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The Neuropsychological Differentiation of Schizophrenic Patients With and Without Abnormal Involuntary Movements

by

David William Colquhoun

Submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Dalhousie University
Halifax, Nova Scotia
May, 1994

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by DAVID COLQUHOUN

in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

Dated November 26, 1993

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Abstract

In two experiments, schizophrenic patients with and without abnormal involuntary movements (AIMs) were assessed on a broad range of neuropsychological tests. It was predicted that cognitive impairment in AIMs schizophrenia would resemble that of Huntington's disease (HD) given the possibility that a basal ganglia pathology may underlie cognitive impairment in both disorders. In Experiment 1, schizophrenic patients with AIMs (N=20) and without AIMs (N=20) were differentiated from non-psychiatric control subjects (N=20) on certain tests of problem solving/abstract reasoning (Modified Card Sorting Test), verbal fluency (FAS and Semantic Verbal Fluency Tests), and memory (Visual Reproductions and Paired Associate Learning subtests of the Wechsler Memory Scale and Rey-Osterreith Complex Figure Delayed Recall). Schizophrenic patients with AIMs performed significantly poorer than schizophrenic patients without AIMs only on the Judgment of Line Orientation Test, a measure of visuospatial ability. The cognitive impairment of AIMs schizophrenic patients did not resemble the problem solving and memory deficits that are characteristic of HD. To compare the problem solving ability of patients with schizophrenia and HD (N=10), simplified and standard versions of the Modified Card Sorting Test were administered in Experiment 2. As with Experiment 1, evidence that the cognitive impairment of AIMs schizophrenic patients resembles that of HD patients was not obtained. The results of the present research question the proposal that a basal ganglia pathology underlies cognitive impairment in AIMs schizophrenia.
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Overview of Thesis

Schizophrenia is a chronic psychiatric disorder that is characterized by loosening of associations, thought disturbances, inappropriate affective responses and, in some cases, movement abnormalities (Hollandsworth, 1990; McGlashan & Fenton, 1991). A prolonged deterioration of behaviour in schizophrenia evolves largely from a distorted perception of reality coupled with the presence of residual symptoms involving reduced motivation and drive (Mueser, Douglas, & Bellack, 1991; Pogue-Geile & Harrow, 1985). Biologically based theories assert that schizophrenia arises from structural, physiological, and biochemical alterations of the central nervous system (Andreasen, 1989; Crow, 1980). However, the present understanding of the etiology and the disease process involved in its progression is far from being complete (Buchsbaum & Haier, 1987; Carpenter, Buchanan, Kirkpatrick, Tamminga, & Wood, 1993).

Schizophrenia is not a unitary disorder. It is generally accepted that the constellation of symptoms associated with schizophrenia represents a variety of psychoses (Carpenter et al., 1993). The diversity of schizophrenia exists in its symptomatology, etiology, course, and treatment response. The variability of schizophrenia also extends to the underlying disease processes, as is indicated by the variable presence of cortical and subcortical brain abnormalities in a proportion of schizophrenic patients (Buchsbaum & Haier, 1987).

The features of schizophrenia have been investigated in terms of psychiatric (e.g., acute versus chronic symptoms), neuropsychological
(e.g., left versus right hemispheric deficits) and biological (Type I versus Type II brain abnormalities) profiles (see Chapter 2). The recognition that schizophrenia is not a homogeneous disorder has led to suggestions that the different clusters of psychiatric symptoms are associated with distinguishable neuropsychological profiles (Liddle & Morris, 1991). At present, however, there is not a consistent body of evidence to suggest that the various phenomenological dichotomies (e.g., paranoid/nonparanoid) may be segregated on the basis of divergent neuropsychology (Goldstein & Halperin, 1977; Kolb & Whishaw, 1983).

The presence in schizophrenia of abnormal involuntary movements (AIMs) provides the opportunity to investigate the clinical symptoms associated with a specific disease process of schizophrenia (Cohen & Cohen, 1993). In recent years, the view that AIMs arise from a basal ganglia pathology intrinsic to schizophrenia has been supported by epidemiological evidence indicating that the length and/or intensity of neuroleptic exposure does not consistently differentiate schizophrenic patients with and without AIMs (Waddington, O’Callaghan, Larkin, & Kinsella, 1993). In this context, the terms AIMs schizophrenia and non-AIMs schizophrenia are used to denote two possible subtypes of schizophrenia which are distinguished by the presence or absence of a specific basal ganglia disorder (see Chapter 2).

Since basal ganglia pathology may disrupt some cortical functions (Cummings, 1993), schizophrenic patients with AIMs may present with symptoms that are not typical of non-AIMs schizophrenia (Brown, White,
& Palmer, 1992). In order to investigate AIMs-related cognitive impairment, the neuropsychology of schizophrenic patients with and without AIMs has been subjected to greater scrutiny recently (Brown et al., 1992; Manschreck, Keuthen, Schneyer, Celada, Laugher, & Collins, 1990; Waddington et al., 1993). Interest in examining the neuropsychology of AIMs schizophrenia stems from the realization that in disorders such as Huntington’s disease, basal ganglia pathology is associated with specific deficits on tests sensitive to frontal lobe function, memory, and visuospatial perception (Brandt & Butters, 1986). The association between basal ganglia pathology and cognitive impairment is supported by evidence that specific deficits involving frontal lobe functions are mediated by a series of circuits which connect the frontal lobes with basal ganglia structures (Cummings, 1993; see Chapter 3). Thus, there is reason to expect that schizophrenic patients with AIMs may present with a specific pattern of cognitive impairment given that AIMs can be considered to be a physical marker for basal ganglia pathology (Cohen & Cohen, 1993).

The severity of neuropsychological deficits in schizophrenia is variable, with some patients displaying little, if any, impairment (Braff, Heaton, Kuck, Cullum, Moranville, Grant, & Zisook, 1991). The factors that are related to the cognitive variability of schizophrenia are not clear. The possible cognitive impairment associated with AIMs is seldom considered in studies examining the neuropsychology of schizophrenia, especially if movement abnormalities are subtle in
nature. Therefore, the extent to which the abnormal cognitive performance of schizophrenic patients reflects an AIMs related basal ganglia pathology is unknown. The investigation of the neuropsychology of schizophrenic patients with AIMs may broaden the current understanding of the cognitive diversity of schizophrenia.

In order to investigate whether AIMs in schizophrenia are associated with a specific pattern of deficits, two experiments were conducted. The purpose of the first experiment was to determine the degree to which the presence of AIMs is an indicator of a pattern of cognitive deficits that diverges from the deficits experienced by non-AIMs schizophrenic patients. In this experiment, schizophrenic patients with and without AIMs were examined on a test battery designed to assess mental flexibility, verbal fluency, memory, and visuospatial/constructional abilities.

A further purpose of Experiment 1 was to investigate the extent to which the cognitive profile of AIMs schizophrenia resembles previous reports of cognitive impairment in Huntington’s disease (see Chapter 5). This comparison was mainly based on the finding that in Huntington’s disease, basal ganglia pathology leads to both cognitive impairment and psychiatric symptoms (Folstein, 1989). The testing of both Huntington’s disease and schizophrenic patients would be advantageous for comparison purposes; however, patients with Huntington’s disease were not included in Experiment 1 due to a relatively small number of patients available for recruitment. As is discussed in Experiment 1, it is probable that
the assessment of a small sample of Huntington's disease patients on numerous tests would have jeopardized the statistical validity of the analysis.

A direct neuropsychological assessment of patients with schizophrenia and Huntington's disease was made in Experiment 2 which involved a relatively small number of comparisons. In Experiment 2, patients with schizophrenia (AIMs and non-AIMs) were compared specifically for mental flexibility and problem solving, as assessed by standard and simplified versions of the Modified Card Sorting Test (MCST; Nelson, 1976). Previous research has suggested that poor card sorting performance is a characteristic of schizophrenia (Berman, Zec, & Weinberger, 1988; Liddle & Morris, 1991) and Huntington's disease (Brandt & Butters, 1986; Goldberg, Berman, Mohr, & Weinberger, 1990). At the onset of Experiment 2, the primary purpose of employing the MCST was to assess schizophrenic patients with and without AIMs in an area of cognitive functioning that had not been investigated previously. Recently, however, it has been reported that schizophrenic patients with AIMs have greater card sorting deficits than schizophrenic patients without AIMs (Brown et al., 1992). In this context, the purpose of Experiment 2 was 1) to determine whether Brown et al.'s (1992) finding that poor card sorting performance is more prominent in AIMs than in non-AIMs schizophrenic patients can be replicated, and 2) to investigate whether schizophrenic patients with AIMs and Huntington's disease patients experience the same degree of impairment on the MCST.
In Experiments 1 and 2, the relationship between AIMs and cognitive performance in schizophrenia was investigated from the perspective that the pathology of the frontal-subcortical circuits (Alexander, Delong, & Strick, 1986) may underlie the presence of both movement disturbances and particular cognitive impairments. As is discussed in Experiment 1, there are several reasons to predict that AIMs and non AIMs schizophrenic patients may be differentiated in terms of cognitive performance: 1) AIMs schizophrenia is characterized by an organic disorder which is not typical of schizophrenia (Lohr, Wisniewski, & Jeste, 1986), 2) the pathology of frontal-subcortical circuits is known to cause focal deficits in frontal lobe functioning (Cummings, 1993), and 3) schizophrenic patients with AIMs display mental flexibility and verbal fluency deficits which resemble the deficits produced by the disruption of the frontal-subcortical circuits (Brown et al., 1992).

This thesis is divided into seven chapters. In Chapter 1 the terminology specific to schizophrenia is defined. Chapter 2 begins with a description of the movement disturbances characteristic of schizophrenia, and is followed by a review of the biological aspects involved in the pathophysiology of movement disturbances. In Chapter 3 the neuropsychology of the frontal lobe is reviewed with the purpose of providing the framework for discussing the neuropsychology of schizophrenia (Chapter 4) as well as the neuropsychology of AIMs schizophrenia and Huntington’s disease (Chapter 5). Experiments 1 and 2 are presented in Chapters 6 and 7, respectively.
Chapter 1
General Introduction to Schizophrenia

Current concepts of schizophrenia reflect an evolving process entailing the integration of biological anomalies with observable psychiatric features. The challenge of understanding schizophrenia involves both the identification of the core symptoms of the disorder, and the manner in which they are precipitated by the interaction of pathological processes and environmental factors. However, marked variation in the course of illness, severity of symptoms, and response to pharmacological agents has impeded most aspects of schizophrenia research. Consequently, the relative significance of biological and environmental correlates of schizophrenia remains uncertain. The psychiatric heterogeneity of schizophrenia has led to the recognition that either multiple independent (Crow, 1980) or interdependent (Andreasen, 1989; Weinberger, 1988) pathologies underlie the variability of schizophrenia.

In terms of phenomenology, current diagnostic systems, such as the Diagnostic and Statistical Manual of Mental Disorders III-Revised (1987), define schizophrenia by the presence of psychosis marked by disturbances of thought content (delusions), form of thought (loosening of associations), and perception (auditory, visual and tactile hallucinations). Other characteristic features include inappropriate affect, poor motivation, and movement disturbances (e.g., stereotypies and mannerisms). In addition to these symptoms, there is growing evidence that schizophrenia is marked by the impairment of memory (Koh,
Kayton, & Schwartz, 1978; Raulin & Chapman, 1976), attention (Shakow, 1962), perception (Braff et al., 1991; Moon, Mefford, Wieland, & Falconer, 1968), and complex cognitive abilities, possibly reflecting a defect of the prefrontal cortex (Goldberg, Weinberger, Berman, Piliskin, & Podd, 1987).

The classification of schizophrenia in terms of other psychiatric disorders has been primarily influenced by Kraepelin (1919) and Bleuler (1950), both of whom regarded schizophrenia as a biological disorder. Disagreements, however, concerning the pathognomonic symptoms of schizophrenia have existed from the time that Kraepelin referred to dementia praecox (subsequently renamed schizophrenia by Bleuler, 1950) as a discrete disorder characterized by a syndrome of psychotic features and intellectual deterioration. Kraepelin viewed schizophrenia as a chronic disorder resulting from structural and chemical disturbances of the brain, both of which typically became manifested during adolescence and led to a gradual and irreversible dilapidation of thought processes. The characteristics of dementia praecox included hallucinations, delusions, disturbances of emotional expression, inattention, negativism, and stereotypies. While no one symptom was considered to be unique to schizophrenia, Kraepelin’s emphasis on chronicity distinguished schizophrenia from affective disorders which he considered to have an episodic course.

In contrast, Bleuler (1950) stressed the importance of associative disturbances which he considered to produce fundamental symptoms such as
autism, loose associations, inappropriate affect and ambivalence. Other symptoms, such as hallucinations and delusions, were considered to be accessory symptoms in the sense that they are common to other mental disorders. Further, Bleuler de-emphasized the inevitability of poor outcome and, thereby, dismissed the diagnostic importance of chronicity. Moreover, Bleuler considered the course of the disorder as being variable with intermittent episodes of illness being common. Bleuler’s (1950) observation that symptoms were not necessarily expressed early in life or associated with dementia led him to view the term dementia praecox as being inaccurate. In its place Bleuler (1950) proposed the term schizophrenia which reflected his belief that the primary process of schizophrenia is the splitting of "psychic functions" resulting in a dissolution of associative thought.

Interested in the pragmatics of diagnostic accuracy, Schneider (1957) proposed that first rank symptoms could be used to define the presence of schizophrenia. A central component of first rank symptoms, which Schneider considered to have diagnostic importance, pertains to the inability of schizophrenic patients to differentiate between internal and external experiences (e.g., the belief that thoughts of others are being inserted in one’s consciousness). More specifically, the first rank symptoms described by Schneider include: 1) audible thoughts (the perception of hearing one’s thoughts being spoken aloud), 2) voices arguing (the presence of hallucinatory voices in disagreement), 3) voices commenting (hallucinatory voices making remarks
concerning one's actions as they occur), 4) thought withdrawal (perception of thoughts being removed from one's head by an external force, 5) thought insertion (perception that one's thoughts are being imposed by others, 6) thought broadcasting (the perception that personal thoughts are escaping uncontrollably from one's head, 7) made feelings (the perception that one's feeling are being imposed by others), 8) made volitional acts (the perception that one's actions are being controlled by others), and 9) delusional perception (the attribution of a personal, unrealistic meaning to an action or event). Schneider's second rank symptoms consist of 1) depression, 2) emotional blunting, 3) euphoric affect, and 4) all other forms of hallucinations (e.g., olfactory hallucinations). Schneider did not attempt to associate first or second rank symptoms to theoretical or biological processes (Mellor, 1970).

Although the biology of schizophrenia has been examined extensively, the relationship of physiological and anatomical anomalies to psychiatric symptoms is poorly understood. Many early neuropathological studies reported a host of anatomical anomalies which included cell loss and histopathological alterations of both subcortical and cortical areas (Alzheimer, 1913; Hassin, 1918; Josephy, 1930). As discussed by Weinberger, Wagner and Wyatt (1983), pneumoencephalographic studies also indicated the presence of enlarged lateral ventricles, which could be suggestive of degenerative processes. The absence of consistent findings resulted in a failure to localize structural
abnormalities in schizophrenia.

Improvements in the resolution of neuroimaging techniques (e.g., computed tomography and magnetic resonance imaging) and the introduction of sophisticated physiological measures (e.g., regional cerebral blood flow and positron emission tomography) have provided a greater opportunity to examine structural and physiological abnormalities in schizophrenia. Recent studies investigating the biological aspects of schizophrenia have suggested that numerous brain regions are involved in the mediation of clinical symptoms. Included in the list of brain areas which have received increased attention in the pathology of schizophrenia are the frontal lobes (Ingvar & Franzen, 1974; Weinberger, Berman, & Zec, 1986), the temporal lobes (Abrams & Taylor, 1980), the limbic system (Iversen, 1975; Klawans, Goetz, & Westheimer, 1976), the basal ganglia structures (Lidsky, Weinhold, & Levine, 1979), and the brainstem (Davison & Bagley, 1969). Of the many theoretical models, brain dysfunction in schizophrenia has been thought of mainly in terms of both cortical and subcortical processes (Robbins, 1990) and hemispheric laterality processes (Flor-Henry & Yeudall, 1979; Nasrallah, 1985). Notwithstanding the technological advancements, a comprehensive theory which provides an adequate integration of the biological data has not yet been put forth.

