true neurocognitive differences. However, secondary
analyses comparing the FH+ and FH- groups divided according to positive and negative symptom dimensions revealed no significant differences between the FH- groups on the neurocognitive variables. This finding suggests that heterogeneity in the FH- and FH+ groups may not have accounted for the lack of significant differences noted between the FH+ and FH- groups on most neuropsychological tests. It should be noted that these comparisons were performed with very few subjects in each group, and again differences may have emerged with a larger sample.

The possibility also exists that the relatives in the family history group may have been atypical. The literature documents a potential subtype of schizophrenia characterized by "normal" neuropsychological functioning (Allen, Goldstein, & Warnick, 2002; Goldstein et al, 1999; Kremen et al, 1999; Palmer, 1997). It may be that the relatives of these "neuropsychologically normal" schizophrenics are more likely to be high functioning as well, and thus attend college. If this were the case a severe restriction of the range of cognitive functioning may have occurred by inadvertently selecting the high functioning relatives of "neuropsychologically normal" schizophrenics. However, although there may be some truth to this, still it would be unlikely that all participants came from neuropsychologically normal families, and even if they did, it might be expected that the same selection bias would apply to the schizotypy group, which would balance out across groups and not work in a systematic way to bias the results.

There were significantly more females than males in the current sample. The overrepresentation of females in the final sample may represent a selection bias or may reflect the epidemiology of schizophrenia. Prior studies have demonstrated that males develop symptoms of schizophrenia earlier in life than do females and, consequently, have an earlier age of onset. Males also have a more severe course of illness with poorer prognosis and more severe psychosocial impairment. For the current study, these factors may have contributed to the increased number of females in the sample, in
that males were less available for participation due to earlier age of onset, and that they were less willing to participate because of increased severity of symptoms. The predominance of females in the sample would probably have biased the results of the study toward finding fewer significant differences between groups, given their less severe form of the illness.

The goal of the current study was to recruit primarily first-order relatives, however, 50% of the individuals in the family history group were second-order relatives. Although it could be speculated that greater genetic variation in the family history positive high-risk group diluted the trait sufficiently causing too much noise in the data, this theory seems unlikely since second-order relatives still have a prevalence rate significantly greater than that of the general population (Gottesman, 1991). Additionally, even if this were the case, such a dilution would work against finding significant results in this study not for it.

A related methodological problem involves the studies reliance upon the accuracy of the participants with regard to knowledge of their relative's diagnosis. Inspection of the data indicated a significant bias in student reporting of their family histories in the direction of an underreporting of schizophrenia and over reporting of bipolar disorder. Because no corroborating evidence was collected, it is always possible that either group was wrong about their family member's diagnosis. However, given the students overall propensity to under report schizophrenia, it might be argued that those who endorsed a family history of schizophrenia were better informed as to their families psychiatric history. This would not be unusual given the extremely disruptive effect of schizophrenia on families.

Finally, it may be that nonsignificant differences between the groups was a valid finding. Nonsignificant differences were not entirely unexpected since the groups are at risk for the same disorder. Additionally, these findings are consistent with previous studies indicating that few neurocognitive differences exist between high-risk groups and
normals and that the ones that do exist are subtle. Therefore, although methodological difficulties experienced in the study may have decreased the likelihood of finding significant differences between the groups, the possibility that this is a real finding seems likely considering that a significant pattern of differences between the groups emerged even in this high functioning, relatively small sample of college students.

Conclusions

Harris and colleagues (1996) suggested that a heritable component of the neuropsychological deficit in schizophrenia is a primary dysfunction in attention and that a secondary or additional deficit in learning may be evident in family members who actually express the disorder of schizophrenia. This proposal seems to have partially been born out in the current study. Furthermore, the current results provide support for unique phenotypes that are associated with different dimensions of risk for developing schizophrenia. The FH+ phenotype is characterized by greater vulnerability to disruption of memory consolidation, and poorer performance on right hemisphere spatial working memory tasks relative to analogous left hemisphere auditory working memory tasks. In contrast, the FH- phenotype exhibits a greater impairment on verbal tasks including verbal learning and auditory working memory suggesting greater left hemisphere dysfunction relative to the FH+ phenotype.

The identification of unique neurocognitive phenotypes also has clinical implications. In schizophrenia, cognitive deficits are significantly associated with a variety of outcomes, including vocational and social functioning (Green, 1996). Studies of individuals with schizophrenia have generally concluded that the greater the severity of cognitive dysfunction the worse the outcome. Additionally, specific cognitive domains have unique relationships with discrete functional outcomes. For example, deficits in problem solving ability are more strongly associated with social dysfunction, attention
deficits are associated with social problem solving difficulties, and verbal memory deficits are associated with poor outcomes across a variety of functional domains. For the two at-risk groups in the current study, differences in learning and memory ability may differentially predict impairment across a wide range of functional outcomes, likewise group differences with regard to specific forms of attentional deficits may be more or less related to verbal or nonverbal social problem solving deficits (Green, 1996). Also, the association noted between verbal memory performance and symptom severity may suggest that as symptoms and the associated memory deficits increase, functional outcomes will decrease. However, specific predictions regarding outcome can not be made with the current data, because functional outcomes were not assessed.

A second area of clinical relevance is that of early intervention. Studies of individuals who are at genetic risk for schizophrenia indicate that some cognitive deficits (vigilance) differentiate between those individuals who go on to develop schizophrenia and those who do not. The possibility of differentiating between at risk groups who do and do not develop schizophrenia has received a great deal of attention because it may be possible to intervene prior to onset of illness and thus attenuate the negative effects associated with schizophrenia onset. Some programs currently being developed have already used antipsychotic medications and behavioral interventions in a preventative manner with success (McGorry, Edwards, Mihalopoulos, Harrigan, & Jackson, 1996). Specific phenotypes for the FH+ and FH- groups must be considered in early intervention strategies where cognitive deficits are used as one variable in the prediction models.