The lack of understanding of the biological substrate of schizophrenia is partially a result of methodological difficulties. Specifically, a serious research problem of recent pathophysiological
studies is the failure to consider the various psychiatric expressions of schizophrenia. It is, therefore, not surprising that consistent results have not been reported since a variety of biological anomalies may underlie the psychiatric diversity associated with schizophrenia.

The recognition that the phenomenology of schizophrenia is not comprised of a uniform cluster of symptoms, corresponding to a unitary biological defect, prompted efforts to categorize the psychiatric heterogeneity into discrete, and usually dichotomous categories. Crow (1980), borrowing from Hughlings-Jackson's concept of positive and negative symptoms, proposed a biological basis for the categorization of symptoms. In this model, Crow (1980) divided schizophrenia into Type I and Type II syndromes. The Type I syndrome, which is considered a result of a subcortical disturbance of dopamine transmission, is characterized by positive symptoms (e.g., hallucinations, delusions, and formal thought disturbances). In the Type II syndrome, structural abnormalities are thought to produce negative symptoms (also referred to as deficit symptoms) such as alogia, anhedonia, and flattening of affect. The division between positive and negative symptoms is phenomenologically consistent with Bleuler's distinction between fundamental and accessory symptoms and the current DSM-III-R division between acute symptoms and residual symptoms. Further, the psychiatric features of the Type I syndrome include all of Schneider's first rank symptoms (Crow, 1989) while certain second rank symptoms (e.g., blunted affect) resemble Type II symptoms. Although Crow's model has been generally criticized on the
basis of its oversimplification of biological mechanisms (Andreasen, 1989), the division between positive and negative symptoms has provided a model for researchers to address the psychiatric heterogeneity of schizophrenia in terms of biological processes.

The uncertainty regarding the biological substrate of schizophrenia is not consistent with pharmacological advancement which has led to an unprecedented ability to manage psychotic features. During the 1950's the introduction of neuroleptic drugs, which selectively block subcortical dopamine receptors, provided a method for ameliorating psychotic behaviour. Subsequently, the most influential explanation of schizophrenia became the dopamine hypothesis which proposes that acute symptoms are caused by excessive subcortical dopamine activity. The dopamine hypothesis was further supported by evidence that dopamine agonists, such as amphetamines, produce features that mimic schizophrenia psychosis (Ramdrupt & Munkvad, 1974). Although the precise role of faulty dopamine transmission in the pathology of schizophrenia is controversial (Carlton & Manowitz, 1984; Freed, 1988; Pickar, 1990), the dopamine hypothesis has served to advance the understanding of both the anatomical and physiological properties of the dopamine systems implicated in schizophrenia.

While neuroleptics have enhanced the treatment of acute symptoms (e.g., delusions and hallucinations), the widespread use of pharmacotherapy may have introduced a complicating factor in understanding the phenomenology of schizophrenia. Some researchers, for
instance, have suggested that the present descriptions of schizophrenia are markedly different from descriptions prior to the era of neuroleptics (Hogarty, 1977; Wilson, Garbutt, Lanie, Moylan, Nelson, & Prange, 1983). For instance, Wilson et al. (1983) proposed that neuroleptics induce a state of hypomania (i.e., elevated or irritable mood coupled with excessive involvement in activities). The influence of neuroleptics on cognition and brain metabolism of schizophrenic patients is discussed in Chapter 4.

The most recognized side-effect of medication is AIMS. The presence of AIMS may dramatically alter the physical appearance of an affected individual. These movements are primarily characterized by orofacial movements (i.e., grimaces, lip smacking, pouting and tongue protrusions) and choreiform movements (short and jerky movements which may appear as parts of gestures and expressions). Although phenomenologically indistinguishable, AIMS in schizophrenia may occur in association with neuroleptic drugs or spontaneously (Jeste & Caligiuri, 1993). Further, the descriptions of AIMS in the era prior to the use of neuroleptics suggest that AIMS may occur independently of pharmacological intervention. For example, Kraepelin (1919) described movement abnormalities of schizophrenic patients as being characterized by facial spasmodic movements which resemble the abnormal movements of choretic patients. Bleuler (1950) also reported that the presence of abnormal movements, consisting of grimaces and eccentric movements of the lips and tongue, are typical of schizophrenia.
The salience of AIMs in schizophrenic patients has heightened the awareness of the adverse effect of neuroleptics to the degree that the presence of any form of AIMs is considered an indication of an iatrogenic effect of medication (Manschreck et al., 1990). However, attributing AIMs to a medication effect may be incorrect in many cases insofar as the development of AIMs may occur equally often in medicated and unmedicated schizophrenic patients (Owens, Johnstone, & Frith, 1982). It may be more accurate to view AIMs as arising from biological processes, intrinsic to schizophrenia, which are exacerbated by the effects of neuroleptics (Cadet, Lohr, & Jeste, 1987). In Chapter 2, AIMs are further discussed in terms of phenomenology and underlying biological processes.
Chapter 2
Movement Disturbances

The term abnormal involuntary movements is used in the present review to refer to dyskinetic and choreiform movements that occur in schizophrenia. As indicated in the Overview, the terms AIMs schizophrenia and non-AIMs schizophrenia denote two possible forms of schizophrenia which differ in terms of the presence or absence of AIMs and, therefore, a specific basal ganglia pathology. Although AIMs refer to movements which occur in tardive dyskinesia, the term tardive dyskinesia is often incorrectly used in that the dyskinetic movements described do not meet the severity and/or medication criteria used to diagnose tardive dyskinesia.

This chapter presents a brief description of the movement disturbances that occur in schizophrenia and Huntington’s disease. The purpose of this comparison is to discuss the extent to which the movement anomalies of these two disorders overlap. Current proposals regarding the biological basis of AIMs are also discussed in order to present the rationale for the hypothesis that the pathological processes intrinsic to AIMs schizophrenia may be responsible for the coexistence of psychiatric and movement disturbances. A basic assumption of this discussion is the view of Awouters, Niemegeer and Janssen (1990) that neuroleptics may exacerbate dyskinetic movements that are endogenous to schizophrenia. Appendix 1 provides a description of the various terms used in Chapter 2 to refer to the abnormal movements which occur in schizophrenia and Huntington’s disease.
In addition to AIMs, schizophrenia is associated with other forms of movement disturbances. In catatonic schizophrenia psychomotor movement anomalies (e.g., stupor, rigidity, and posturing) dominate the psychiatric features. Voluntary and involuntary movement disturbances, however, occur in all types of schizophrenia. The types of voluntary movement disturbances characteristic of schizophrenia in general, include poor coordination, stereotyped postures, mannerisms and bradyphrenia (Manschreck, 1986). Involuntary movement disturbances, such as tics, akathisia, choreiform movements and dyskinesia, are also present in chronic schizophrenia (Gerlach & Casey, 1988).

Kraepelin (1919) described a diversity of movement disturbances in both hebephrenic and paranoid types of schizophrenia. Included in his early description of schizophrenia were reports of movement anomalies such as echopraxia, catalepsy, negativism, and stupor. More generally, Kraepelin also noted a loss of muscle coordination leading to uncoordinated gait and a decline in performing skilled tasks.

The inclusion of movement disturbances in the phenomenology of schizophrenia has traditionally been secondary to the consideration of other features of schizophrenia. To a certain degree, this lack of emphasis stems from a conceptual difficulty involved with reconciling movement disturbances with psychologically salient features associated with psychosis. Manschreck (1986) proposed that the fundamental reason for the paucity of research on movement disorders in schizophrenia is the absence of a model which explains the relationship between movement
disturbances and other symptoms of schizophrenia. Specifically, involuntary movement disorders are typically attributed to the basal ganglia, a structure whose pathological involvement in schizophrenia is usually considered removed from the manifestation of psychiatric features (Weinberger, 1986). Thus, the presence of movement disturbances has been attributed to either the adverse effects of neuroleptics or neurological conditions which coincide with schizophrenia. This conceptualization of movement disturbances of schizophrenia appears to be inaccurate in that there is a growing recognition that basal ganglia structures have an important involvement in the mediation of cognitive processes in a number of disorders (e.g., Huntington's disease) including schizophrenia (Lidsky et al., 1979).

While an association between AIMs and neuroleptic treatment was made in the late 1950's (Schonecker, 1957), it was not until the mid 1960's that the presence of AIMs received increased attention. At present, AIMs refer to a syndrome of abnormal involuntary movements characterized by bucco-linguo-masticatory involuntary movements consisting of chewing, pouting, licking and rotating tongue movements. Facial tics and grimaces may also be present. Choreiform and athetoid movements, which affect fingers, arms and legs, are usually present in AIMs (Gerlach & Casey, 1988). Additionally, both choreiform and athetoid movements may be accompanied by akathisia.

In the early stages of Huntington's disease, choreiform movements of the face are typically the most noticeable movement abnormality. As with
AIMs, abnormal facial movements in Huntington’s disease include pouting, grimacing, chewing, and rotating tongue movements (Hayden, 1981). As Huntington’s disease progresses, facial movements are eventually accompanied by choreiform movements of the hands, arms and legs. The severity of choreiform movements typically peaks approximately ten years after the onset of movement abnormalities (Folstein, 1989). Similar to AIMs, choreiform and athetoid movements in Huntington’s disease are accompanied by akathisia. In later stages of Huntington’s disease, involuntary movements lessen in severity as voluntary movements become increasingly impaired (Folstein, 1989).

In terms of schizophrenia, it was the spread of neuroleptic treatment that drew attention to the movement abnormalities. Reports of AIMs became more common during the early 1960’s (Kruse, 1960; Drukman, Seelinger, & Thulin, 1962; Uhrbrand & Faurbye, 1960); however, at that time AIMs were mainly considered an uncommon medication effect (Lohr, Wisniewski, & Jeste, 1986). The epidemiological studies of the 1970’s led to the realization that the prevalence of AIMs may be as high as 40% in neuroleptically-treated schizophrenic patients (Crane, 1973). The higher estimate of AIMs prevalence may have been a consequence of a number of factors including 1) a greater awareness of AIMs among clinicians, 2) the development of standardized rating scales for assessing AIMs, and 3) an actual increase of AIMs incidents resulting from the prolonged, cumulative effects of two decades of neuroleptic exposure in some patients.
The course of AIMs is marked by considerable variability. In approximately one-third of all cases of AIMs, abnormal movements occur intermittently with remissions after withdrawal from neuroleptics (Jeste & Wyatt, 1982). In other cases, AIMs become persistent with no reversal after medication is discontinued. In a prospective study, Glazer, Morganster, and Doucette (1991) determined that of the 112 patients they examined, 58% expressed a chronic, persistent form of AIMs.

A number of studies have identified factors which place psychiatric patients at risk of developing AIMs. Other than neuroleptic medication, the most important factor is age, with older individuals being more prone to developing AIMs (Gerlach & Casey, 1988). For example, after two years of exposure to neuroleptics, the probability of developing AIMs is 10% for a 20-year-old patient while it is 18% for a 50-year-old patient (Kane, Woerner, Borenstein, Wegner, & Lieberman, 1986). A second predisposing factor is psychiatric diagnosis. Patients with affective disorders are more at risk of developing AIMs than schizophrenic patients (Kane et al., 1986). As with schizophrenia, the pathophysiological process underlying AIMs in affective disorders is considered to involve the basal ganglia (Gerlach & Casey, 1988).

The focus placed on AIMs has led to a general view that all forms of movement abnormalities in schizophrenia are associated with neuroleptic medication (Manschreck et al., 1990). In contradiction to this view, AIMs occur regularly in never-medicated schizophrenic patients.
(Morgenstern, Glazer, & Niedzwiecki, 1987; Owens et al., 1982). In a comparison of chronic never-medicated and medicated patients, Owens et al. (1982) examined the prevalence, severity, and body distribution of dyskinesia. An important finding was that the prevalence (approximately 50%) and severity of AIMs did not differ between the patient groups. This result suggests that AIMs are a feature of some chronic schizophrenic patients, regardless of medication status. A methodological difficulty with AIMs prevalence studies is that while multiple diagnostic groups (e.g., schizophrenia and bipolar disorders) which differ in their susceptibility to the development of AIMs are investigated, separate analysis for each diagnostic group is not provided. This methodological limitation may be reflected in the discrepancies in the estimated prevalence of AIMs across studies (Gerlach & Casey, 1988). Therefore, a major drawback of studies with this flaw is that they do not accurately reflect the prevalence of AIMs for specific groups of patients.

Summary. While epidemiological studies initially raised a concern of a causal relationship between neuroleptic treatment and the development of AIMs, neuroleptics may be only one of a number of factors which underlie the development of AIMs in schizophrenic patients. A second important factor, which appears to be related to the manifestation of AIMs, is the increased age of patients with psychiatric disorders. The finding that older patients are at a higher risk of developing abnormal movements suggests that age-related changes of the
basal ganglia in combination with the action of neuroleptics may evoke AIMs. Moreover, the finding that AIMs may frequently occur in the absence of neuroleptic treatment suggests that movement disturbances occur spontaneously in a proportion of schizophrenic patients.

To a certain degree, the movement disturbances of Huntington's disease and AIMs schizophrenia are similar in appearance. In both disorders, choreiform and athetoid movements are accompanied by akathisia. The two disorders may be distinguished on the basis that voluntary movements are more severely impaired in Huntington's disease than in AIMs schizophrenia (David, Jeste, Folstein, & Folstein, 1987).

**Brain Areas Implicated**

A review of basal ganglia and frontal lobe structures is presented since it provides background information regarding the biological processes that may underlie the relationship between AIMs and schizophrenia symptomatology. A central aspect of this discussion is the assessment of dopamine-based hypotheses which have been emphasized in the traditional views of the pathophysiology of both AIMs and schizophrenia. The review of the biological aspects of AIMs is also meant to facilitate the discussion in Chapter 3 in which the cognitive features of frontostriatal pathology are presented.

The basal ganglia, located in both the basal forebrain and midbrain, form the greatest subcortical area of gray matter in the cerebral hemispheres (Divac & Oberg, 1979). Included in the basal ganglia are the caudate nucleus, the globus pallidus, the putamen, the nucleus
accumbens, the olfactory tubercle the substantia nigra and the subthalamic nucleus. The caudate nucleus and the putamen, which are separated by the internal capsule, compose the striatum (also referred to as the neostriatum or the dorsal striatum). The ventral striatum of the basal ganglia consists of the nucleus accumbens and the olfactory tubercle.

The basal ganglia receive inputs from the cerebral cortex, limbic system, the substantia nigra, the ventral tegmentum, the reticular formation (via the interlaminar thalamic nucleus), the locus ceruleus, and the raphe nucleus. Afferent cortical pathways arise on ipsilateral sides and mainly terminate at the level of the striatum. These corticostriatal inputs utilize glutamate as an excitatory neurotransmitter. To a lesser extent the subthalamic nucleus also receives afferent projections from the cerebral cortex. Efferent basal ganglia fibers project to the thalamus, superior colliculus, and reticular formation of the brain stem.

With the exception of the occipital lobe, the striatum receives projections from all of the major regions of the cerebral cortex. The head of the caudate nucleus receives projections from the association areas of the frontal, parietal, and the temporal lobes (Weiner & Lang, 1989). The putamen receives somatopically arranged innervation from the sensorimotor and premotor areas. The posterior areas of the caudate nucleus and putamen are innervated by widespread areas of the cerebral cortex. The ventral striatum receives innervation primarily from the
cingulate cortex.

The substantia nigra and globus pallidus are each divisible into two distinct anatomical regions. The substantia nigra is composed of the pars compacta (PC) and pars reticulata (PR) while the globus pallidus has internal (i.e., medial) and external (i.e., lateral) regions. The internal globus pallidus and the substantia nigra (PR) contain morphologically and chemically identical cells, and on this basis the substantia nigra (PR) is considered to be a part of the pallidum (Weiner & Lang, 1989).

All of the main outputs of the striatum are directed to the internal globus pallidus and the substantia nigra (PR). The striato-pallidal pathway mainly uses the neurotransmitter gamma-aminobutyric acid (GABA). The primary efferents of the substantia nigra (PR) and the internal globus pallidus project to the thalamus. The external globus pallidus projects to the subthalamic nucleus which, in turn, projects to the internal globus pallidus and substantia nigra (PR).

There are three dopamine projection systems which have been implicated in schizophrenia pathology. The majority of dopamine neurons are located in the substantia nigra (PC) and the ventral tegmentum of the mesencephalon. The nigrostriatal pathway originates from the substantia nigra (PC) and projects dorsolaterally in to the median dorsal bundle, traverses the internal capsule, and terminates at the putamen, caudate nucleus, and globus pallidus. Axons of dopaminergic neurons of the ventral tegmentum ascend via the median dorsal bundle to
form the mesolimbocortical pathway. The target structures of this pathway are the amygdala, hippocampus, cingulate cortex, and prefrontal cortex. The mesolimbocortical pathways may be divided into the mesolimbic and mesocortical pathways (Lindvall & Bjorklund, 1987). This division is based on the different anatomical and neurochemical properties of the dopaminergic neurons projecting to limbic and prefrontal structures.

Dopamine neurons, arising from the substantia nigra (PC), innervate both cholinergic and GABA-ergic neurons of the neostriatum (see Figure 1). Two types of GABA neurons project from the striatum. GABA neurons of the posterior striatum, which project to internal globus pallidus and substantia nigra (PR), are excited by dopamine. In contrast, dopamine inhibits anterior striatal GABA neurons which innervate the external globus pallidus. The internal globus pallidus GABA neurons innervate the anteroventral and ventrolateral nuclei of the thalamus. The ventromedial nucleus of the thalamus receives GABA projections from the substantia nigra (PR).

The thalamus, which is located between the midbrain and cerebral hemispheres, has a central role in transmitting subcortical information from the brain stem, limbic structures, and basal ganglia to the cerebral cortex. While the lateral portions of the thalamus are separated by the third ventricle, they are joined in the midline by the massa intermedia. The various nuclei of the thalamus are classified as either diffuse-projecting nuclei or relay nuclei. Relay nuclei transmit
Figure 1. Primary pathways and neurotransmitters of the basal ganglia. Abbreviations: PC, pars compacta; PR, pars reticulata; VI ventrolateral; VA, ventroanterior; VM, ventromedial.
information to specific areas of the cortex whereas diffuse projecting nuclei innervate a wide range of the cerebral cortex. The diffuse projecting nuclei, principally composed of the intralaminar nuclei, are involved with arousal. Relay nuclei, including the lateral nuclei, send information pertaining to sensory and movement inputs while the anterior and medial nuclei provide relays to the association cortex.

The prefrontal cortex, which consists of Brodmann’s areas 9, 10, 11, and 46, is traditionally defined as the portion of the frontal lobe innervated by the mediodorsal thalamic nuclei (Golden, 1981). The mediodorsal nucleus innervates all aspects of the prefrontal cortex although other thalamic nuclei (e.g., nucleus ventralis anterior and anterior intralaminar nuclei) also project to the prefrontal cortex. The mediodorsal nucleus further divides the prefrontal cortex into three regions. The medial portion of the mediodorsal nucleus projects to the orbital prefrontal cortex while the lateral portion innervates the dorsal prefrontal cortex. The frontal eye field of the prefrontal cortex receives projections from the laterally located pars paralamellaris of the mediodorsal nucleus.

The prefrontal cortex has reciprocal cortical connections with association areas of the occipital, temporal, and parietal lobes. These afferents originate from non-primary sensory areas involved with vision, audition and somesthesis. The convergence of these sensory pathways may make the prefrontal cortex a cross modality association center (Fuster, 1989). The prefrontal cortex is also reciprocally connected with
subcortical structures including the thalamus, limbic system and brain stem. The complexity of intrinsic and extrinsic connections of the prefrontal cortex suggests that it is involved with the integration of a diverse range of inputs from cortical and subcortical structures (Golden, 1981).

Biology of AIMs

Hypotheses based on altered dopamine metabolism have had a prominent influence in directing the investigation of the pathophysiology of both schizophrenia and AIMs. The initial support for the view that the psychotic features of schizophrenia are primarily associated with a subcortical increase in dopamine metabolism may be summarized by three key findings: 1) neuroleptic drugs act to block postsynaptic dopamine receptors (Carlsson & Lindqvist, 1963), 2) the degree of symptom relief appears to correspond to the antagonistic effect of neuroleptics (Creese Burt, & Snyder, 1976), and 3) amphetamines, which are dopamine agonists, exacerbate certain psychotic features of schizophrenia (Meltzer & Stahl, 1976).

The dopamine hypothesis was refined by Crow (1980) who proposed that only Type I features are linked to subcortical dopamine physiology on the basis that the amelioration of psychotic symptoms is associated with the neuroleptic blockade of subcortical dopamine receptors. In contrast, Type II features are related to the neuronal loss in the cerebral cortex. The finding, however, that Type II symptoms, rather than Type I symptoms, are more are closely associated with AIMs (e.g., Waddington &
Youssef, 1986) apparently contradicts the assumption that AIMs and Type I symptoms are both a manifestation altered dopamine metabolism. A second weakness of the dopamine hypothesis is its inability to explain the time lag between the rapid antagonistic effects of neuroleptics and the reduction of psychotic symptoms which usually occur weeks after neuroleptic administration (Hollandsworth, 1990). In an attempt to explain this lag, Pickar (1990) has suggested that an adaptive presynaptic increase in dopamine metabolism may counteract the immediate antipsychotic effects of the neuroleptic blockade. A third weakness is that the psychotic features induced by amphetamines are now recognized not to accurately mimic the core symptoms of schizophrenia such as formal thought disorder and negative symptoms (Joyce, 1988). On a conceptual level, Carlton and Manowitz (1984) have suggested that the dopamine hypothesis is vaguely formulated in terms of 1) the symptoms associated with altered dopamine activity, 2) the brain area(s) involved in the mediation of symptoms, 3) the relationship between dopamine activity and other neurotransmitters, and 4) the consideration of altered dopamine activity as a symptom or an etiology.

The proposed association between Type I schizophrenia and increased dopamine activity suggests that dopamine metabolism has little relevance to chronic schizophrenia which is mainly characterized by Type II symptoms. Recent additions to the dopamine hypothesis have included speculation that it is the interaction between mesocortical and mesolimbic dopamine pathways that underlies the manifestation of
positive and negative symptoms. For example, Weinberger (1986) has proposed that decreased mesocortical activity may cause reduced frontal lobe activity which, in turn, produces deficit symptoms. It is further proposed by Weinberger (1986) that the alteration of mesocortical dopamine activity mediates positive symptoms by causing increased activity of mesolimbic dopamine pathways through a process of disinhibition of dopamine neurons. While this proposal attempts to integrate physiological properties of the mesocortical dopamine pathway with possible pathophysiological aspects of schizophrenia (i.e., reduced frontal lobe metabolism), the involvement of the mesocortical dopamine pathway in altering frontal lobe activity in schizophrenia is mainly speculation.

The involvement of altered subcortical dopamine activity as a cause of AIMs has also been reevaluated. Early proposals emphasized that AIMs were primarily associated with post synaptic striatal dopamine receptor supersensitivity which occurs in response to neuroleptic blockade of dopamine receptors. As reviewed by Gerlach and Casey (1988), key evidence favoring a supersensitivity dopamine hypothesis of AIMs consists of findings that include 1) withdrawal from neuroleptics, which increases dopamine activity, exacerbates dyskinesia, 2) drugs which deplete presynaptic dopamine neurons (e.g., reserpine) may ameliorate AIMs, and 3) dopamine agonists may worsen dyskinesia.

The weakness of the supersensitivity model is that it does not account for the observation that dyskinesia only occurs in certain
neuroleptically-treated schizophrenic patients while increased dopamine receptor sensitivity presumably occurs in all neuroleptically-treated schizophrenic patients (Lieberman & Riefe, 1989; Lohr et al. 1986). Moreover, the supersensitivity model has been criticized on the basis that dopamine agonists do not consistently exacerbate dyskinesia in humans (Carroll, Curtis, & Kohmen, 1977; Smith, Tamminga, & Haraszti, 1977) and the absence of evidence that schizophrenic patients with AIMs have an increased number of dopamine receptors (Cross, Crow, & Owens, 1981; Nguyen, Thaker, & Tamminga, 1989). Therefore, the current model of neuroleptically-induced AIMs appears to be incomplete in its ability to account for pathophysiological anomalies of neuroleptically treated schizophrenic patients.

Recently, reduced striatal GABA activity has been implicated in the pathology of AIMs (Gerlach & Casey, 1988; Jeste & Caligiuri, 1993). Striatal GABA activity has been recognized to play a part in the regulation of movements (Thaker, Tamminga, & Alps, 1987). The clearest support for the GABA hypothesis is the finding that AIMs in primates are associated with a reduction of GABA and glutamic acid decarboxylase (an enzyme necessary for the synthesis of GABA) in the striatum (Gunne, Haggestrome, & Sjoquist, 1984). Importantly, AIMs persisted after neuroleptic withdrawal and, unlike dopamine supersensitivity, AIMs only occurred in subjects with decreased GABA activity. These findings have led to the proposal that AIMs are caused by a neuroleptic-induced destruction of GABA neurons located in the striatum (Jeste & Caligiuri,
1993; Fibiger & Lloyd, 1984).

The evidence from neuropathological studies suggests that AIMs are associated with structural changes of the basal ganglia (Lohr et al., 1986). A number of researchers have indicated that the pathophysiology of the striatum (e.g., caudate nucleus and putamen) may be the primary feature of AIMs (Granholm, Bartzokis, Asarnow, & Marder, 1992; Lohr et al., 1986). The involvement of striatal pathology in the development of AIMs is supported by Jellinger (1977) who reported that AIMs are accompanied by pathological changes (i.e., glial satellitosis and swelling of large neurons) involving the caudate nucleus and putamen. Bartels and Themelis (1983) reported that AIMs in schizophrenia are associated with the atrophy of the head of the caudate nucleus. Magnetic resonance imaging studies have found decreased caudate nucleus size in schizophrenic patients with AIMs as compared to schizophrenic patients without AIMs (Granholm et al., 1992; Mion, Andreasen, Arndt, Swayze, & Cohen, 1991).

It is thought that the pathology of the striatum leads to the loss of coordinated movement that is characteristic of AIMs schizophrenia (Lohr et al., 1986). In particular, the involvement of the putamen in the pathology of AIMs is derived from histopathological evidence suggesting that the putamen along with the motor cortex, the globus pallidus, the substantia nigra and the thalamus form a motor circuit that mediates the programming and control of movement (Alexander, Delong, & Stick, 1986; see Chapter 3). In general, Brooks (1986)
proposed that the functional importance of the motor circuit is that it compares intended plans, via efferent copies, with the execution of the plans. When the intended plans are not in agreement with the executed plans, the motor circuit alters the executed plans by correcting the discrepancy. The specific motor function of the putamen is considered to involve the adjustment of the amplitude and the velocity of simple motor programs (i.e., movements of one muscle group or joint) arising from the motor cortex (Georgopoulos, Delong, & Crutcher, 1983). The development of orofacial dyskinesia may result from the disruption of the ventromedial putamen insofar as it is this aspect of the putamen which is associated with the control of facial musculature (Alexander et al., 1986).

The factors leading to possible striatal pathology in schizophrenic patients with AIMs have not been determined. Although AIMs are traditionally considered to be primarily an iatrogenic effect of neuroleptics, there is a growing view that AIMs may arise from a basal ganglia pathology intrinsic to schizophrenia (Awouters, Niemegeer, & Jannsen, 1990). On a phenomenological level, an endogenous view is supported by reports of AIMs prior to the neuroleptic era (Crow, 1989) coupled with the finding that non-medicated schizophrenic patients often develop AIMs (Owens, et al., 1982).

Cadet et al. (1987) have offered an explanation of AIMs schizophrenia in which the relationship between neuroleptic effects and basal ganglia pathology is considered. A primary assumption of their
proposal is that excess dopamine activity results in an increase of neurotoxic free radicals. Free radicals may be defined as reactive compounds, possessing at least one unpaired electron, which are produced as by-products of biochemical reactions (Cadet et al., 1987). In the case of catecholamine metabolism, free radicals are produced by the reactions catalyzed by monoamine oxidase (Tipton, 1968).

A neurotoxicity view of schizophrenia is consistent with other proposals pertaining to catecholamine toxicity involvement in Parkinson’s disease (Barbeau, 1984). In terms of the pathology leading to AIMs, the supersensitivity of postsynaptic striatal dopamine receptors, occurring in response to neuroleptic blockade, is considered to result in cell loss subsequent to the culmination of neurotoxic free radicals. Moreover, reduced striatal GABA turnover that has been associated with AIMs is considered to occur secondarily to the loss of GABA neurons innervated by dopamine neurons. In this proposal, susceptibility to AIMs, in both medicated and never-medicated schizophrenic patients, occurs in response to a low level of endogenous protective enzymes which nullify the neurotoxic effects of catecholamine-produced free radicals.

The limitation of Cadet et al.’s (1987) model of AIMs is that the underlying assumption of free radical toxicity has not been adequately researched in schizophrenia or AIMs. For example, the proposed association between the accumulation of free radicals and cell loss may occur secondarily to other factors underlying both increased
catecholamine activity and the presence of degenerative processes. On the basis of these limitations, a free radical hypothesis of AIMs must be considered to be mainly speculative.

A weakness, in general, of AIMs research is that while AIMs is included as a feature of Type II schizophrenia (Crow, 1989), AIMs is traditionally viewed as primarily a result of neuroleptic drugs. It is perhaps inconsistent to label AIMs as a negative symptom, while traditional explanations of AIMs continue to emphasize the role of neuroleptics in their development.

The proposal that basal ganglia pathology in AIMs occurs, to a certain extent, independently of neuroleptic treatment provides a theoretical framework for the inclusion of AIMs within the phenomenology of schizophrenia. Although AIMs are not a primary feature of schizophrenia, their presence may be associated with a specific course of illness (see Chapter 5). Regardless of whether neuroleptics are the cause of AIMs in schizophrenia, the presence of AIMs-related basal ganglia pathology may alter specific areas of cognitive functioning (see Chapter 3). However, the specific cognitive and psychiatric features which differentiate schizophrenic patients with and without AIMs have not been adequately investigated.
Chapter 3

Functional Considerations

In Chapter 3, an overview of frontal lobe function is presented in the context of the neuropsychological tests which are sensitive to brain damage localized to the prefrontal cortex. The review of frontal lobe function provides background information pertinent to the discussion of the possible involvement of frontal lobe impairment in schizophrenia. In the latter part of Chapter 3, frontal lobe function is considered in terms of a series of corticostriatal circuits (Alexander et al., 1986), which are considered to have an important role in mediating complex cognitive processes (Cummings, 1993). As discussed, the basal ganglia disruption of these circuits in AIMs schizophrenia provides the rationale for predicting that AIMs in schizophrenia are associated with greater cognitive deficits, especially in the area of frontal lobe functioning.

Frontal Lobe Function

General Description. The views concerning the function of the frontal lobe have varied considerably since the turn of this century. The early belief that frontal lobe processes are integral to many intellectual functions fell in disfavor as it became apparent that patients with frontal lobe damage are not impaired on tests of intellectual functioning (Hebb, 1945; Teuber, 1964). Subsequently, neuropsychological tests have been devised and validated on subjects with frontal lobe pathology. Through neuropsychological examination, it became evident that the frontal lobe is important to a broad range of
perceptual, memory, and complex cognitive functions (Stuss & Benson, 1984). The most overt effects of frontal lobe deficits, however, are personality changes and the deterioration of adaptive behaviour.

The cognitive and behavioural aspects of frontal lobe functions have been well documented (Milner, 1964; Ramier & Hecaen, 1970; Stuss & Benson, 1984; Taylor, 1979). Bilateral damage of the prefrontal cortex results in a disintegration of voluntary behaviour, and with more severe lesions there may be a total non-involvement in the environment resulting in akinesia, mutism, and abulia (Golden, 1981). Less severe damage may cause difficulties in performing complex activities which require successive movements (Fuster, 1981). Generally, pathology of the prefrontal cortex results in a reduction in spontaneous movements and in perseveration of movements (in which previous patterns of movements occur in the context of changing environmental demands). Moreover, perseveration of movements may continue even though affected individuals recognize the inappropriateness of their actions.