Recommendations

Future studies should attempt to replicate these findings in a larger group of clinically confirmed first-order relatives. A normal control group should be added and a more thorough examination of lateralizing tests should be included. Tests expected to
show differences in the current study should be kept in order to allow a stronger statement to be made about the presence or absence of differences in these areas between FH+ and FH- groups. Additionally, the role that positive schizotypy symptoms play in producing the verbal learning deficits noted in the current study should be pursued in future investigations. Finally, the clinical relevance of the neurocognitive differences present between the FH+ and FH- groups should be explored. Areas of particular relevance may include the manner in which specific deficits are related to specific functional outcomes, as well as the potential utility of the neurocognitive test scores in predicating disease onset. The latter area may provide direction for early intervention programs.
APPENDIX A

INFORMED CONSENT FOR PARTICIPATION

IN THE SCREENING PROCESS
CONSENT TO PARTICIPATE IN RESEARCH

Erin Warnick, doctoral student, and Dr. Dan Allen of the UNLV Psychology Department request that you accurately fill out the questionnaire called the Perceptual Aberrations and Magical Ideation Scale. This questionnaire, which takes 10-15 minutes to complete, is a widely used procedure for measuring unique beliefs and experiences. We would also like you to answer several questions about yourself and your background. We intend to use your responses as background information for future projects. There are no known risks involved in the tasks you will be asked to complete, other than the possibility of fatigue or boredom. If you choose to participate you will receive ____ extra credit points for your participation.

I understand:

a. that I may change my mind and decline to participate at any time during the filling out of this questionnaire without penalty;
b. that my responses to this questionnaire may result in my being invited to participate in some future study conducted by Erin L. Warnick and Dr. Dan Allen of the UNLV Psychology Department.
c. I am under no obligation to participate in any such further study; and
d. that my responses to this questionnaire will be used for no other purposes.

All information will remain strictly confidential. Only investigators working within the laboratory will have access to the data, which will be kept for three years in a locked filing cabinet in the Department of Psychology, UNLV. If you have any questions or concerns about your participation in this research, you may contact Dr. Daniel Allen at 895-0121 or Erin Warnick at 895-3305. If you have in questions regarding the rights of research subjects, please contact the UNLV Office of Sponsored Programs at (702) 895-1357.

Name ________________________________

Signature ________________________________

Date ________________________________
APPENDIX B

INFORMED CONSENT FOR PARTICIPATION IN THE
COGNITIVE TESTING PHASE
1. Introduction: You are being asked to participate in a study being conducted by Erin L. Wamick, Doctoral Student & Daniel N. Allen, Ph.D., Department of Psychology, University of Nevada, Las Vegas (UNLV).

2. Purpose of the study and how long it will last: The study you are being asked to participate in looks at ways in which cognitive abilities, such as memory and attention, vary among individuals. The study will last approximately 4 hours. During these 4 hours, you will be asked to participate in an evaluation that is described below. It is hoped that the information obtained as a result of this study may eventually help researchers to better understand how cognitive abilities relate to both genetic and environmental factors. Upon completion of the evaluation, you will be informed about the purpose of the study in greater detail, so you may learn more about this area of behavioral research.

3. Description of the study including procedures to be used: If you agree to participate, we will assess your attention, memory, and problem solving abilities. To assess memory, attention, and problem solving, you will be asked to complete tasks that are standard and fairly straight-forward. Some will seem quite easy while others may feel more difficult. For the attention and problem solving tasks, you will be asked to do such things as connect letters and numbers with a pencil, sort cards into different categories, and watch a television screen and press a button when you see certain numbers flash on the screen. On the memory tasks, you will be asked to remember certain words or pictures, remember lists of words and remember series of numbers and letters. The tasks should take about four hours to complete. You will be able to take breaks between tasks.

4. Expected risks of study: There are no known risks involved in the tasks you will be asked to complete, other than the possibility of fatigue or boredom.

5. Expected benefits of study: For your time, you will receive 4 credit hours toward the fulfillment of course requirements. Also, your participation in this study will help researchers to better understand how cognitive abilities relate to both genetic and environmental factors.

6. Confidentiality: All material gathered in this research will be kept private and confidential. Research records will be kept in a locked filing cabinet the Department of Psychology, UNLV, for a period of three years. Your identity will not be revealed in any publication that results from this research.
Your participation is strictly voluntary and you may withdraw from participating in this study at any time with no penalty other than forsaking the credit you would have received from the remaining portion of the experiment.

7. Questions regarding the study: If you have any questions regarding this research, please contact Dr. Daniel N. Allen at the UNLV Department of Psychology at 895-0121 or 895-3305. For questions regarding the rights of human subjects, please contact the UNLV Office of Sponsored Programs at 895-1357.

I have read all of the above information and my questions have been answered. I understand my rights as a research subject and voluntarily agree to participate in this research. I understand what this study is about and how and why it is being done. I will receive a copy of this signed consent form.

Signature of Participant  Date  Participant Name  (please print)

Signature of Witness  Date  Witness Name  (please print)

Signature of Principal Investigator  Date  Revised 1/3/01
APPENDIX C

FAMILY HISTORY QUESTIONNAIRE
ID # ___________________ Telephone Number: ________________________

QUESTION 1: Please answer all three parts (A-C)
A. Please indicate whether any individuals in your immediate biological family have ever been treated for psychiatric or psychological conditions with medication or individual counseling
PLEASE DO NOT INDICATE WHICH FAMILY MEMBER (for this portion include only biological MOTHER, FATHER, SISTERS, BROTHERS, CHILDREN in your considerations)?
Yes _____ No _____

B. Some individuals are very certain of their family's history of treatment for psychiatric and psychological conditions, while other individuals are not. How certain are you of your biological family's history of treatment for psychiatric or psychological conditions (Check all that apply)?
_____ Very Certain of my family's history
_____ Somewhat Certain of my family's history
_____ Do not know my family's history

C. If biological family members were treated for a psychiatric or psychological condition, what do you think that condition was (Check all that apply)?
_____ Schizophrenia
_____ Bipolar Affective Disorder or Manic-Depression
_____ Depression
_____ Anxiety
_____ Other
_____ Do Not Know

QUESTION 2: Please answer all three parts (A-C)
A. Please indicate whether any individuals in your extended biological family have ever been treated for psychiatric or psychological conditions with medication or individual counseling
PLEASE DO NOT INDICATE WHICH FAMILY MEMBER (for this portion include only biological AUNTS, UNCLEs, NEPHEWS, NEICES, GRANDFATHERS, GRANDMOTHERS, & GRANDCHILDREN in your considerations)?
Yes _____ No _____

B. Some individuals are very certain of their family's history of treatment for psychiatric and psychological conditions, while other individuals are not. How certain are you of your family's history of treatment for psychiatric or psychological conditions (Check all that apply)?
_____ Very Certain of my family's history
_____ Somewhat Certain of my family's history
_____ Do not know my family's history

C. If a biological family members was treated for a psychiatric or psychological condition, what do you think that disorder was (Check all that apply)?

_____ Schizophrenia
_____ Bipolar Affective Disorder or Manic-Depression
_____ Depression
_____ Anxiety
_____ Other
Table 1. 
Schedule of study procedures.

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<th>PROCEDURES</th>
<th>Time 1</th>
<th>Time 2</th>
<th>Time 3</th>
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<td>• Informed Consent A</td>
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<td>• Demographics¹</td>
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<tr>
<td>• Informed Consent B</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>• W-9 Tax Form</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>• Lateral Dominance</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>• WAIS-III (Verbal IQ)</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>• Cognitive Measures⁴</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>• Alcohol Screen⁵</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>• SCID for DSM-IV</td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

1. Includes race, gender, age, and contact. 2. Includes Perceptual Aberration Scale, Magical Ideation Scale, Physical and Social Anhedonia Scales, the Hypomanic Personality Scale, Impulsive Nonconformity Scale, and the Infrequency Scale. 3. See page 44. 4. See page 48. 5. Includes: Frequency of alcohol consumption; Total amount of consumption each drinking occasion; Frequency of negative outcomes due to alcohol consumption.
Table 2.
Cognitive domains, neuropsychological instruments and dependent variables.

<table>
<thead>
<tr>
<th>DOMAINS</th>
<th>INSTRUMENTS</th>
<th>DEPENDENT VARIABLES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Attention</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Sustain Visual</td>
<td>Continuous Performance Test</td>
<td>• Total mean reaction time; b. d'</td>
</tr>
<tr>
<td></td>
<td></td>
<td>c. Beta</td>
</tr>
<tr>
<td>• Apprehension: Auditory</td>
<td>WAIS-III Digit Span</td>
<td>a. Forward Raw Score</td>
</tr>
<tr>
<td>• Apprehension: Visual</td>
<td>WMS-III Corsi Blocks</td>
<td>a. Forward Raw Score</td>
</tr>
<tr>
<td>• Interference</td>
<td>Stroop</td>
<td>a. Word (sec); b. Color (sec); c. Color-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>word interference effect (sec)</td>
</tr>
<tr>
<td><strong>Executive</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Shift</td>
<td>Wisconsin Card Sorting Test</td>
<td>a. Perseverative errors; b. Total</td>
</tr>
<tr>
<td></td>
<td></td>
<td>categories; c. Trials to completion;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>a. Total errors</td>
</tr>
<tr>
<td></td>
<td></td>
<td>a. Trails B time; b. Trails A time -Trails</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B time</td>
</tr>
<tr>
<td>• Flexibility</td>
<td>Trail Making A and B Verbal Fluency</td>
<td>a. Total Correct Letter; b. Total</td>
</tr>
<tr>
<td></td>
<td>(Letter &amp; Category)</td>
<td>Correct Category</td>
</tr>
<tr>
<td><strong>Memory</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Secondary Auditory Immediate</td>
<td>CVLT</td>
<td>a. Recall List A 1-5; b. Recall List B; c.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Recall A</td>
</tr>
<tr>
<td>• Secondary Auditory Cued</td>
<td>CVLT</td>
<td>a. Cued Immediate Recall; b. Cued</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Delayed Recall</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Delayed Recall; b. Recognition</td>
</tr>
<tr>
<td>• Secondary Auditory Delayed</td>
<td>CVLT</td>
<td></td>
</tr>
<tr>
<td>• Working Auditory</td>
<td>WMS-III Letter Number</td>
<td>a. Scaled score</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b. Backward Raw Score</td>
</tr>
<tr>
<td>• Working Visual</td>
<td>WAIS-III Digit Span</td>
<td>b. Backward Raw Score</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Working Visual</td>
<td>WMS-III Corsi Blocks</td>
<td></td>
</tr>
<tr>
<td><strong>Verbal IQ</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• WAIS-III</td>
<td>Vocabulary Information</td>
<td>a. Scaled score</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b. Scaled score</td>
</tr>
<tr>
<td><strong>Motor</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Dexterity</td>
<td>Purdue Peg Board</td>
<td>a. Pegs, Dominant Hand; b. Nondominant</td>
</tr>
<tr>
<td></td>
<td>Finger Tapping</td>
<td>Hand; c. Both Hands</td>
</tr>
<tr>
<td></td>
<td></td>
<td>a. Total number of taps, Dominant Hand;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b. Nondominant Hand</td>
</tr>
</tbody>
</table>