The impact of frontal lobe deficits on personality has been traditionally categorized in terms of orbitomedial and dorsolateral deficits (Hecaen & Albert, 1978). Damage to the orbitomedial prefrontal cortex is characterized by a reduction of inhibitions and poor impulse control. Behavioural changes are typically marked by increased promiscuity, a greater use of profanity, and an escalation of irritability. Mood changes are common and are marked by episodes of euphoria which are frequently accompanied by grandiosity and paranoia.
In contrast, personality changes resulting from damage to the dorsolateral prefrontal cortex results in an apathetic syndrome. The mood of an affected individual is typically marked by a blunted affect and a general indifference to the environment. A lack of initiative may lead to a decrease in spontaneous behaviour to the point that an affected individual displays symptoms of a major depression.

The various facets of frontal lobe function may be organized in terms of basic features. Stuss and Benson (1984) have proposed a set of categories which describes the behavioural components of frontal lobe deficits. Their categories are organized in terms of cognitive impairment in the areas of 1) monitoring and correcting behaviour, 2) establishing and altering cognitive operations, 3) associating thought with action, 4) maintaining a cognitive operation in the context of distracting stimuli, and 5) processing sequential information. It is important to note that an error on a neuropsychological test may arise from the combined effects of one or more of these areas of impairment. The categories of Stuss and Benson (1984) are discussed in order to provide a general introduction to the neuropsychological deficits of patients with frontal lobe damage.

The inability to monitor errors of behaviour and use error information to modify responses is a primary feature of frontal lobe damage. The typical manifestation of this defect is the generation of behaviour in which there is an inability to alter responses which have become inappropriate due to changing environmental demands. Also,
inflexible behaviour may be produced by the second category; an inability to establish or alter cognitive operations. On verbal fluency tests, which require the naming of words belonging to successive orthographic categories, inflexibility may result in a diminished ability to switch between categories. Inflexibility may also impair performance on tests which require the advanced planning of solutions. For example, on the Porteus Maze Test (Porteus, 1959), which involves the planning of routes to a target area, cognitive inflexibility may impair the ability of frontal lobe patients to consider alternative solutions needed to solve the maze.

The dissociation of thought from action, the third category, is manifested by an inability to correctly perform a task even though the rules of the task are understood. On card sorting tasks, which require the sorting of cards according to changing sets of rules, an individual with a frontal lobe deficit may be able to recite the sorting rules while unable to correctly sort the cards (Goldberg & Weinberger, 1991). Thus, frontal lobe patients are often less able to use knowledge effectively to modify their responses to test items.

Frontal lobe patients may also have difficulty maintaining a cognitive operation in the presence of distracting information. Fuster (1989), for example, has proposed that the distractability associated with frontal lobe damage results in memory deficits caused by a compromised ability to attend to information. Thus, information that does not become meaningful is less likely to be preserved in memory.
The last category, the processing of sequential information, involves the organization of information in terms of the temporal order of events. Temporal organization involves remembering the temporal order of events and utilizing temporal information to devise plans of action. Milner (1982), for example, has demonstrated that frontal lobe patients have difficulty with retaining temporal order information as measured by recency discrimination tasks. Impairment in the use of temporal information, the second aspect of processing sequential information, may cause deficits on tasks which require the subject to devise strategies to order test items according to specified rules of the test (Milner & Petrides, 1984).

A recent influence on accounts of frontal lobe function is the mapping of corticostriatal circuits (Alexander et al., 1986; Delong & Georgopoulos, 1981) which are illustrated in Figure 2. Specifically, Alexander et al. (1986) have provided anatomical and histochemical evidence of five circuits, each defined by the cortical area encompassed in the circuit. As illustrated, the circuits arise from the dorsolateral frontal cortex, the orbitofrontal cortex, the anterior cingulate cortex, the supplemental motor cortex, and the oculomotor frontal cortex. For all of the circuits cortical innervation originates from multiple areas which are interconnected (Alexander et al., 1986). Distinct areas of the caudate nucleus, putamen and nucleus accumbens are the primary recipients of cortical input. The neostriatum and the ventral striatum innervate the globus pallidus and the substantia nigra, both of which
Figure 2. The arrangement of the frontal-subcortical circuits described by Alexander et al. (1986)
Figure 2 (continued). The arrangement of the frontal-subcortical circuits described by Alexander et al. (1986)
project to the thalamus. Each circuit is closed by thalamocortical connections to a specific area of the cortex from which the cortical innervation originated.

Cummings (1993) demonstrated that the cognitive and behavioural (i.e., changes in mood and personality) syndromes associated with lesions limited to the prefrontal cortex are reproduced by lesions of the caudate nucleus. The disruption of the dorsolateral circuit produces deficits in verbal fluency, set shifting, memory retrieval, problem solving, and motor programming. The dorsolateral circuit is particularly important when the neuropsychology of AIMs schizophrenia is considered. Specifically, the greater cognitive impairment of schizophrenic patients with AIMs (see Chapter 5) suggests the involvement of the dorsolateral circuit on the basis that it is the only frontostriatal circuit which is associated with cognitive functions (Cummings, 1993).

Support for Cummings' (1993) proposal was derived from studies which examined the cognitive and/or behavioural consequences of caudate nucleus pathology. Mendez, Adams, and Lewandowski (1989), for example, have determined that caudate nucleus pathology produces behavioural and cognitive changes which closely resemble deficits seen in frontal lobe-lesioned patients. It was further found that the area of caudate nucleus damage determines the specific features of the behavioural change. Patients with dorsolateral caudate nucleus damage were apathetic and disinterested; the same deficits which follow damage limited to the dorsolateral prefrontal cortex. The disinhibited and inappropriate
behaviour of patients with medial caudate nucleus damage resembled deficits caused by damage limited to the medial prefrontal cortex. Further, Cummings (1993) has reported that Huntington’s disease patients with dorsolateral caudate nucleus damage have deficits on tests of verbal fluency, card sorting, and recall of recently learned information. As noted by Cummings (1993), these neuropsychological deficits resemble the deficits produced by dorsolateral prefrontal impairment.

Studies that have investigated changes in personality following focal caudate nucleus lesions provide further evidence that the disruption of the frontostriatal circuits produces impairment that closely resembles frontal lobe syndromes. Specifically, it has been reported that lesions confined to the dorsolateral caudate nucleus resulted in an apathetic state in which spontaneous speech was inhibited (Fernandez, Micheli, Asconape, & Paradiso, 1985). Further, Richfield, Twyman, and Berent (1987) have reported that bilateral caudate nucleus lesions, which involved the orbitofrontal circuit, produced behaviour which was impulsive and inappropriate.

The circuit-specific function proposed by Cummings (1993) has specific implications for the neuropsychology of AIMs and non AIMs schizophrenia. Robbins (1990) has hypothesized that the diverse expression of psychopathology in schizophrenia reflects different patterns of frontostriatal circuit damage. Specifically, Robbins (1990) has suggested that deficits in frontal lobe functioning in schizophrenia
arise from the interaction between the dorsolateral prefrontal cortex and its subcortical inputs. Further, symptom diversity in schizophrenia is explained by Robbins (1990) by variation in terms of the sites of damage within each circuit. In terms of AIMs schizophrenia, the consideration of the cognitive/behavioural syndromes proposed by Cummings (1993) in the context of AIMs-related basal ganglia pathology provides the basis for expecting that schizophrenic patients with and without AIMs may be differentiated in terms of cognitive and behavioural features. Specifically, Brown et al. (1992) have proposed that the cognitive features of AIMs schizophrenia (see Chapter 5) are caused by the disruption of cortical functions, and that basal ganglia pathology is one pathological mechanism by which cortical function is disrupted.
Introduction

In Chapter 4, the neuropsychology of schizophrenia is reviewed with the purpose of presenting the features of cerebral dysfunction that are frequently implicated in schizophrenia. A second purpose of the review is to provide a reference point for considering the neuropsychological deficits which may differentiate AIMs and non-AIMs schizophrenia. A Critique Section is presented in order to discuss the methodological and conceptual limitations of the neuropsychological studies that have investigated schizophrenia. Following the critique of neuropsychological research, the cerebral blood flow and positron emission tomographic studies that have investigated schizophrenia are reviewed. The chapter is concluded with a discussion of the neuropsychological impairment of schizophrenic patients in terms of cortical-subcortical circuits.

Early psychological conceptualization of schizophrenia stressed the importance of differentiating schizophrenia (as an example of a functional psychosis) from organic conditions (Golden, 1981). The lack of success, however, in distinguishing schizophrenic and organic patients (Goldstein, 1977; Watson, Thomas, Andersen, & Felling, 1968) in conjunction with neurophysiological and anatomical neuroimaging evidence of brain abnormalities in schizophrenia (Buchsbaum & Haier, 1987) led to the reappraisal of the view that schizophrenia and organic conditions represent mutually exclusive categories (Goldstein, 1986). The current conceptualization of schizophrenia is that cognitive impairment in
schizophrenia is a result of physiological and structural brain abnormalities, although such factors as poor motivation, hospitalization, neuroleptic medication, and psychotic ideation may also alter test performance (Goldberg et al., 1987).

Neuropsychological Investigations

Focal Versus Generalized Deficits. In an attempt to identify the brain anomalies that underlie schizophrenia, numerous neuropsychological studies have investigated deficits involving specific areas of functioning. Table 1 provides a summary of the neuropsychological studies which are reviewed. Kolb and Whishaw (1983) compared 30 medicated schizophrenic patients and 30 non-psychiatric control subjects on tests sensitive to bilateral frontal lobe, temporal lobe, and parietal lobe functions. It was determined that schizophrenic patients were impaired on tests of bilateral frontal lobe (e.g., Wisconsin Card Sorting Test, Chicago Word Fluency Test, and Design Fluency Test) and temporal lobe (e.g., Paired Associate Learning Subtest of the Wechsler Memory Scale, Dichotic Words Test, and Geometric Figures Test) functions. In contrast, patients were not impaired on tests sensitive to parietal lobe function (e.g., copy of Rey-Osterreith Complex Figure and Mooney Closure Test). A drawback of Kolb and Whishaw's (1983) study is the absence of information concerning the psychiatric characteristics of the schizophrenic patients. Since an attempt was made to test all patients within 24 hours of being placed on neuroleptics, it may be reasonable to expect that the performance of some subjects was
Table 1. Summary of Selected Neuropsychological Studies Investigating Schizophrenia.

<table>
<thead>
<tr>
<th>Study</th>
<th>Subject characteristics</th>
<th>Tests/Results</th>
<th>Interpretation/Comment</th>
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<tbody>
<tr>
<td>Kolb &amp; Whishaw (1983)</td>
<td>30 schizophrenic patients -in-patients</td>
<td>Schizophrenics below Controls on WAIS, IQ, Immediate recall, delayed recall, Rey Figure (Recall), Geometric Figures (Immediate &amp; Delay), Dichotic Words (Left &amp; Right Ears), WCST, Chicago Word Fluency, Semmes Body Placing, and Design Fluency, FAS Verbal Fluency, WCST</td>
<td>Schizophrenics reported to have bilateral frontal and temporal lobes impairment. A subgroups of five patients reported not to be impaired on the battery. The lower intellectual ability of schizophrenic patients may have contributed to the differences between control and schizophrenic groups.</td>
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<td></td>
<td>-all patients medicated -mean age 30.1 years</td>
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<td></td>
<td>30 non-psychiatric controls -mean age 28.5 years</td>
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<tr>
<td>Moses, 1983</td>
<td>81 schizophrenic patients 19 schizoaffective patients -combined mean age 35.13</td>
<td>On Luria-Nebraska Battery, schizophrenic normal &amp; borderline impairment groups differed on Motor, Rhythm, Tactile, Visual Receptive Speech, Memory, Intellect, Pathognomonic, right and left hemisphere scales. Borderline and abnormal groups differed on Receptive Speech, Expressive Speech, Writing and Reading scales. Normal &amp; Abnormal groups differed on all scales.</td>
<td>Normal and abnormal patients differed on all scales while normal and borderline patients differed on frontotemporal, perceptual, and sensorimotor scales. The inclusion of schizoaffective group limits the diagnostic specificity of results.</td>
</tr>
<tr>
<td>Gruzelier et al. (1988)</td>
<td>36 schizophrenic patients -in-patients -12 drug free 21 affective patients -9 manic, 12 depression 29 non-psychiatric controls</td>
<td>Schizophrenic more impaired more than affective patients on Recurring Digit Span Test, but not on Recurring Block Span. Affective patients impaired on Spatial Conditional Associate Learning. Schizophrenic patients less fluent than controls on FAS and Semantic Fluency.</td>
<td>Test results of schizophrenic patients reported to indicate a non-generalized deficit involving temporal/hippocanal frontal lobe functions. The specificity and sensitivity of tests calls into question interpretation of test performance.</td>
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<tr>
<td>Study</td>
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<td>Tests/Results</td>
<td>Interpretation</td>
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<tr>
<td>Braff et al. (1991)</td>
<td>40 schizophrenic patients -chronic out-patients -all patients medicated -mean age of 29.7 years 40 nonpsychiatric controls</td>
<td>Discriminant analysis of Halstead-Reitan, WCST, and Story Learning Test distinguished schizophrenic and control subjects. Story learning, Category Test, Tactile Performance, Grooved Pegboard, had highest structured correlations.</td>
<td>Schizophrenics reported to have deficits in complex conceptual reasoning, psychomotor speed, new and incidental learning, Subgroup of patients, with negative symptoms, impaired on WCST.</td>
</tr>
<tr>
<td>Goldstein and Halperin (1977)</td>
<td>140 schizophrenic patient -mean age 38.3 years</td>
<td>Discriminant analysis of Halstead-Reitan &amp; WAIS differentiated long and short term patients on basis of a broad range of tests. Paranoid &amp; nonparanoid and normal &amp; abnormal groups only marginally differentiated.</td>
<td>Level of cognitive impairment altered by length of institutionalization rather than paranoia or neurological abnormalities. A generalized pattern of deficits was reported.</td>
</tr>
<tr>
<td>Flor-Henry &amp; Yeudall (1979)</td>
<td>54 schizophrenic patients -mean age 36 years 60 affective disorder patients -mean age 38 years</td>
<td>Tests which differed between schizophrenic and manic patients: Memory for Design, Tactile Form Board, Seashore Rhythm, Verbal Learning, Oral Word Fluency.</td>
<td>Schizophrenic patients reported to be impaired on frontotemporal tests while affective patients impaired on right hemisphere tests.</td>
</tr>
<tr>
<td>Taylor, Greenspan &amp; Abrams (1979)</td>
<td>22 schizophrenic patients -mean age 37.1 years 105 affective patients -mean age 40.6 years</td>
<td>On Modified Halstead-Wepman Aphasia Screening Test, schizophrenic patients made more than 3 times as many errors as affective patients on anemia, neologisms, paraphasia and letter/number agnosia.</td>
<td>Schizophrenic patients reported to have greater dominant temporal/parietal impairment than affective patients. A more extensive battery may have indicated bilateral impairment.</td>
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<tr>
<td>Study</td>
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<td>Taylor, Redfield &amp; Abrams (1981)</td>
<td>17 schizophrenic patients - mean age 37.8 years</td>
<td>Schizophrenic patients below affective patients on Verbal IQ, Right Handed Pegboard, Sentence Repetition, &amp; Peabody Vocabulary, (Dominant Hemisphere), but not on Performance IQ, Left Handed Pegboard, Benton Visual Retention, Raven’s Matrices &amp; Hooper Visual Organization (Non-dominant hemisphere).</td>
<td>Unlike affective patients, schizophrenic patients reported to have bilateral impairment which resembled impairment of patients of with coarse brain disorder.</td>
</tr>
<tr>
<td>Silverstein et al. (1991)</td>
<td>59 schizophrenic/schizo-affective patients - mean age 30.8 years</td>
<td>Discriminant analysis of Halstead-Reitan &amp; WAIS found positive thought disorder associated with Speech Sounds Perception Test. Negative Thought disorder associated with Verbal and Performance IQ</td>
<td>Positive thought disorder considered to reflect left hemisphere deficit. Both left and right hemisphere deficits related to negative disorder.</td>
</tr>
<tr>
<td>Taylor &amp; Abrams (1984)</td>
<td>62 schizophrenic patients</td>
<td>On Halstead-Wepman Aphasia test and Luria Nebraska Battery, schizophrenics impaired on frontotemporal scale, but not on parietal/occipital scales.</td>
<td>Schizophrenic patients reported to have dominant frontotemporal impairment. 75% of schizophrenic patients displayed bilateral hemispheric impairment.</td>
</tr>
<tr>
<td>Sengel and Lovallo (1983)</td>
<td>2° schizophrenic patients - mean age 29.8 years</td>
<td>On four word lists, control and depressive subjects benefited from cues at recall more so than schizophrenic patients.</td>
<td>The use of categorical cues overcame the effects of delay for normal controls and depressives more so than for schizophrenics</td>
</tr>
<tr>
<td>Study</td>
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<tr>
<td>Goldberg &amp; Weinberger (1988)</td>
<td>31 schizophrenic patients</td>
<td>Analysis of Selective Reminding Test not published.</td>
<td>Schizophrenic patients reported to be able to learn new information, but total recall below control subjects.</td>
</tr>
<tr>
<td>Landre et al. (1992)</td>
<td>10 schizophrenic patients</td>
<td>On Boston Naming Test, Token Test Spontaneous Speech, Raven's Coloured Matrices schizophrenic and Aphasic pts. performed at a comparable level. Aphasic patients older than schizophrenic pts.</td>
<td>Schizophrenic and aphasic patients did not differ in naming auditory comprehension, repetition, spontaneous speech and intelligence.</td>
</tr>
<tr>
<td>Liddle (1987 b)</td>
<td>47 schizophrenic patients</td>
<td>Disorganization group correlated with Orientation, Cancelling e's, Sentence Repetition, and word Learning. Psychomotor group correlated with Famous Personality Test, Oxford Naming Test, Similarities, and Object Classification.</td>
<td>Disorganization and Psychomotor groups associated with two different sites of frontal lobe deficits.</td>
</tr>
<tr>
<td>Goldberg et al. (1987)</td>
<td>44 schizophrenic patients</td>
<td>WCST scores of schizophrenic patients remained impaired while explicit instructions were provided. WCST performance only improved under card-by-card instruction condition</td>
<td>The apparent inability of schizophrenic patients to improve on WCST when detailed instructions provided considered evidence of frontal lobe deficit. Psychometric properties of WCST altered by paradigm.</td>
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</table>
detrimentally altered by psychotic symptoms not yet ameliorated by neuroleptics.