**NOTE:** CVLT = California Verbal Learning Test; DS = Digit Span; Stroop = Stroop Color Word Test; WCST = Wisconsin Card Sorting Test; WAIS -III = Wechsler Adult Intelligence Scale Third Edition.
Table 3.
Skewness and Kurtosis statistics for cognitive variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Kurtosis</th>
<th>Skewness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive Variables</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVLT Recall 1</td>
<td>-1.26</td>
<td>-.07</td>
</tr>
<tr>
<td>CVLT Recall 5</td>
<td>-1.00</td>
<td>0.23</td>
</tr>
<tr>
<td>CVLT Recall 1-5</td>
<td>0.17</td>
<td>0.34</td>
</tr>
<tr>
<td>CVLT Recall A</td>
<td>0.20</td>
<td>-.15</td>
</tr>
<tr>
<td>CVLT Recall List B</td>
<td>-.80</td>
<td>-.09</td>
</tr>
<tr>
<td>CVLT Recall Delayed</td>
<td>1.24</td>
<td>-.73</td>
</tr>
<tr>
<td>CVLT Recognition</td>
<td>-.29</td>
<td>-.53</td>
</tr>
<tr>
<td>Peg Board Dominant</td>
<td>0.79</td>
<td>-.97</td>
</tr>
<tr>
<td>Peg Board Nondominant</td>
<td>0.87</td>
<td>-.77</td>
</tr>
<tr>
<td>WAIS Digit Span</td>
<td>-.16</td>
<td>0.66</td>
</tr>
<tr>
<td>WAIS Digit Span Forward</td>
<td>-.31</td>
<td>0.62</td>
</tr>
<tr>
<td>WAIS Digit Span Backward</td>
<td>-.69</td>
<td>0.36</td>
</tr>
<tr>
<td>WMS Visual Span</td>
<td>0.08</td>
<td>0.34</td>
</tr>
<tr>
<td>WMS Visual Span Forward</td>
<td>0.35</td>
<td>0.49</td>
</tr>
<tr>
<td>WMS Visual Span Backward</td>
<td>-.83</td>
<td>-.06</td>
</tr>
<tr>
<td>WAIS Letter Number Span</td>
<td>-.22</td>
<td>-.48</td>
</tr>
<tr>
<td>COWA</td>
<td>0.23</td>
<td>-.18</td>
</tr>
<tr>
<td>VFCATA</td>
<td>-.76</td>
<td>-.25</td>
</tr>
<tr>
<td>Stroop Word</td>
<td>13.61</td>
<td>3.32</td>
</tr>
<tr>
<td>Stroop Word Log</td>
<td>7.69</td>
<td>2.20</td>
</tr>
<tr>
<td>Stroop Color</td>
<td>-1.43</td>
<td>0.30</td>
</tr>
<tr>
<td>Stroop Interference</td>
<td>1.16</td>
<td>0.77</td>
</tr>
<tr>
<td>WCST % Perseverative Errors</td>
<td>-.34</td>
<td>-.31</td>
</tr>
<tr>
<td>DS-CPT d'</td>
<td>0.18</td>
<td>-.43</td>
</tr>
<tr>
<td>DS-CPT Beta</td>
<td>-.15</td>
<td>-.30</td>
</tr>
</tbody>
</table>

Note: CVLT = California Verbal Learning Test; (1/5/DR) = CVLT trial 1 trial 5, and Delayed Recall trial; DS-CPT = Degraded Stimulus version of the Continuous Performance Test; DS-CPT d' = sensitivity; DS-CPT B' = Response Bias; Peg Board = Purdue Peg Board; COWA = Controlled Oral Word Association (FAS); VFCATA = Verbal Fluency Category (Animals); WMS = Wechsler Memory Scale Third Edition; WCST = Wisconsin Card Sorting Test; WAIS = Wechsler Adult Intelligence Scale Third Edition.
Table 4.

**Descriptive statistics for valid and invalid subjects from the initial sample.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Chapman Infrequency Valid (N = 1017)</th>
<th>Chapman Infrequency Invalid (N = 128)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Age</td>
<td>20.82</td>
<td>4.85</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males (n = 438)</td>
<td>82%</td>
<td>18%</td>
</tr>
<tr>
<td>Females (n = 709)</td>
<td>92%</td>
<td>8%</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian (n = 701)</td>
<td>90%</td>
<td>10%</td>
</tr>
<tr>
<td>African American (n = 95)</td>
<td>82%</td>
<td>18%</td>
</tr>
<tr>
<td>Asian (n = 203)</td>
<td>84%</td>
<td>16%</td>
</tr>
<tr>
<td>Hispanic (n = 122)</td>
<td>90%</td>
<td>10%</td>
</tr>
<tr>
<td>American Indian (n = 14)</td>
<td>86%</td>
<td>14%</td>
</tr>
<tr>
<td>Do not Know (n = 11)</td>
<td>91%</td>
<td>9%</td>
</tr>
<tr>
<td>SZ status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FH+ (n = 51)</td>
<td>92%</td>
<td>8%</td>
</tr>
<tr>
<td>FH- (n = 1096)</td>
<td>88%</td>
<td>12%</td>
</tr>
<tr>
<td>Contact</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (n = 893)</td>
<td>91%</td>
<td>9%</td>
</tr>
<tr>
<td>No (n = 254)</td>
<td>81%</td>
<td>19%</td>
</tr>
</tbody>
</table>

**Note:** SZ = schizophrenia; FH+ = family history positive for schizophrenia, FH- = family history negative for schizophrenia.
Table 5.

Descriptive statistics for valid subjects who agreed to further contact and those who did not agree to further contact.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Agree to Participate</th>
<th></th>
<th>Agree to Participate</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(n = 811)</td>
<td>(n = 206)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>20.85</td>
<td>20.66</td>
<td>4.94</td>
<td>4.50</td>
</tr>
<tr>
<td>SD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percent</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (n = 361)</td>
<td>75%</td>
<td>25%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female (n = 656)</td>
<td>82%</td>
<td>18%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian (n = 635)</td>
<td>82%</td>
<td>18%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>African American (n = 78)</td>
<td>81%</td>
<td>19%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian (n = 171)</td>
<td>76%</td>
<td>24%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic (n = 110)</td>
<td>75%</td>
<td>25%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>American Indian (n = 12)</td>
<td>92%</td>
<td>8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SZ status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FH+ (n = 47)</td>
<td>62%</td>
<td>38%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FH- (n = 970)</td>
<td>80%</td>
<td>20%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: SZ = schizophrenia, FH+ = family history positive for schizophrenia, FH- = family history negative for schizophrenia.
Table 6.

T-tests for Chapman Scales for valid subjects who agreed to further contact and those did not agree to further contact.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Agree to Participate Yes (N =811)</th>
<th>Agree to Participate No (N =206)</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chapman Scales</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Magical Ideation</td>
<td>9.61 5.71</td>
<td>8.88 5.38</td>
<td>2.75</td>
<td>&gt;.05</td>
</tr>
<tr>
<td>Impulsive Nonconformity</td>
<td>17.91 7.79</td>
<td>16.76 7.78</td>
<td>3.61</td>
<td>&gt;.05</td>
</tr>
<tr>
<td>Physical Anhedonia</td>
<td>14.04 6.60</td>
<td>15.74 6.89</td>
<td>10.64</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Perceptual Aberration</td>
<td>5.58 5.32</td>
<td>4.70 4.51</td>
<td>4.93</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Hypomanic Personality</td>
<td>22.42 8.58</td>
<td>20.78 7.94</td>
<td>6.20</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Social Anhedonia</td>
<td>9.39 5.50</td>
<td>9.78 5.67</td>
<td>.84</td>
<td>&gt;.05</td>
</tr>
<tr>
<td>Infrequency</td>
<td>.49 .705</td>
<td>.573 .725</td>
<td>2.26</td>
<td>&gt;.05</td>
</tr>
<tr>
<td>Chapman Indices</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per/Mag</td>
<td>15.20 10.1</td>
<td>13.56 9.20</td>
<td>4.41</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Phy/Soc</td>
<td>23.43 9.92</td>
<td>25.52 10.34</td>
<td>7.16</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>

Note: Per/Mag = Perceptual Aberration and Magical Ideation Scales; Phy/Soc = Physical Anhedonia and Social Anhedonia Scales.
Table 7.

Descriptive statistics and T-tests for Chapman Scales for subjects who met Chapman criteria and agreed to further contact and those who met criteria but did not agree to further contact.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Agree to Participate Yes</th>
<th>Agree to Participate No</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Chapman Scales</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Magical Ideation</td>
<td>13.58</td>
<td>7.32</td>
<td>11.51</td>
<td>6.24</td>
</tr>
<tr>
<td>Impulsive Nonconformity</td>
<td>20.74</td>
<td>7.18</td>
<td>21.31</td>
<td>7.76</td>
</tr>
<tr>
<td>Physical Anhedonia</td>
<td>17.19</td>
<td>9.02</td>
<td>21.63</td>
<td>9.11</td>
</tr>
<tr>
<td>Perceptual Aberration</td>
<td>10.64</td>
<td>7.87</td>
<td>7.86</td>
<td>6.53</td>
</tr>
<tr>
<td>Hypomanic</td>
<td>25.38</td>
<td>8.82</td>
<td>22.37</td>
<td>7.41</td>
</tr>
<tr>
<td>Social Anhedonia</td>
<td>13.89</td>
<td>6.92</td>
<td>15.23</td>
<td>6.73</td>
</tr>
<tr>
<td>Infrequency</td>
<td>.624</td>
<td>.783</td>
<td>.857</td>
<td>.772</td>
</tr>
<tr>
<td>Chapman Indices</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per/Mag</td>
<td>24.21</td>
<td>14.19</td>
<td>19.37</td>
<td>12.20</td>
</tr>
<tr>
<td>Phy/Soc</td>
<td>31.08</td>
<td>13.07</td>
<td>36.86</td>
<td>12.22</td>
</tr>
</tbody>
</table>

Note: Per/Mag = Perceptual Aberration and Magical Ideation Scales; Phy/Soc = Physical...
Table 8.

**Descriptive statistics for demographic variables for subjects who met Chapman criteria and agreed to further contact and those who met criteria but did not agree to further contact.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Contact Yes (n = 132)</th>
<th>Contact No (n = 35)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>20.78</td>
<td>5.15</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (n = 55)</td>
<td>69%</td>
<td>31%</td>
</tr>
<tr>
<td>Female (n = 112)</td>
<td>84%</td>
<td>16%</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian (n = 90)</td>
<td>85%</td>
<td>15%</td>
</tr>
<tr>
<td>African American (n = 16)</td>
<td>94%</td>
<td>6%</td>
</tr>
<tr>
<td>Asian (n = 32)</td>
<td>63%</td>
<td>37%</td>
</tr>
<tr>
<td>Hispanic (n = 25)</td>
<td>68%</td>
<td>32%</td>
</tr>
<tr>
<td>American Indian (n = 3)</td>
<td>100%</td>
<td>0%</td>
</tr>
<tr>
<td>Don't Know (n = 1)</td>
<td>0%</td>
<td>100%</td>
</tr>
<tr>
<td><strong>SZ status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FH+ (n = 47)</td>
<td>81%</td>
<td>19%</td>
</tr>
<tr>
<td>FH- (n = 120)</td>
<td>81%</td>
<td>19%</td>
</tr>
</tbody>
</table>

*Note: SZ = schizophrenia; FH+ = family history positive for schizophrenia, FH- = family history negative for schizophrenia.*
Table 9.

**Descriptive Statistics for subjects who met study criteria, agreed to further contact, but did not participate in the neuropsychological evaluation.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Participated Yes (n = 25)</th>
<th>Participated No (n = 107)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Age</td>
<td>20.24</td>
<td>3.42</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (n = 38)</td>
<td>13%</td>
<td></td>
</tr>
<tr>
<td>Female (n = 94)</td>
<td>21%</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian (n = 77)</td>
<td>18%</td>
<td></td>
</tr>
<tr>
<td>African American (n = 15)</td>
<td>13%</td>
<td></td>
</tr>
<tr>
<td>Asian (n = 20)</td>
<td>30%</td>
<td></td>
</tr>
<tr>
<td>Hispanic (n = 17)</td>
<td>17%</td>
<td></td>
</tr>
<tr>
<td>American Indian (n = 3)</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>SZ status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FH+ (n = 38)</td>
<td>26%</td>
<td></td>
</tr>
<tr>
<td>FH- (n = 94)</td>
<td>16%</td>
<td></td>
</tr>
</tbody>
</table>

**Note:** SZ = schizophrenia; FH+ = family history positive for schizophrenia, FH- = family history negative for schizophrenia.
Table 10.