Moses (1983) examined the neuropsychological profiles of schizophrenic patients with different levels of impairment. In their study, 81 chronic schizophrenic patients and 19 schizoaffective patients were tested on the Luria-Nebraska Neuropsychological Battery. The schizoaffective patients were grouped with the schizophrenic patients to make a total sample size of 100 patients. On the basis of test performance, patients were classified as normal, borderline or abnormal. While normal and abnormal groups differed on all scales, the differences between normal and borderline groups were evident on tests sensitive to frontotemporal functions as well as sensorimotor and perceptual abilities. The pattern of impairment indicated both left and right hemisphere dysfunction. The inclusion, however, of patients with schizoaffective disorder in the schizophrenic patient group limits the extent to which these results are representative of schizophrenia. As is discussed later in this chapter, schizoaffective disorder has been associated with the impairment of the right hemisphere (Flor-Henry & Yeudall, 1979). Therefore, it is not clear to what degree the right hemisphere impairment reported by Moses (1983) reflects the presence of schizoaffective patients in the schizophrenia sample.

Gruzelier, Seymour, Wilson, Jolley and Hirsch (1988) investigated the performance of 36 schizophrenic patients, 21 affective patients, and 29 control subjects on tests of frontal/hippocampal (Spatial and Nonspatial
Conditional Learning Tests) and temporal/hippocampal functions (Recurring Digit- and Block Span Tests). The pattern of performance on the test battery was interpreted as indicating a non-generalized pattern of deficits in approximately 80 percent of the schizophrenic patients. Further, schizophrenic patients were considered to be characterized by impairment on tests of left hippocampal function while on tests of frontal lobe function, only schizophrenic patients with remitting illness were impaired. Affective disorder patients were characterized by bilateral impairment. A difficulty with this study pertains to the validity of the experimental neuropsychological tests employed. That is, the specificity and sensitivity of the various tests (e.g., Memory for Recurring Digit-Span Test) may be questioned on the basis that they have not been subjected to the same scrutiny as tests from standard batteries (e.g., Halstead-Reitan). This criticism echoes Flor-Henry's (1983) view that standardized and validated neuropsychological tests provide the most sensitive method of localizing cerebral dysfunction. Thus, Gruzelier et al. (1988) may not have been justified to conclude that a left hippocampal deficit is present in schizophrenia in the absence of other standardized tests of temporal/hippocampal function.

A generalized pattern of neuropsychological impairment was reported by Braff, Heaton, Kuck, Cullum, Moranville, Grant, and Zisook (1991). In their study, 40 medicated schizophrenic out-patients were compared to 40 non-psychiatric control subjects on the extended Halstead-Reitan Neuropsychological Battery, Brief Psychiatric Rating Scale, and Scales
for Assessment of Positive and Negative Symptoms. Discriminant analysis indicated that schizophrenic patients demonstrated deficits on tests of complex conceptual reasoning, sensory-perceptual abilities, new learning, and incidental memory. The overall finding that schizophrenic patients performed at the same level as control subjects on the Wisconsin Card Sorting Test (i.e., perseverative response) is at odds with previous studies reporting the presence of card sorting deficits in schizophrenia (e.g., Berman et al., 1988; Liddle & Morris, 1991; Weinberger et al., 1986). Braff et al. (1991) did report, however, that a subgroup of patients, with prominent negative symptoms, tended to display impaired card sorting performance as well as impairment on other tests of the battery. The absence of a psychiatric control group (e.g., affective disorder) makes it impossible to assess whether these results are specific to schizophrenia.

Goldstein and Halperin (1977) also reported generalized deficits in the 140 schizophrenic patients that they tested on the Halstead-Reitan Neuropsychological Battery and the Wechsler Adult Intelligence Scale. In addition to finding a generalized deficit, which was considered to be suggestive of diffuse cortical damage, length of hospitalization was determined to have had a greater impact on test performance than psychotic ideation (paranoia) and neurological abnormalities. This result was interpreted as indicating that long-term institutionalization acts to dull cognitive operations and, thereby, contributes to poor test performance. However, it is possible that the cognitive impairment of
long-term patients reflects a greater degree of negative psychopathology which interferes with independent living, rather than the adverse influences of institutionalization.

Hemispheric Differences. The hypothesis that schizophrenic patients are impaired in left hemispheric functioning arose from Flor-Henry's (1969) report that "schizophrenic-like" psychotic features occur in patients with left hemisphere epilepsy. A number of neuropsychological studies have identified a left hemispheric dysfunction in schizophrenia (Flor-Henry & Yeudall, 1979; Silverstein, Marengo, & Fogg, 1991; Taylor, Greenspan, & Abrams, 1979). In a study employing 54 schizophrenic and 60 affective disorder patients, Flor-Henry and Yeudall (1979) determined that while both schizophrenic and affective patients displayed a right hemisphere dysfunction, only schizophrenic patients displayed a left frontotemporal impairment (e.g., Oral Word Fluency, Trail Making B, and Seashore Rhythms Tests). The placement of patients with schizophreniform disorder in the schizophrenia group limits the generalizability of their results to schizophrenia alone.

Taylor, Greenspan, and Abrams (1979) also reported differences in lateralized hemispheric function in their investigation of 22 schizophrenic and 105 affective patients. Specifically, on the Halstead-Wepman Aphasia Screening Test, schizophrenic patients made more dominant temporal/temporoparietal errors than did affective patients. More recently, Silverstein, Marengo, and Fogg (1991) reported that left hemisphere dysfunction is related to positive symptoms while bilateral
impairment is related to negative symptoms. Computed tomography evidence has confirmed that impaired neuropsychological performance (Luria-Nebraska Battery) is associated with reduced left frontal lobe density (Golden, Moses, Zelazowski, Braber, Zatz, & Horvath 1980).

A major theory of left hemispheric dysfunction in schizophrenia is based on Gur's (1978) hypothesis that schizophrenic patients over activate the left hemisphere. Gur's (1978) proposal was generally based on evidence that 1) schizophrenic patients are impaired in the right hemifield on tachistoscopic stimulation tasks and 2) schizophrenic patients have a high frequency of rightward eye movements, presumably suggesting a left hemisphere over activation. The dysfunction of left hemispheric functioning in schizophrenia is also generally supported by dichotic listening (Gruzelier & Hammond, 1979), evoked potentials (Connolly, Gruzelier, & Manchanda et al., 1983), electroencephalography (Abrams & Taylor, 1979) and regional cerebral blood flow (Gur et al., 1983) studies.

Not all neuropsychological studies have found a left hemisphere dysfunction in schizophrenia. Taylor and Abrams (1984), using the Luria-Nebraska Battery and visual half-field identification of letters and shapes, found that 75% of patients had bilateral impairment. Patients with more severe deficits were found to have dominant frontotemporal impairment. Further, Kolb and Whishaw (1983) reported that schizophrenia is characterized by bilateral neuropsychological impairment. Nasrallah (1987) suggests that inconsistent findings, in
studies investigating lateralization differences, may be attributed to the employment of tests which are not equally sensitive to left and right hemispheric differences. Further, Nasrallah (1986) proposes that bilateral impairment would be evident in most studies reporting lateralization differences if more extensive test batteries were employed.

Memory. The investigation of memory ability has shown that schizophrenic patients are impaired in recall memory (Koh et al., 1978), but not recognition memory (Bauman & Kolisnyk, 1976). On the Wechsler Memory Scale, schizophrenic patients have been found to be impaired on immediate recall, delayed recall and memory quotient (Kolb & Whishaw, 1983). To investigate the effects of cuing on immediate and delayed recall, Sengel and Lovallo (1983) presented schizophrenic patients, depressive patients and control subjects with categorical word lists which were either cued or not cued at recall. The results indicated that cuing overcame the effects of delay more so for depressive and control subjects than for schizophrenic patients, although the recall of schizophrenic patients was also enhanced by cues. Because Sengell and Lovallo (1983) only manipulated the retrieval context of recall, it was not possible in this study to determine the degree that memory impairment in schizophrenia arises from deficits in the encoding of information. Goldberg and Weinberger (1988) examined recall deficits in chronic schizophrenic patients through the administration of the Selective Reminding Test. While schizophrenic
patients were able to learn new material, their absolute recall level was below non-psychiatric control subjects. Unfortunately, neither the statistical analysis nor the data base was reported by Goldberg and Weinberger (1988). It is, therefore, not possible to subject their findings to critical analysis. Nevertheless, the finding that only recall memory was impaired agrees with the majority of studies reporting that recognition memory is superior to recall memory in schizophrenia.

Language Disturbances. The presence of disturbed speech in schizophrenia has been investigated in a number of studies from the point of view that the speech of schizophrenic patients is characterized by aphasic-like errors. McGrath (1991) has proposed that the aphasic-like speech of schizophrenic patients is related to an impairment involving executive planning and editing. Recently, Landre, Taylor, and Kerns (1992) determined that the language impairment of 10 schizophrenic patients and 10 patients with fluent aphasia did not differ in terms of word naming, auditory comprehension, repetition, and spontaneous speech. Moreover, only negative symptoms were associated with language abnormalities in schizophrenic patients. These results are in agreement with previous studies which have found similarities between schizophrenic and aphasic patients (Faber, Abrams, Taylor, Kasprisin, Morris, & Weiss, 1983; Portnoff, 1982). Other studies, however, have not reported this similarity (Rausch, Prescott, & Dewolfe, 1980). This inconsistency may be due to imprecise comparisons in which there was a lack of distinction made between schizophrenic patients with and without
disturbed speech (Landre et al., 1992).

**Frontal Lobe Impairment.** In an effort to examine frontal lobe impairment in schizophrenia, Liddle (1987a & b) examined the neuropsychological performance of schizophrenic patients who presented with different symptom clusters. A second part of their investigation involved the use of regression statistical procedures to determine which neuropsychological tests correlated with the different clusters of symptoms. The advantage of this method over comparisons involving Type I and Type II groups, is that it eliminates the problem of quantifying the results of schizophrenic patients with mixed symptomatology. Based on this analysis, Liddle (1987a) reported that schizophrenic patients with persistent symptoms formed three categories characterized by 1) flat affect and a lack of spontaneous movements (psychomotor poverty group), 2) disturbance of form of thought and inappropriate affect (disorganization group) and 3) delusions and hallucinations (reality distortion group).

In further analysis, Liddle (1987b) provided evidence that these groups were associated with a different pattern of psychiatric and neuropsychological functioning. Based primarily on psychiatric symptoms, Liddle (1987b) proposed that the characteristics of the disorganization and the psychomotor poverty groups resulted from frontal lobe deficits. Specifically, the disorganization and psychomotor poverty groups were associated with the dorsolateral and mediobasal prefrontal cortex respectively while the reality distortion group was linked with temporal
lobe pathology. More recently, Liddle and Morris (1991) have focused their investigation on the frontal lobe characteristics of the disorganization and psychomotor poverty groups. The two groups were differentiated on a test battery which was composed largely of frontal lobe tests. A common element of the performance of the disorganization group was a poor ability to inhibit perseverative responses on the Modified Card Sorting Test (Nelson, 1976) and the FAS Verbal Fluency Test (Benton & Hamsher, 1976). In contrast, the psychomotor group was characterized by a slowness of cognitive activity, especially on the verbal fluency test.

A number of studies have mainly used the Wisconsin Card Sorting Test to investigate frontal lobe impairment in schizophrenia (e.g., Goldberg et al., 1987). In some studies, modified paradigms have been developed to determine whether poor performance is influenced by altering the instructions (Goldberg et al., 1987) and/or the reward systems (Goldman, Axelrod, & Tompkins, 1992). The rationale for using altered procedures is that poor card sorting performance may reflect poor motivation of schizophrenic patients. That is, schizophrenic patients may be able to do the task, but do poorly because of a lack interest in the task. As discussed in Experiment 2, these studies indicate that under appropriate circumstances, poor card sorting performance is reversible.

Summary.

Both generalized (e.g., Braff et al., 1991; Goldstein & Halperin,
neuropsychological deficits have been associated with schizophrenia. The
generalized deficits reported by Braff et al. (1991) involve conceptual
reasoning, incidental memory, psychomotor speed, and sensory-perceptual
abilities. Goldstein and Halperin (1977), who tested a relatively large
sample of 140 schizophrenic patients, reported that the level of
generalized cognitive loss distinguished long- and short-term
hospitalized patients.

In neuropsychological studies finding focal impairment, some studies
have reported left hemispheric deficits (e.g., Flor-Henry & Yeudall
1979; Silverstein et al., 1991; Taylor et al., 1979). Evidence for a
left hemisphere dysfunction in schizophrenia is derived from dichotic
listening (Gruzelier & Hammond, 1979), evoked potentials (Connolly et
al., 1983), electroencephalography (Abrams & Taylor, 1979) and regional
cerebral blood flow (Gur et al., 1983) studies.

Other studies investigating schizophrenia have found differences
along the anterior-posterior axis (e.g., Berman et al., 1988; Weinberger
et al., 1986). Specifically, there is increasing support for a bilateral
fronto-temporal pattern of neuropsychological deficits in schizophrenia
(Kolb & Whishaw, 1983; Moses, 1983; Taylor & Abrams, 1984). Kolb &
Whishaw (1983), using a battery reportedly sensitive to bilateral
cerebral impairment, determined that schizophrenic patients are impaired
on tests sensitive to bilateral frontal and temporal functions, but
perform in the normal range on tests of parietal lobe function. Taylor
and Abrams (1984) determined that schizophrenic patients are impaired in terms of bilateral fronto-temporal functions as measured by the Halstead-Reitan and the Luria-Nebraska Batteries. In recent years, support for the view that schizophrenia is associated with frontal lobe impairment has been derived from a number of studies (Goldberg et al., 1987; Liddle & Morris, 1991; Goldman et al., 1992). Other focal deficits in schizophrenia include lower performance on recall memory as compared to recognition memory (Goldberg & Weinberger, 1988; Sengell & Lovallo, 1983) as well as poor performance on language tests which measure naming ability, auditory comprehension, repetition, and spontaneous speech (Landre et al., 1992).

Critique of Schizophrenia Research

The conceptualization of schizophrenia as a left hemisphere disorder is based on both biological (Abrams & Taylor, 1979; Gur et al., 1983; Gruzelier & Hammond, 1979) and neuropsychological (Flor Henry & Yeudall 1979; Silverstein et al., 1991; Taylor et al., 1979) research. Gur's (1978) hypothesis that schizophrenic patients over activate the dysfunctional left hemisphere has been questioned by a number of researchers (Taylor & Abrams, 1984; Goldberg & Weinberger, 1986). For example, Gur's (1978) results (see preceding section) may actually indicate bilateral dysfunction insofar as schizophrenic patients did poorly on tasks which presented information to both hemifields. Additionally, the interpretation of left hemispheric evidence derived from dichotic listening studies (e.g., Nachshon, 1980) and galvanic skin
response studies (e.g., Gruzelier, 1979) is considered controversial (Goldstein, 1986), and may actually indicate the presence of bilateral dysfunction in schizophrenia (Goldberg & Weinberger, 1986; Taylor & Abrams, 1984).

The neuropsychological evidence supporting a left hemispheric dysfunction in schizophrenia must be considered in regards to the test battery used to assess patients. Specifically, in some studies reporting left hemisphere dysfunction, schizophrenic patients were assessed on a limited number of tests (e.g., Taylor et al., 1979). As previously mentioned, Nasrallah (1986), proposed that bilateral impairment in schizophrenic patients only becomes evident with the employment of extensive test batteries which are equally sensitive to left and right hemispheric lesions. In studies employing the Halstead-Reitan or Luria-Nebraska batteries, bilateral impairment has been reported (Moses, 1983; Taylor & Abrams, 1984).

The absence of consistent neuropsychological and biological evidence of a left hemispheric impairment, provides the basis for questioning the degree to which a dysfunction of the left hemisphere is pertinent to the psychopathology of schizophrenia. Additionally, the importance of a possible left hemispheric dysfunction in schizophrenia must be reconciled with biological evidence which suggests that structural (e.g., Buchsbaum & Haier, 1987) and metabolic (Weinberger et al., 1988) abnormalities occur along the anterior-posterior axis. Physiological evidence of a frontal lobe impairment in schizophrenia is presented
later in this chapter.

The frontal lobe conceptualization of schizophrenia emphasizes the apparent similarities between schizophrenic and frontal lobe patients in terms of behavioural changes and cognitive impairment (Goldberg et al., 1987; Liddle & Morris, 1991). Additionally, the similarities between frontal lobe syndromes and negative symptoms have been emphasized in recent years (Morihisa & Weinberger, 1984; Andreasen, 1989). The popularity of the frontal lobe explanation of schizophrenia has also led to the proposal that positive symptoms, such as delusional ideation, may reflect frontal lobe impairment (Benson & Stuss, 1990). However, while the frontal lobe conceptualization of schizophrenia has gained support, there is a paucity of studies which have directly compared schizophrenic and frontal lobe patients (Goldberg & Weinberger, 1986). Therefore, without direct comparison studies it is not possible to accurately assess the degree to which patients with schizophrenia and focal frontal lobe lesions are similar on neuropsychological measures.

While schizophrenic patients may exhibit similar types of impairment as patients with frontal lobe lesions (Andreasen, 1989), the conclusion that schizophrenia is a frontal lobe disorder may overly simplify the psychopathology of schizophrenia (Goldstein, 1986). Goldberg and Costa (1987) suggest that the similarities between schizophrenic and frontal lobe patients does not necessarily reflect an actual frontal lobe pathology in schizophrenia. Specifically, frontal lobe impairment may be simulated in patients (e.g., the elderly) who do
not necessarily have a frontal lobe pathology (Goldberg & Costa, 1987). Also, Miller (1986) has cited studies (e.g., Robinson, Heaton, Lehman, & Stilson, 1980) which have not found differences on tests sensitive to frontal lobe impairment between patients with focal frontal lobe lesions and diffuse brain damage. With the uncertainty regarding the anatomical basis of schizophrenia, it may be more appropriate to attribute the impairment of schizophrenic patients in planning and problem-solving to a loss of executive functioning (Goldberg & Costa, 1987). Executive functions refer to higher order abilities (e.g., planning, problem-solving, and monitoring of behaviour) that are necessary for the initiation of goal-directed, appropriate behaviour (Lezak, 1983). The advantage of conceptualizing schizophrenia in terms of a loss of executive functioning is that it emphasizes that deficits in higher order abilities are mediated by integrated brain systems (Stuss, 1992).

As suggested by a number of researchers, it is probable that the poor performance of schizophrenic patients on tests associated with frontal lobe impairment is dependent, in part, on the diagnostic criteria used to select schizophrenic patients (Braff et al., 1991; Goldman, Axelrod, Tompkins, 1992). For example, Wisconsin Card Sorting deficits are usually reported in studies employing more severely impaired patients (e.g., Goldberg et al., 1987); whereas, schizophrenic patients who are less severely impaired (as assessed by mental status) have minimal card sorting impairment (Braff et al., 1991).

In conclusion, neuropsychological evidence suggests that a certain
proportion of schizophrenic patients are impaired on tests of frontal lobe ability (Liddle & Morris, 1991; Moses, 1983; Goldberg et al., 1987). The presence of frontal lobe deficits appear to be associated with more severe negative psychopathology (Braff et al., 1991). However, poor performance on tests sensitive to frontal lobe functions does not necessarily implicate the frontal lobe as the anatomical locus of the impairment (Miller, 1986). As suggested by Robbins (1991), it is plausible that frontal lobe deficits in schizophrenia may arise from different combinations of cortical and subcortical damage (see Chapter 3). The advantage of Robbins' (1991) conceptualization of schizophrenia is that it considers cognitive functions as being mediated by multiple, integrated brain regions. This approach is more likely to be successful in explaining the heterogeneity of schizophrenia than conceptualizations which emphasize that schizophrenia arises solely from a frontal lobe pathology (Robbins, 1991).

More generally, caution must be exercised when interpreting the results of neuropsychological studies investigating schizophrenia. Specifically, the neuropsychological interpretation of test performance of schizophrenic patients is not straightforward. Specifically, the interpretation of test performance of brain-damaged patients is based on well-documented evidence that specifies the relationship between the lesion site and resulting alterations in behaviour. In contrast, the
structural abnormalities underlying schizophrenia are uncertain, and interpretation of test performance must take into consideration the possibility that cognitive abnormalities may reflect changes involving psychotic ideation as well as subtle and inconsistent changes involving diffuse neurotransmitters systems and cerebral metabolism (Goldberg & Weinberger, 1986). Thus, given the probability that the neuropsychological performance of schizophrenic patients is altered, in part, by variability in both physiological processes and symptom severity, a consistent neuropsychological profile may be difficult to obtain. Although the localization of cognitive deficits in schizophrenia is not straightforward (Miller, 1986), neuropsychological evaluation provides information necessary for determining the nature of subtle cognitive alterations that may take place in schizophrenia.

Effects of Medication on Cognition and Metabolic Brain Activity

Introduction. There are few studies that have used schizophrenic patients to examine the influence of neuroleptics on the performance of neuropsychological tests. The paucity of studies investigating the effects of neuroleptics may reflect the difficulties in recruiting suitable numbers of unmedicated patients and in testing patients with prominent psychotic symptoms. In one of the first studies to examine the behavioural side-effects of neuroleptics, Rifkin, Quitkin, and Klein (1975) concluded that in some schizophrenic patients neuroleptics induce a state of akINESIA which mimics the deficit symptoms of schizophrenia. Their conclusion was largely based on the observation that deficit
symptoms (e.g., apathy, psychomotor retardation, and poverty of speech) were reduced in severity when neuroleptics were discontinued or when prophylactic parkinsonian medications were administered.

Regional cerebral blood flow (rCBF) and positron emission tomographic (PET) studies have played an important part in investigating the pathophysiology of schizophrenia. Studies which have employed rCBF and PET techniques are reviewed with the purpose of discussing 1) the effects of neuroleptic medication on both neuropsychological test performance and metabolic brain activity and 2) the brain areas that are frequently implicated in schizophrenia research.

Regional Cerebral Blood Flow Studies. In an attempt to establish whether frontal lobe deficits are present in schizophrenia, various studies have examined cognitive performance concurrently with rCBF (see Table 2). In an early rCBF study, Ingvar and Franzen (1974) measured the pattern of blood flow of chronic, medicated schizophrenic patients (mean age 61 years) and normal control subjects (mean age 25 years) while performing the Raven's Progressive Matrices (Raven, 1960), a test which measures non-verbal reasoning abilities. The main finding indicated that blood flow remained constant in schizophrenic patients while control subjects displayed elevated blood flow to prefrontal structures. Further, reduced activation of prefrontal areas in chronic schizophrenic patients was positively associated with cognitive impairment. However, the relatively lower prefrontal blood flow of older subjects may reflect an age-related decline in the activation of the prefrontal cortex.
Table 2. Summary of Studies Reporting Neuropsychological Deficits in Conjunction with Reduced Prefrontal Blood Flow.

<table>
<thead>
<tr>
<th>Study</th>
<th>Subject characteristics</th>
<th>Tests/Results</th>
<th>Interpretation/Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ingvar &amp; Franzen</td>
<td>20 schizophrenic patients</td>
<td>Reduced frontal lobe rCBF associated with poor Raven's Matrices in chronic</td>
<td>Reduced blood flow to frontal lobe considered to underlie poor test performance. Lower</td>
</tr>
<tr>
<td></td>
<td>11 young, 25 years</td>
<td>schizophrenia patients</td>
<td>frontal lobe blood flow may be attributed to the older age of patients.</td>
</tr>
<tr>
<td></td>
<td>9 old, 61 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bernan et al.</td>
<td>Experiment 1, 24 schizophrenic patients on medication</td>
<td>Reduced frontal lobe rCBF associated with poor WCST performance, but not with</td>
<td>Results considered to replicate the hypofrontality result of Ingvar &amp; Franzen (1975)</td>
</tr>
<tr>
<td></td>
<td>25 normal controls</td>
<td>Number Matching Test.</td>
<td>on tests which considered to measure prefrontal function.</td>
</tr>
<tr>
<td></td>
<td>Experiment 2, 18 schizophrenic patients medication-free</td>
<td>Reduced frontal lobe blood flow associated with poor WCST.</td>
<td>The finding of hypofrontality in unmedicated patients considered to demonstrate that</td>
</tr>
<tr>
<td></td>
<td>17 normal controls</td>
<td></td>
<td>hypofrontality is not an epiphenomenon of medication.</td>
</tr>
<tr>
<td>Weinberger et al.</td>
<td>20 schizophrenic patients medication-free</td>
<td>Reduced Frontal lobe Blood flow associated with Poor WCST performance</td>
<td>Results considered to replicate Bernan et al. (1988) results.</td>
</tr>
<tr>
<td></td>
<td>-mean age 28.9 years</td>
<td></td>
<td>Reduced prefrontal blood flow positively correlated with WCST performance</td>
</tr>
<tr>
<td></td>
<td>25 control subjects</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>-mean age 30.7 years</td>
<td></td>
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</table>
(Buchsbaum, Nuechterlein, Haier, Wu, Sicotte, Hazlett, Asarnow, Potkin, & Guich, 1990), rather than a pathological process specific to schizophrenia. Nevertheless, in response to the reported lack of increase in prefrontal blood flow in chronic schizophrenic patients, the term hypofrontality is commonly used to refer to a possible frontal lobe defect which may characterize schizophrenia.

Using a similar testing paradigm, Weinberger et al. (1986) reported further rCBF evidence that reduced frontal lobe blood flow in schizophrenia is associated with cognitive impairment. In their investigation, the blood flow of unmedicated schizophrenic patients and control subjects was specifically measured in the dorsolateral prefrontal cortex while completing the Wisconsin Card Sorting Test (WCST), a test which is considered to primarily assess frontal lobe function (Milner, 1964). Support for hypofrontal metabolism was obtained in that only control subjects had an increase in blood flow to the prefrontal cortex while performing the WCST. In a second study, Berman, Zec and Weinberger (1988) examined whether the medication status of schizophrenic patients had an effect on the observed failure of schizophrenic patients to activate the dorsolateral prefrontal cortex. In order to control for a possible medication effect, normal control subjects were compared to unmedicated and medicated schizophrenic patients using a similar procedure as the Weinberger et al. (1986) study. As hypothesized, poor WCST performance of both schizophrenic patient groups was associated with reduced activation of the
dorsolateral prefrontal cortex. Although Berman et al. (1988) reported hypofrontality in unmedicated schizophrenic patients, it is not clear whether the residual effects of neuroleptics influenced the results. Specifically, the withdrawal of schizophrenic patients from neuroleptics for two weeks may have been an insufficient period to diminish the effects of neuroleptic drugs on brain metabolism.

A limitation of the three rCBF studies reviewed is that chronic subjects, who had a high probability of being neuropsychologically impaired, were selected. It is, therefore, difficult to generalize the hypofrontality finding to other groups of schizophrenic patients, such as those who perform within the normal limits on the WCST. A further criticism of rCBF studies is that the use of a limited number of neuropsychological tests did not provide an adequate opportunity to examine whether WCST performance is an artifact of other cognitive defects, such as distractability or poor motivation.

In rCBF studies which have not employed neuropsychological tests, the finding of reduced frontal lobe blood flow in schizophrenic patients has been replicated, but on an inconsistent basis. Mathew, Duncan, Weinman and Barr (1982) tested 14 medicated and 9 unmedicated schizophrenic patients, and 18 normal control subjects while breathing in time to a metronome. This procedure was used to ensure that the respiratory rate of all the subjects was constant. It was determined that schizophrenic patients (regardless of medication) did not have decreased prefrontal blood flow even though blood flow was reduced in
both hemispheres.

An overall decrease in resting cerebral blood flow was reported by Ariel, Golden, Berg, Dirksen, Quaife, Forsell, Wilson, & Graber, (1983) in their comparison of 29 medicated schizophrenic patients and 22 age-matched control subjects. A post hoc comparison, however, indicated that blood flow was reduced to a greater extent in the anterior region of the frontal lobe. Unlike the results of Ingvar and Franzen (1974), hypofrontality in Ariel et al.'s (1983) study was found in relatively young patients (mean age 33 years).

Chabrol, Guell, Bes, and Moron (1986) also reported a hypofrontality result in young, never-medicated schizophrenic patients (mean age 17.3 years) while at rest. This result suggests an independence between neuroleptics and frontal lobe processes at the onset of illness. Further, Chabrol et al.'s (1986) results are consistent with the Berman et al.'s (1988) rCBF study in which unmedicated schizophrenic patients experienced reduced frontal lobe blood flow.

In a more recent study, Liddle, Friston, Frith, Hirsch, Jones, and Frackowiak (1992) examined the pattern of blood flow associated with three groups of schizophrenic patients. These groups consisted of schizophrenic patients who had symptoms characteristic of the disorganized, psychomotor poverty, and reality distortion groups (see Neuropsychological Investigation Section in the present chapter). In a sample of 30 schizophrenic patients with a mean age of 36.3 years, it was determined that each syndrome was associated with an unique pattern
of blood flow to the frontal and temporal lobes. The psychomotor poverty group was reported to have reduced blood flow to the left dorsolateral prefrontal cortex. This result was interpreted to be consistent with Ingvar and Franzen (1974), who reported an association between reduced frontal lobe blood flow and catatonic symptoms of schizophrenia. The disorganized and reality distortion groups were found to have reduced blood flow to the right prefrontal cortex and the left medial temporal lobe, respectively.

In two rCBF studies which did not report hypofrontality, medicated schizophrenic patients (Gur, Skolnick, Gur, Caroff, Rieger, Obrist, Younkin, & Reivich, 1983) and unmedicated schizophrenic patients (Gur, Gur, Skolnick, Caroff, Obrist, Resnick, & Reivich, 1985) were tested while performing spatial and verbal cognitive tasks. Regardless of medication status, schizophrenic patients had rCBF lateralization differences as compared to control subjects. Specifically, schizophrenic patients showed no lateralization effect for the verbal task and greater left hemisphere activity for the spatial task. In contrast, control subjects had increased rCBF in left and right hemispheres in response to the verbal and spatial tasks, respectively. The increase in blood flow to the left hemisphere in schizophrenic patients was interpreted as being consistent with the theory that left hemispheric over activation is a primary feature of the pathophysiology of schizophrenia (Gur, 1978) This interpretation, however, does not not account for the finding that schizophrenic patients did not have a left hemispheric
increase in blood flow while performing the verbal task. A second finding of the Gur et al.'s (1985) study was that unmedicated schizophrenic patients, unlike medicated schizophrenic patients, had a higher left hemispheric rCBF while at rest. Gur et al. (1985) interpreted this result as evidence that neuroleptics act to restore hemispheric asymmetries.