T-tests for Chapman Scales for subjects who met study criteria and originally agreed to further contact, but did not participate in the neuropsychological evaluation.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Participated</th>
<th>$F_{1,131}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (n = 25)</td>
<td>No (n = 107 )</td>
</tr>
<tr>
<td>Chapman Scales</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Magic ideation</td>
<td>13.84</td>
<td>7.29</td>
</tr>
<tr>
<td>Impulsive noncomformity</td>
<td>22.64</td>
<td>5.37</td>
</tr>
<tr>
<td>Physical anhedonia</td>
<td>16.12</td>
<td>6.72</td>
</tr>
<tr>
<td>Perceptual aberration</td>
<td>12.28</td>
<td>8.55</td>
</tr>
<tr>
<td>Hypomanic personality</td>
<td>26.16</td>
<td>8.31</td>
</tr>
<tr>
<td>Social anhedonia</td>
<td>15.20</td>
<td>7.22</td>
</tr>
<tr>
<td>Infrequency</td>
<td>0.58</td>
<td>0.80</td>
</tr>
<tr>
<td>Chapman Indices</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per/Mag</td>
<td>26.12</td>
<td>14.79</td>
</tr>
<tr>
<td>Phy/Soc</td>
<td>31.32</td>
<td>11.99</td>
</tr>
</tbody>
</table>

Note: Per/Mag = Perceptual Aberration and Magical Ideation Scales; Phy/Soc = Physical Anhedonia and Social Anhedonia Scales.
Table 11.

Descriptive statistics for Chapman Scales from the total sample of valid responders.

<table>
<thead>
<tr>
<th>Variable</th>
<th>FH+ (n = 38)</th>
<th>FH- (n = 94)</th>
<th>NC (n = 679)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>Age</td>
<td>20.24</td>
<td>3.42</td>
<td>20.92</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (n = 270)</td>
<td>2%</td>
<td>12%</td>
<td>86%</td>
</tr>
<tr>
<td>Female (n = 541)</td>
<td>6%</td>
<td>11%</td>
<td>83%</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian (n = 519)</td>
<td>4%</td>
<td>11%</td>
<td>85%</td>
</tr>
<tr>
<td>African American (n = 63)</td>
<td>11%</td>
<td>13%</td>
<td>76%</td>
</tr>
<tr>
<td>Asian (n = 130)</td>
<td>5%</td>
<td>11%</td>
<td>84%</td>
</tr>
<tr>
<td>Hispanic (n = 82)</td>
<td>3%</td>
<td>18%</td>
<td>79%</td>
</tr>
<tr>
<td>American Indian (n = 11)</td>
<td>9%</td>
<td>18%</td>
<td>73%</td>
</tr>
</tbody>
</table>

Note: NC = normal controls; FH+ = family history positive for schizophrenia, FH- = family history negative for schizophrenia.
Table 12.

Descriptive statistics, F test results, and post hoc comparisons for Chapman Scales for NC's, FH+, and FH-.

<table>
<thead>
<tr>
<th>Variable</th>
<th>FH+</th>
<th>FH-</th>
<th>NC</th>
<th>F</th>
<th>Post hoc~</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 38)</td>
<td>(n = 94)</td>
<td>(n = 679)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Chapman Scales</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Magical Ideation</td>
<td>11.11</td>
<td>14.57</td>
<td>8.83</td>
<td>48.05**</td>
<td>2 &gt; 1,3 &amp; 1 &gt; 3</td>
</tr>
<tr>
<td>Impulsive Nonconformity</td>
<td>17.92</td>
<td>21.88</td>
<td>17.10</td>
<td>14.34**</td>
<td>2 &gt; 1,3</td>
</tr>
<tr>
<td>Physical Anhedonia</td>
<td>14.50</td>
<td>18.28</td>
<td>13.65</td>
<td>23.60**</td>
<td>2 &gt; 1,3</td>
</tr>
<tr>
<td>Perceptual Aberration</td>
<td>6.11</td>
<td>12.47</td>
<td>4.49</td>
<td>115.97**</td>
<td>2 &gt; 1,3</td>
</tr>
<tr>
<td>Hypomanic Personality</td>
<td>23.61</td>
<td>26.10</td>
<td>21.57</td>
<td>10.74**</td>
<td>2 &gt; 3</td>
</tr>
<tr>
<td>Social Anhedonia</td>
<td>10.45</td>
<td>15.29</td>
<td>8.54</td>
<td>74.91**</td>
<td>2 &gt; 1,3</td>
</tr>
<tr>
<td>Infrequency</td>
<td>0.56</td>
<td>0.64</td>
<td>0.47</td>
<td>3.07*</td>
<td></td>
</tr>
<tr>
<td><strong>Chapman Indices</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per/Mag</td>
<td>17.21</td>
<td>27.04</td>
<td>13.22</td>
<td>92.91**</td>
<td>2 &gt; 1,3 &amp; 1 &gt; 3</td>
</tr>
<tr>
<td>Phy/Soc</td>
<td>24.95</td>
<td>33.56</td>
<td>22.20</td>
<td>66.25**</td>
<td>2 &gt; 1,3</td>
</tr>
</tbody>
</table>

Note: NC = UNLV Normal Controls; Per/Mag = Perceptual Aberration and Magical Ideation Scales; Phy/Soc = Physical Anhedonia and Social Anhedonia Scales

~Post hoc comparisons used Scheffe Test

* p < .05, **p < .001.
Table 13.
Descriptive statistics for demographic and clinical variables for FH+ and FH- groups.

<table>
<thead>
<tr>
<th>Variable</th>
<th>FH+ (n = 10)</th>
<th>FH- (n = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Age</td>
<td>20.20</td>
<td>4.76</td>
</tr>
<tr>
<td>Education</td>
<td>12.97</td>
<td>0.17</td>
</tr>
<tr>
<td>Visual Acuity</td>
<td>9.20</td>
<td>1.23</td>
</tr>
<tr>
<td>Alcohol Measure</td>
<td>3.70</td>
<td>3.43</td>
</tr>
<tr>
<td>WAIS Vocabulary</td>
<td>12.20</td>
<td>1.62</td>
</tr>
<tr>
<td>WAIS Information</td>
<td>11.40</td>
<td>1.65</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Percent of Total Sample</th>
<th>Percent of Total Sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>Caucasian (n = 13)</td>
<td>31%</td>
</tr>
<tr>
<td>African American (n = 3)</td>
<td>100%</td>
</tr>
<tr>
<td>Asian (n = 4)</td>
<td>50%</td>
</tr>
<tr>
<td>Hispanic (n = 3)</td>
<td>33%</td>
</tr>
<tr>
<td>American Indian (n = 0)</td>
<td>0%</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male (n = 4)</td>
<td>47%</td>
</tr>
<tr>
<td>Female (n = 19)</td>
<td>25%</td>
</tr>
</tbody>
</table>

FH+ = family history positive for schizophrenia (SZ), FH- = family history negative for SZ
Table 14.

**Descriptive statistics and ANOVAs for Chapman Scales for FH+HR and FH-HR groups.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>FH+ (n = 10)</th>
<th></th>
<th>FH- (n = 13)</th>
<th></th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chapman Scales</td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Magical Ideation</td>
<td>12.70</td>
<td>5.10</td>
<td>14.92</td>
<td>8.65</td>
<td>.51</td>
<td>&gt;.05</td>
</tr>
<tr>
<td>Impulsive Nonconformity</td>
<td>23.30</td>
<td>4.08</td>
<td>22.30</td>
<td>6.26</td>
<td>.19</td>
<td>&gt;.05</td>
</tr>
<tr>
<td>Physical Anhedonia</td>
<td>17.00</td>
<td>5.85</td>
<td>15.15</td>
<td>7.84</td>
<td>.39</td>
<td>&gt;.05</td>
</tr>
<tr>
<td>Perceptual Aberration</td>
<td>8.50</td>
<td>5.70</td>
<td>14.77</td>
<td>9.56</td>
<td>3.36</td>
<td>&gt;.05</td>
</tr>
<tr>
<td>Hypomanic Personality</td>
<td>26.00</td>
<td>7.18</td>
<td>26.46</td>
<td>9.01</td>
<td>.02</td>
<td>&gt;.05</td>
</tr>
<tr>
<td>Social Anhedonia</td>
<td>12.70</td>
<td>4.50</td>
<td>16.08</td>
<td>8.23</td>
<td>1.36</td>
<td>&gt;.05</td>
</tr>
<tr>
<td>Infrequency</td>
<td>0.50</td>
<td>0.97</td>
<td>.46</td>
<td>.66</td>
<td>.01</td>
<td>&gt;.05</td>
</tr>
<tr>
<td>Chapman Indices</td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PER/MAG</td>
<td>21.20</td>
<td>8.61</td>
<td>30.23</td>
<td>16.91</td>
<td>2.36</td>
<td>&gt;.05</td>
</tr>
<tr>
<td>PHY/SOC</td>
<td>29.70</td>
<td>7.96</td>
<td>31.23</td>
<td>14.50</td>
<td>.09</td>
<td>&gt;.05</td>
</tr>
</tbody>
</table>

**Note:** Per/Mag = Perceptual Aberration and Magical Ideation Scales; Phy/Soc = Physical Anhedonia and Social Anhedonia Scales; FH+ = family history positive for schizophrenia, FH- = family history negative for schizophrenia.

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Table 15.

Descriptive statistics for select cognitive variables for FH+ and FH- groups and normative sample data.

<table>
<thead>
<tr>
<th>Cognitive Variables</th>
<th>FH+ (N = 10)</th>
<th>FH- (N = 13)</th>
<th>Normative Sample</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>Memory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVLT Recall 1</td>
<td>6.30</td>
<td>1.83</td>
<td>7.15</td>
</tr>
<tr>
<td>CVLT Recall 5</td>
<td>13.20</td>
<td>1.87</td>
<td>11.92</td>
</tr>
<tr>
<td>CVLT Recall List A</td>
<td>11.10</td>
<td>3.00</td>
<td>10.23</td>
</tr>
<tr>
<td>CVLT Recall List B</td>
<td>7.40</td>
<td>2.12</td>
<td>7.31</td>
</tr>
<tr>
<td>CVLT Delayed Recall</td>
<td>11.50</td>
<td>2.55</td>
<td>11.38</td>
</tr>
<tr>
<td>CVLT Recognition</td>
<td>15.00</td>
<td>0.94</td>
<td>14.46</td>
</tr>
<tr>
<td>Executive Abilities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WCST (Per. Errors)</td>
<td>53.80</td>
<td>9.28</td>
<td>55.15</td>
</tr>
<tr>
<td>Attention</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPT d' (6)</td>
<td>3.32</td>
<td>1.06</td>
<td>3.14</td>
</tr>
<tr>
<td>CPT Bias BETA (6)</td>
<td>1.31</td>
<td>0.73</td>
<td>0.89</td>
</tr>
<tr>
<td>Stroop Word</td>
<td>42.10</td>
<td>5.40</td>
<td>47.08</td>
</tr>
<tr>
<td>Stroop Word Log</td>
<td>1.62</td>
<td>0.06</td>
<td>1.66</td>
</tr>
<tr>
<td>Stroop Color</td>
<td>58.10</td>
<td>8.99</td>
<td>60.08</td>
</tr>
<tr>
<td>Stroop Interference</td>
<td>98.90</td>
<td>22.18</td>
<td>107.38</td>
</tr>
<tr>
<td>Motor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peg Board Dominant</td>
<td>16.36</td>
<td>1.85</td>
<td>16.41</td>
</tr>
<tr>
<td>Peg Board Nondominant</td>
<td>15.35</td>
<td>2.45</td>
<td>14.76</td>
</tr>
<tr>
<td>Working Memory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WAIS Digit Span</td>
<td>12.00</td>
<td>2.98</td>
<td>9.54</td>
</tr>
<tr>
<td>WAIS Digits Forward</td>
<td>11.80</td>
<td>2.74</td>
<td>10.23</td>
</tr>
<tr>
<td>WAIS Digits Backward</td>
<td>8.30</td>
<td>2.16</td>
<td>6.46</td>
</tr>
<tr>
<td>WMS Spatial Span</td>
<td>10.40</td>
<td>2.50</td>
<td>11.31</td>
</tr>
<tr>
<td>WMS Spatial Forward</td>
<td>9.00</td>
<td>1.89</td>
<td>9.84</td>
</tr>
<tr>
<td>WMS Spatial Backward</td>
<td>7.50</td>
<td>1.96</td>
<td>8.30</td>
</tr>
<tr>
<td>WAIS (LNS)</td>
<td>11.60</td>
<td>3.00</td>
<td>10.08</td>
</tr>
</tbody>
</table>

Note: * No norms available, WCST (Per. Errors) = Wisconsin Card Sorting Test percent perseverative errors; CPT d' (6) = Continuous Performance Test (sensitivity), average of six trials; CPT Bias BETA (6) = Continuous Performance Test Response Bias in Beta mean of six trials; Peg = Purdue Peg Board; WAIS = Wechsler Adult Intelligence Scale 3rd Edition; WMS= Wechsler Memory Scale - 3rd Edition; LNS = Letter Number Series.