In conclusion, the results of the rCBF studies reviewed suggest that neuroleptic medication has only a minimum effect on frontal lobe blood flow as determined by studies examining medicated and non-medicated schizophrenic patients (Berman et al., 1988). In terms of the effects of neuroleptic medication on lateralization differences, Gur et al. (1985) proposed that neuroleptics act to restore normal hemispheric activity on the basis that only unmedicated schizophrenic patients had a higher left hemispheric blood flow while at rest. Similarly, Tomer and Flor-Henry (1989) have concluded that neuroleptics act to normalize the dysfunctional activation of the left hemisphere. This conclusion was based on their investigation of the attentional asymmetries of 23 unmedicated schizophrenic patients who were placed on medication. On the Mesulam Cancellation task (Weintraub & Mesulam, 1985), which consists of verbal and non-verbal arrays, it was found that exposure to neuroleptics shifted hemispheric inattention of schizophrenic patients from the left hemisphere to the right hemisphere. This result was considered by Tomer and Flor-Henry (1989) as evidence that in schizophrenia neuroleptics act to normalize the dysfunctional
activation of the left hemisphere.

This review of rCBF studies further indicates that hypofrontality may be a characteristic of schizophrenic patients with chronic symptomatology (Ingvar & Franzen, 1974; Liddle et al., 1992; Weinberger et al., 1986), although one study employing young, unmedicated schizophrenic patients also reported a reduction in frontal lobe blood flow (Chabrol et al., 1986). The reasons for inconsistent hypofrontality results may be attributed to differences in procedures used in the various studies. In some studies (e.g., Gur et al., 1983) the absence of a hypofrontality finding may reflect an inadequate number of blood flow detectors within the frontal lobe (Weinberger & Berman, 1986). A more general shortcoming of the rCBF technique is that it is not possible to assess the contribution of subcortical structures to frontal lobe function. Since frontal lobe dopaminergic activity has been shown to be modulated by subcortical dopamine levels (Jones, Hernandez, Marsden, & Robbins, 1988), the possible involvement of subcortical structures in altering frontal lobe metabolism in schizophrenia cannot be dismissed (Weinberger, 1988). Therefore, by not considering subcortical metabolism, rCBF studies that report hypofrontality in schizophrenia may misrepresent the overall pathophysiology of schizophrenia.

**PET Studies.** In contrast to the rCBF technique, the PET procedure is capable of examining both cortical and subcortical metabolic activity. Brodie, Christman, Corona, Fowler, & Gomez-Mont (1984) examined six chronic schizophrenic patients, who were moderately to severely ill,
before and after the introduction of neuroleptics. Prior to the initial PET assessment, patients were without neuroleptics for a two week period, and then treated between four to ten weeks with the neuroleptic, thiothixene, prior to the second PET assessment. The introduction of neuroleptics, which reduced psychotic symptomatology, had no effect on the metabolism of the frontal lobe in that the hypofrontality recorded at the first assessment remained unchanged at the time of the second assessment. However, basal ganglia metabolism increased over the course of neuroleptic treatment. The differential influence of neuroleptics on the frontal lobe and the basal ganglia may indicate that neuroleptics exert their antipsychotic effect through the blockade of subcortical dopamine receptors.

Volkow et al. (1986) reported that the administration of thiothixene to chronic, never-medicated schizophrenic patients had little influence on brain metabolism which was initially characterized by elevated metabolic activity in the frontal lobes and basal ganglia. The sample of never-medicated schizophrenic patients, however, may have been atypical in that while the mean duration of illness of the never-medicated group was eight years, the severity of symptoms apparently did not warrant neuroleptic treatment. Also, the lack of increase of basal ganglia metabolism after the introduction of neuroleptics is not consistent with other studies (e.g., Brodie et al., 1984; Kling, Metter, Riege & Kuhl, 1986).

Two other PET studies have also reported the absence of
hypofrontality in unmedicated schizophrenic patients (Early, Reiman, Raichle, & Spitznagel, 1987; Sheppard, Gruzelier, Manchanda, Hirsch, Wise, Frackowiach, & Jones, 1983). The results of these studies imply that reduced frontal lobe activity in schizophrenia may be an artifact of medication status. Further, the tendency for hypofrontality to be mainly reported in chronic, medicated schizophrenic patients supports the view that altered brain metabolism reflects the effects of medication and/or age, rather than intrinsic pathophysiological processes. The results, however, of PET studies by Volkow et al. (1986) and Sheppard et al. (1983) have been questioned by Weinberger and Berman (1988) on the basis that they employed small sample sizes consisting of six and four patients, respectively.

The absence of hypofrontality in unmedicated patients should be considered in terms of uncontrolled clinical variables. Specifically, the presence of increased frontal lobe activity has been shown to be associated with the exacerbation of acute symptoms (Geraud, Arne-Bes, Guell, & Bes, 1987). Thus, it is conceivable that the absence of hypofrontality in unmedicated patients may be confounded by the possibility that frontal lobe activity is increased in patients removed from medication due to an exacerbation of psychotic symptoms.

More generally, Delisi (1986) has proposed that PET studies, employing psychiatric patients, must be interpreted cautiously given that artifacts may be produced by a number of technological and experimental difficulties. In terms of the labeled compounds used in the
PET procedure, differences in the rate of decay (e.g., C-deoxyglucose versus F-deoxyglucose) makes it difficult to compare studies which have used different compounds (Delisi, 1986). Another difficulty of PET studies is that the influence of psychotic symptoms (e.g., anxiety and/or agitation related to bizarre ideation) on brain activity is difficult to control experimentally.

**Implications**

This review suggests that the biological basis for cognitive impairment in schizophrenia is far from certain. Although "frontal lobe" theories (e.g., Liddle et al., 1992) have attracted attention, they fail to explain the heterogeneous nature of cognitive impairment reported in certain studies (e.g., Braff et al., 1991). The conceptualization of schizophrenia within the framework of the frontostriatal circuits provides the foundation for understanding the cognitive diversity of schizophrenia. Previous attempts to explain the clinical heterogeneity of schizophrenia have rested on the proposal that both cortical and subcortical disease processes are present in schizophrenia (Crow, 1989). More recently, Robbins (1990) speculated that the nature of symptoms expressed in schizophrenia depends on the location of damage within frontostriatal circuits. Specifically, Robbins (1990) hypothesized that different combinations of cortical and subcortical damage in schizophrenia will result in the expression of different patterns of symptoms.

The question which is addressed in the present research project is
concerned with whether the subcortical pathology that underlies AIMs contributes to the impairment of cognitive functions. On the basis that AIMs schizophrenia is characterized by a subcortical pathology that is not present in non-AIMs schizophrenia, AIMs and non-AIMs schizophrenia may be associated with different patterns of frontostriatal pathology. Thus, a different pattern of frontostriatal damage provides the basic rationale for expecting neuropsychological differences between schizophrenic patients with and without AIMs. The actual neuropsychological difference between schizophrenic patients with and without AIMs is discussed in Chapter 5.
Chapter 5
Neuropsychology of AIMs
Schizophrenia and Huntington’s Disease

In Chapter 5, the studies which have compared the neuropsychological and behavioural aspects of schizophrenic patients with and without AIMs are presented along with a general discussion of the neuropsychology of Huntington’s disease. This review provides evidence that AIMs in schizophrenia are accompanied by more severe negative symptomatology and cognitive deficits. In the last section of Chapter 5, the cognitive features of patients with AIMs schizophrenia and Huntington’s disease are considered.

Cognitive/Behavioural Aspects of AIMs schizophrenia

Behavioural Comparisons. Yarden and Discipio (1971) were among the first to report the presence of choreiform movement in a sample of unmedicated schizophrenic patients who had an early onset and a progressively deteriorating course. Subsequently, numerous studies have examined the relationship between AIMs and negative symptoms in an attempt primarily to identify behavioural markers for AIMs vulnerability (Myslobodsky, Tomer, Holden, Kempler, & Sigel, 1985; Waddington & Youssef, 1986). Thus, Barnes, Liddle, Curson, and Patel (1989) have reported that schizophrenic patients with negative symptoms developed AIMs up to 15 years before schizophrenic patients without negative symptoms. In an examination of schizophrenic patients, who did not differ in level of medication, Waddington and Youssef (1986) determined that AIMs schizophrenic patients possess a greater number of negative
symptoms than those schizophrenic patients without AIMs. Manschreck, Keuthen, Schneyer, Celada, Laugher, and Collins (1990) also reported that the severity of negative symptomatology is greater in AIMs schizophrenia as indicated by the total score on the Scale for the Assessment of Negative Symptoms. Similarly, Davis, Borde, and Sharma (1992) found an association between the severity of AIMs in schizophrenic patients and two subscales of the Scale for the Assessment of Negative Symptoms (avolition/apathy and anhedonia/asociality). The association between AIMs and negative symptoms suggests that schizophrenic patients with AIMs experience a more prominent loss of adaptive behaviour. Specifically, the greater reduction in spontaneous behaviour (i.e., avolition and apathy) of AIMs schizophrenic patients, may indicate that these patients lack executive control in initiating and planning on-going activities.

Cognitive Comparisons. Brown, White, and Palmer (1992) compared 19 AIMs and 27 non-AIMs schizophrenic patients with the purpose of determining whether AIMs are associated with poor performance on tests sensitive to frontal lobe functions (See Table 3). Patients with AIMs scored lower than non-AIMs patients on the three tests used to assess frontal lobe functioning: Wisconsin Card Sorting Test, Trail Making Test, and Thurstone Word Fluency Test. In contrast, the two patient groups did not differ on measures of memory or global cognitive deterioration. The impaired performance of schizophrenic patients with AIMs on frontal lobe tests was attributed to the influence that caudate
Table 3
The Results of Studies Examining Cognitive Deficits in Schizophrenic Patients With and Without AIMs

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Main Finding</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wolf et al. (1983)</td>
<td>Non-AIMs: 7, AIMs: 9</td>
<td>No difference between AIMs &amp; Non-AIMs on Intelligence and memory tests</td>
<td>Small sample size</td>
</tr>
<tr>
<td>Struve &amp; Willner</td>
<td>Non-AIMs: 44, AIMs: 51</td>
<td>AIMs more impaired than Non-AIMs on a test of abstraction</td>
<td>One test assessment</td>
</tr>
<tr>
<td>Myslobodsky et al.</td>
<td>Non-AIMs: 14, AIMs: 17</td>
<td>AIMs performed below Non-AIMs on picture recall test while no differences in language and memory</td>
<td>Group differences explained by mental status</td>
</tr>
<tr>
<td>Sorokin et al.</td>
<td>Non-AIMs: 19, AIMs: 21</td>
<td>AIMs lower than Non-AIMs in visual memory, no difference in verbal memory</td>
<td>AIMs older than Non-AIMs</td>
</tr>
<tr>
<td>Waddington &amp; Youssef</td>
<td>Non-AIMs: 28, AIMs: 17</td>
<td>Impaired intellectual scores of AIMs below Non-AIMs scores</td>
<td>AIMs older than Non-AIMs</td>
</tr>
<tr>
<td>Wade et al. (1987)</td>
<td>30 AIMs with schizos, 24 AIMs with mania</td>
<td>Severity of AIMs predicted cognitive performance on tests of intellect, memory, &amp; mental flexibility</td>
<td>Combined sample of schizos's and mania's tested</td>
</tr>
<tr>
<td>Waddington et al.</td>
<td>Affective patients: Non-AIMs: 26, AIMs: 16</td>
<td>AIMs more impaired than Non-AIMs on a test of orientation, awareness and immediate memory</td>
<td>Bipolar subjects, One test assessment</td>
</tr>
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</table>
### Table 3 (continued).
The Results of Studies Examining Cognitive Deficits in Schizophrenic Patients With and Without AIMs

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Main Finding</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brown et al. (1992)</td>
<td>Non-AIMs: 19 AIMs: 27</td>
<td>Patients with AIMs impaired on tests of card sorting, verbal fluency, and mental flexibility.</td>
<td>Poor test performance attributed to subcortical disruption of dorsolateral cortico-striatal circuit.</td>
</tr>
<tr>
<td>Waddington et al. (1993)</td>
<td>Non-AIMs: 40 AIMs: 24</td>
<td>Impairment in mental flexibility distinguished schizophrenic patients with and without AIMs.</td>
<td></td>
</tr>
<tr>
<td>Gureje (1988)</td>
<td>Non-AIMs: 57 AIMs: 49</td>
<td>Cognitive impairment, as assessed by orientation, attention and digit span, not correlated with severity of AIMs.</td>
<td>Brief assessment used to assess cognitive functioning.</td>
</tr>
<tr>
<td>Kolakowska et al. (1986)</td>
<td>Non-AIMs: 49 AIMs: 49</td>
<td>No association between AIMs and cognitive impairment as assessed by verbal memory, non-verbal, conceptual, and spatial tests.</td>
<td>AIMS not correlated with drug history, age, sex, clinical features, brain ventricle size, and neurological soft signs.</td>
</tr>
<tr>
<td>Waddington et al. (1990)</td>
<td>Non-AIMs: 14 AIMs: 26</td>
<td>Over 5 years no change in cognition of AIMS and non-AIMS schizophrenics Development of AIMS associated with Cognitive deficits</td>
<td>Limited assessment and loss of subjects</td>
</tr>
<tr>
<td>Manschreck et al. (1990)</td>
<td>Non-AIMs: 13 AIMs: 9</td>
<td>AIMS lower immediate verbal recall, current and premorbid intelligence. No difference on language, perceptual organization, &amp; visuospatial memory tests.</td>
<td>Multiple T-tests and possible family-wise error</td>
</tr>
<tr>
<td>Davis et al. (1992)</td>
<td>Non-AIMs: 20 AIMs: 20</td>
<td>AIMS more impaired on a test of orientation, registration, attention calculation and language</td>
<td>One test assessment.</td>
</tr>
</tbody>
</table>
nucleus pathology has on complex cognitive functions (Brown et al., 1992). It was further noted that the frontal lobe profile of schizophrenic patients with AIMs resembled the deficits seen in patients with lesions restricted to the caudate nucleus as well as patients with Huntington's disease. Waddington, O'Callaghan, Larkin, and Kinsella (1993) reported that a deficit in mental flexibility, as assessed by the Trail Making Test B, distinguished schizophrenic patients with and without AIMs. In the overall analysis AIMs patients were older than non-AIMs patients; therefore, one cannot rule out the possibility that the difference in mental flexibility reflects a age-related decline in cognitive functioning (Davies, 1968). It was determined by Waddington et al. (1993), however, that reduced mental flexibility was associated with AIMs schizophrenia in a subgroup of patients who did not differ in age.

On the basis that Huntington's disease and AIMs schizophrenia may arise from a similar pathophysiological process, Wade et al. (1987) tested schizophrenic patients with and without AIMs using a neuropsychological battery which was sensitive to deficits in Huntington's disease. The battery primarily assessed verbal fluency, memory, and concentration. Multiple regression analysis, which statistically controlled for the length of medication and hospitalization, indicated that the severity of AIMs predicted cognitive performance. Age was also significantly correlated with test performance; therefore, the association between cognitive performance and AIMs is confounded by a possible age-related decline in cognitive
In a prospective study, Struve and Willner (1983) measured the abstraction ability of schizophrenic patients with the Conceptual Level Analogy Test. Age-matched schizophrenic patients prior to the onset of AIMs (prospective AIMs) and after the onset of persistent AIMs (baseline AIMs) were tested. Schizophrenic patients, who did not develop AIMs even though exposed to neuroleptics for a five year period (controls), were also tested. The main result was that abstraction ability of prospective and baseline patients did not differ while controls performed better than both prospective and baseline groups. This result suggests that deficits in abstract ability are present prior to the development of AIMs and, thereafter, remain constant.

In a second prospective study, Waddington, Youssef, and Kinsella (1990) examined the cognitive ability of schizophrenic patients over a five year period using a brief mental test which measured awareness, orientation, and immediate verbal memory. While AIMs schizophrenic patients had greater cognitive impairment than non-AIMs schizophrenic patients, the cognitive abilities of both groups remained constant during the course of the study. In contrast, schizophrenic patients, who developed AIMs during the course of the study, displayed greater cognitive impairment after the onset of AIMs.