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Table 17.

Correlation's between schizotypy composite score and the cognitive variables of interest for the family history positive group.

<table>
<thead>
<tr>
<th>Variable</th>
<th>FH+ (n = 10)</th>
<th>Composite Score Correlations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Cognitive Variables</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVLT Recall 1-5</td>
<td>52.20</td>
<td>7.22</td>
</tr>
<tr>
<td>CVLT Recall Delayed</td>
<td>11.50</td>
<td>2.55</td>
</tr>
<tr>
<td>CVLT Recognition</td>
<td>15.00</td>
<td>.94</td>
</tr>
<tr>
<td>Peg Board Dominant</td>
<td>15.33</td>
<td>2.45</td>
</tr>
<tr>
<td>Peg Board Nondominant</td>
<td>16.36</td>
<td>1.85</td>
</tr>
<tr>
<td>WMS-III Digit Span</td>
<td>12.00</td>
<td>2.98</td>
</tr>
<tr>
<td>WMS-III Visual Span</td>
<td>10.40</td>
<td>2.50</td>
</tr>
<tr>
<td>WMS-III Letter Number</td>
<td>11.60</td>
<td>2.99</td>
</tr>
<tr>
<td>WCST Perseverative Errors</td>
<td>53.80</td>
<td>9.28</td>
</tr>
<tr>
<td>CPT d'</td>
<td>3.32</td>
<td>1.06</td>
</tr>
</tbody>
</table>

Note: CVLT = California Verbal Learning Test; WCST = Wisconsin Card Sorting Test; WMS-III = Wechsler Memory Scale Third Edition; CPT d' = Continuous Performance Test sensitivity measure.
Table 18.

Univariate tests comparing the FH+ low schizotypy, FH+ high schizotypy and the FH-
subgroups on the cognitive variables of interest.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FH+ (low) (n = 5)</td>
<td>FH+ (high) (n = 5)</td>
<td>FH- (n = 13)</td>
<td></td>
</tr>
<tr>
<td>Cognitive Variables*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVLT Recall 1-5</td>
<td>54.40 5.22</td>
<td>50.00 8.83</td>
<td>50.85 5.84</td>
<td></td>
</tr>
<tr>
<td>CVLT Delayed</td>
<td>11.40 1.52</td>
<td>11.60 3.51</td>
<td>11.38 1.61</td>
<td></td>
</tr>
<tr>
<td>CVLT Recognition</td>
<td>14.80 1.10</td>
<td>15.20 0.84</td>
<td>14.46 1.27</td>
<td></td>
</tr>
<tr>
<td>Peg Board</td>
<td>15.92 2.64</td>
<td>16.79 0.51</td>
<td>16.41 1.92</td>
<td></td>
</tr>
<tr>
<td>Peg Board</td>
<td>14.80 3.41</td>
<td>15.01 1.07</td>
<td>14.77 1.92</td>
<td></td>
</tr>
<tr>
<td>WAIS Digit Span</td>
<td>12.20 3.27</td>
<td>11.80 3.03</td>
<td>9.54 1.90</td>
<td></td>
</tr>
<tr>
<td>WMS Visual Span</td>
<td>11.80 2.39</td>
<td>9.00 1.87</td>
<td>11.31 2.29</td>
<td></td>
</tr>
<tr>
<td>WMS LNS</td>
<td>11.20 2.39</td>
<td>12.00 2.12</td>
<td>10.08 2.22</td>
<td></td>
</tr>
<tr>
<td>WCST</td>
<td>55.0 5.34</td>
<td>52.60 12.72</td>
<td>55.15 17.54</td>
<td></td>
</tr>
<tr>
<td>CPT d’</td>
<td>3.76 0.96</td>
<td>2.88 1.05</td>
<td>3.16 0.71</td>
<td></td>
</tr>
</tbody>
</table>

Note: CVLT = California Verbal Learning Test; Peg = Purdue Peg Board; WAIS = Wechsler Adult Intelligence Scale Third Edition; WMS = Wechsler Memory Scale Third Edition; WCST = Wisconsin Card Sorting Test; WMS-III = Wechsler Memory Scale Third Edition; CPT d’ = Continuous Performance Test; *All significance tests were > .05.
Table 19.

Correlation's between the positive and negative dimensions of schizotypy and DS-CPT variables for the entire experimental sample (N = 23).

<table>
<thead>
<tr>
<th>Cognitive Variables</th>
<th>Descriptive Statistics</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
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<tr>
<td></td>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>r</td>
<td>p</td>
<td>r</td>
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<tr>
<td>DS-CPT Sensitivity d'</td>
<td></td>
<td>3.23</td>
<td>0.70</td>
<td>-.18</td>
<td>&gt;.05</td>
<td>-.04</td>
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<tr>
<td>DS-CPT Bias Beta</td>
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<td>1.15</td>
<td>11.89</td>
<td>-.35</td>
<td>&lt;.05</td>
<td>.51</td>
</tr>
<tr>
<td>DS-CPT Hit Rate</td>
<td></td>
<td>83.55</td>
<td>15.03</td>
<td>.08</td>
<td>&gt;.05</td>
<td>-.28</td>
</tr>
</tbody>
</table>

Note: DS-CPT = Degraded Stimulus Version of the Continuous Performance Test; Negative Schizotypy = Social & Physical Anhedonia Scales; Positive Schizotypy = Perceptual Aberration & Magical Ideation Scales.
Appendix E

Figures
Figure 3.

Interaction effect for FH- and FH+ groups on Digit and Visual Span Forward.
Figure 4.

Interaction effect for FH- and FH+ groups on Digit and Visual Span Forward.

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Figure 6.

Correlation between negative schizotypy symptoms and CPT Beta scores.
Figure 7.

Correlation between positive schizotypy symptoms and CPT Beta Scores
REFERENCES

References marked with an asterisk indicate studies included in the meta-analysis.


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