AIMs and non-AIMs schizophrenic patients have also been compared in terms of memory. Famuyiwa, Eccleston, Donaldson, and Garside (1979) determined that AIMs schizophrenic patients had greater deficits in
verbal memory; however, the inclusion of patients with known brain damage limits the validity of this finding. In a study, which controlled for the severity of psychosis and age, Sorokin, Giordani, Mohs, Losonczy, and Davidson (1988) determined that AIMS schizophrenic patients were lower than non-AIMS schizophrenic patients on a visual recall and recognition memory task while a group difference did not exist on a verbal recall and recognition test. Manschreck et al. (1990) reported that schizophrenic patients with AIMS have poorer verbal recall than schizophrenic patients without AIMS. In contrast, the two patient groups did not differ on visuospatial memory, recognition memory, contextually restrained immediate memory, and perceptual organization. The fact that schizophrenic patients with and without AIMS did not differ in terms of the level of neuroleptic treatment, age, and length of hospitalization reduces the possibility that the interpretation of significant differences was confounded by uncontrolled variables.

A number of studies, which compared schizophrenic patients with and without AIMS, have reported that AIMS are not associated with cognitive impairment. Wolf, Ryan, and Mosnaim (1983), for example, did not report differences between AIMS and non-AIMS schizophrenic patients on the Wechsler Memory Scale. Myslobodsky et al. (1985) attributed the poor verbal recall of AIMS schizophrenic patients to a general impairment in mental status. On a test which measured orientation, attention and sensorium, Gureje (1988) determined that AIMS in schizophrenia are not correlated with cognitive impairment. Similarly, Kolakowska, Williams,
PM-1 3½"x4" PHOTOGRAPHIC MICROCOPY TARGET
NBS 1010a ANSI/ISO #2 EQUIVALENT

PRECISION\textsuperscript{SM} RESOLUTION TARGETS
Ardern, and Reveley (1986) reported that AIMs and non AIMs schizophrenic patients did not differ on an index score derived from the combined results of verbal and non-verbal memory tests as well as from conceptual and spatial tests.

Summary. The majority of studies reviewed have reported that schizophrenic patients with AIMs have more prominent cognitive deficits than schizophrenic patients without AIMs (see Table 3). A number of studies have reported that AIMs in schizophrenia are associated with impairment in mental status (Wade et al., 1987), abstracting ability (Struve & Willner, 1983), memory (Sorokin et al., 1988), mental flexibility (Waddington et al., 1993), and complex problem solving (Brown et al., 1992).

Not all studies, however, have reported significant differences between schizophrenic patients with and without AIMs (e.g., Wolf et al., 1983). The inconsistent findings across studies must be considered in terms of several common methodological weaknesses. First, a number of studies employed a limited number of tests (e.g., Gureje, 1988; Waddington et al., 1990; Davis et al., 1992) which may have provided an inadequate assessment of the different dimensions of cognitive functioning. Consequently, it is not possible to determine whether reported deficits are focal or a manifestation of a global decline in functioning. Second, patients are not usually screened for dementing syndromes, and this raises the possibility that in some cases poor performance on cognitive tasks may be due to the presence of
degenerative disorders. Third, most studies investigating the 
neuropsychological of AIMs schizophrenia have not employed psychiatric 
control subjects (e.g., Brown et al., 1992; Manschreck et al., 1990; 
Waddington et al., 1993). Without psychiatric control subjects it is not 
possible to determine whether neuropsychological deficits associated 
with AIMs schizophrenia are generalizable to other psychiatric disorders 
which are also accompanied by AIMs (e.g., affective disorders). Fourth, 
the method of combining the results of several tests to derive a 
impairment index (e.g., Kolakowska et al., 1986) does not permit the 
examination of specific areas of cognitive functioning. If cognitive 
deficits are focal rather than generalized in AIMs schizophrenia, a 
single impairment index may not be sensitive to specific cognitive 
deficits that may differentiate AIMs and non-AIMs schizophrenia.

Huntington's Disease

Clinical features of Huntington’s disease include neuropsychological 
deficits, personality/mood changes, and chorea (Folstein, 1989). The 
degree of caudate nucleus pathology correlates with both clinical 
impairment (Myers, Vonsattel, & Stevens, 1988) and cognitive loss 
(Goldberg, Berman, Mohr, & Weinberger, 1990). The association between 
cognitive impairment and caudate nucleus pathology implicates the 
involvement of the frontostriatal circuits in the pathophysiology of 
Huntington’s disease (Cummings, 1993).

In an attempt to quantify the observed decline in adaptive 
behaviour in Huntington’s disease, early studies (e.g., Aminoff,
Marshall, Smith, & Wyke, 1975; Norton, 1975) primarily examined intellectual abilities using the Wechsler Adult Intelligence Scale (WAIS). In these studies a non-focal decline of intellectual ability was reported with Verbal Scale IQ superior to Performance Scale IQ (Aminoff et al., 1975). In certain Huntington's disease studies, the goal of testing has been to identify early symptoms which could be used to predict the occurrence of Huntington's disease in high risk individuals who have a 50% probability of inheriting the disorder. In the longitudinal study by Lyle and Gottesman (1977), who examined intellectual deficits in patients with Huntington's disease and at risk relatives, it was determined that intellectual changes occur prior to the advent of chorea. Further, at-risk relatives, who later developed Huntington's disease, had a WAIS profile similar to that of symptomatic Huntington's disease patients.

The progression of sensory-perceptual deficits in subjects at risk was examined by Hayward, Zubrick, and Hall (1985) in an eight year longitudinal study which employed neuropsychological and neurological tests. Consistent with previous studies (e.g., Fedio, Cox, Neophylides, Canal-Fredrick, & Chase, 1979), it was found that sensory perceptual deficits, as measured by visual, tactile and auditory neuropsychological tests, occurred prior to the onset of movement abnormalities. More importantly, using discriminant analysis of sensory-perceptual deficits, Hayward et al., (1985) were able to identify with over 95% accuracy the at-risk subjects who would later develop Huntington’s disease.
Similarly, in a cross-sectional study, Josiassen, Curry, and Mancall (1983) determined that deficits in the areas of visuospatial judgment, perceptuomotor integration, motor speed, and visual memory, occur early and progressively deteriorate. These results are in agreement with a factorial analysis study by Bamford, Caine, Kido, Plassche, and Shoulson (1989) in which it was found that mildly and moderately impaired Huntington’s disease patients were impaired on tasks measuring visuospatial and psychomotor functions. Josiassen et al. (1983) were able to differentiate two groups of patients at risk of Huntington’s disease based on their performance on a battery of visuospatial tasks. However, as a result of the limitations of the cross-sectional design, it was not possible to investigate the predictive significance of the divergence in the test performance of at-risk patients.

In recent reviews, the neuropsychological features of Huntington’s disease have been mainly considered in terms of deficits on tests of frontal lobe function, memory, and visuospatial cognition (Brandt & Butters, 1986; Folstein, 1989). Within a year of diagnosis, Huntington’s disease patients of average intellectual ability show impairment in verbal fluency and memory (Butters, Sax, Montgomery & Tarlow, 1978). Visuospatial deficits also occur early and remain stable until advanced stages of Huntington’s disease (Brandt & Butters, 1986). Brandt, Folstein, and Folstein (1989), employing the Mini-Mental State Examination, described the pattern of cognitive loss that occurs as Huntington’s disease advances. In early stages, Huntington’s disease
patients have difficulty on tests requiring concentration, calculation, and verbal recall while performance on tests of orientation, reading, and naming are preserved until latter stages of the disorder.

In Huntington's disease cognitive deficits resembling a frontal lobe syndrome are thought to underlie personality changes which are characterized by inappropriate and impulsive behaviour (Hayden, 1981). The deficits of Huntington's disease patients on card sorting, verbal fluency, and maze learning tests (Butters et al., 1978; Wexler, 1979; Weinberger, Berman, Iadarola, Driesen, & Zec, 1988) resemble deficits seen in patients with lesions of the dorsolateral prefrontal cortex (Brandt & Butters, 1986). In contrast to schizophrenia, Weinberger et al. (1988) reported that poor Wisconsin Card Sorting performance of Huntington's disease patients was related to the extent of caudate nucleus pathology rather than reduced blood flow to the prefrontal cortex. On the basis of this result, Weinberger et al. (1988) concluded that caudate nucleus damage underlies the loss of prefrontal function in Huntington's disease.

Memory impairment in Huntington's disease is marked by difficulties in the retention of new information and the retrieval of previously learned information (Brandt & Butters, 1986; Moses, Golden, Berger, & Wisniewski, 1981). In a comparison of Huntington's disease and schizophrenia, Goldberg et al. (1990) reported that patients with Huntington's disease had greater deficits on recall memory (Visual Reproduction and Paired Associate Learning Tests). Remote memory
deficits are marked by the loss of fine details (Caine, Ebert, & Weingartner, 1975). Fisher, Kennedy, Caine, and Shoulson (1983) reported memory difficulties (Selective Reminding Test) are slowly progressive based on memory differences between mildly and moderately disabled Huntington's disease patients. The retrieval of information may be enhanced with the use of verbal mediators (Butters, Albert, Sax, Miliotis, Nagode, & Sterste, 1983). In contrast to recall memory, recognition memory is not usually impaired in Huntington's disease (Albert, Butters, & Brandt, 1981). The pattern of greater recall memory loss in the context of intact recognition memory is present in both early and advanced stages of Huntington's disease (Folstein, 1989).

Impairment of Huntington's disease patients on visuospatial tests include deficits in visuospatial discrimination and left-right direction judgment (Fedio, Cox, Neophytides, Canal-Frederick, & Chase, 1979). Additionally, Huntington's disease patients are impaired in terms of egocentric spatial perception (Brouwers, Cox, Martin, Chase, & Fedio, 1984; Potegal, 1971), the ability to identify one's position in space in relationship to a fixed point. Compared to schizophrenic patients, patients with Huntington's disease perform worse on visuospatial tests (Goldberg et al., 1990).

Methodological Issues. This review presents evidence that Huntington's disease is associated with cognitive impairment involving frontal lobe functions (Weinberger et al., 1988), visuospatial abilities (Brouwers et al., 1984), and recall memory (Brandt & Butters, 1986;
Goldberg et al., 1990). The neuropsychology of Huntington's disease must be considered in the context of several methodological concerns. First, a common difficulty with early studies (e.g., Aminoff et al., 1979) is that patients differed in the severity of psychopathology; consequently, subtle changes in intellectual abilities may not have been observed. Second, in some studies using cross-sectional designs (e.g., Fisher et al., 1983), the results are interpreted in terms of the progression of cognitive loss over the course of the disorder. It would be advantageous to determine the progression of cognitive impairment by employing prospective studies (Hayward et al., 1985). The third criticism pertains to the selection of Huntington's disease patients on the basis of the duration of the disorder (Josiassen et al., 1983). Specifically, because the course of Huntington's disease is variable (slower rates of progression are associated with later onset; Hayden, 1981), Huntington's disease patients of the same duration may have different levels of cognitive loss. Further, it is often difficult to identify the specific onset of Huntington's disease, especially if emotional and cognitive changes occur prior to the manifestation of AIMS (Folstein, 1989). A more reasonable method of selecting Huntington's disease patients of similar ability is to rate patients in terms of mental status or functional ability (Fisher et al., 1983).

Implications

Certain aspects of the neuropsychological profiles of AIMS schizophrenia and Huntington's disease appear to be similar. While
reports of memory impairment in AIMs schizophrenia are inconsistent, there is evidence that AIMs schizophrenic patients have more prominent recall memory deficits relative to recognition memory deficits (Manschreck et al., 1990). Similarly, recall deficits in Huntington’s disease are more evident than recognition deficits (Folstein, 1989). The presence of frontal lobe deficits in both AIMs schizophrenia and Huntington’s disease are indicated by neuropsychological testing (Brandt & Butters, 1986; Brown et al., 1992), and by the presence of behavioural changes marked by increased apathy, impulsiveness, and decreased spontaneity (Davis et al., 1992; Hayden, 1981). A key difference between AIMs schizophrenia and Huntington’s disease may lie in the area of visuospatial ability. Specifically, schizophrenic patients with and without AIMs have been found not to differ on visuospatial tasks (Manschreck et al., 1990). Also, deficits in visuospatial ability are not commonly regarded as being prominent in schizophrenia (Kolb & Whishaw, 1983). In contrast, visuospatial deficits in Huntington’s disease are consistently reported, and are marked by deficits of spatial perception (Brouwers et al., 1984) and visuospatial discrimination (Fedio et al., 1979). Further, in comparison with schizophrenia, patients with Huntington’s disease perform worse on visuospatial tasks (Goldberg et al., 1990).
Chapter 6

Experiment 1

Introduction

The primary purpose of Experiment 1 was to determine whether schizophrenic patients with and without AIMs may be differentiated on the basis of cognitive impairment, especially on tests associated with frontal lobe functions. The second purpose of Experiment 1 was to determine the extent to which the neuropsychology of AIMs schizophrenia resembles the reported descriptions of cognitive loss in Huntington's disease. More generally, the presence of AIMs in schizophrenia presents an opportunity to investigate the possible impact of basal ganglia pathology on cognitive functions (Cohen & Cohen, 1993). At the end of the Introduction, the specific research questions and hypotheses are presented.

As reviewed in the following section, there are a number of reasons for hypothesizing that cognitive impairment is more prominent in AIMs than in non-AIMs schizophrenia. First, the decline of adaptive behaviour associated with AIMs schizophrenia (Barnes et al., 1989; Davis et al., 1992; Manschreck et al., 1990), may suggest a loss of executive functioning. Second, a number of studies have reported that AIMs in schizophrenia are associated with a variety of cognitive deficits that involve memory, abstract reasoning, problem solving and verbal fluency (Brown et al., 1992; Sorokin et al., 1988; Waddington et al., 1993). Third, the psychopathology of AIMs schizophrenia may involve the disruption of the frontostriatal circuits (see Chapter 3). It has been
proposed that the disruption of these circuits is associated with a decline in both complex cognitive abilities and executive functions (Cummings, 1993).

**Rationale for Experiment 1.** In studies that have made behavioural comparisons between schizophrenic patients with and without AIMs, it has been observed that AIMs are associated with a reduction of spontaneous behaviour. These patients are characterized by increased apathy, reduced social interests, and difficulty with initiating regular activities (Davis et al., 1992; Goldberg, 1985; Rifkin et al., 1975). The impaired social functioning of schizophrenic patients with AIMs is further illustrated by the association between AIMs and negative symptoms that reflect social withdrawal, apathy, and decreased spontaneity (Barnes et al., 1989; Davis et al., 1992; Manschreck et al., 1990; Waddington et al., 1986).

The greater behavioural deficits of AIMs schizophrenic patients may represent a lack of executive control involving the planning and implementing of goal-directed activities. While impaired executive functioning may not implicate a specific area of brain dysfunction (Soblberg, Mateer, & Stuss, 1993), it has been proposed that a frontal lobe impairment underlies the inability of schizophrenic patients to effectively carry out goal-directed behaviour (Andreasen, 1989; Morihisa & Weinberger, 1984). Insofar as the behavioural deficits in AIMs schizophrenia reflect a decline of executive functioning, AIMs schizophrenic patients would be expected to have greater impairment on
neuropsychological tests that place a premium on planning, problem solving, and mental flexibility (Lezak, 1983).

In terms of the neuropsychology of AIMs schizophrenia, it has been reported that schizophrenic patients with AIMs are impaired in abstracting ability (Struve & Willner, 1983), memory (Sorokin et al., 1988), mental flexibility (Waddington et al., 1993), and complex problem solving (Brown et al., 1992). However, these results may have been compromised by several research limitations that obscure the extent to which schizophrenic patients with and without AIMs actually differ on cognitive measures. First, with the practice of employing a limited number of tests (e.g., Davis et al., 1992; Struve & Willner, 1983; Waddington et al., 1986), it is not clear whether reported deficits in AIMs schizophrenia reflect a focal or a generalized impairment. Second, there is a lack of consistent results with respect to studies reporting either the presence (Sorokin et al., 1988) or the absence (Kolakowska, 1988) of memory impairment in AIMs schizophrenia. Third, while it has been reported that AIMs schizophrenia is characterized by specific cognitive deficits suggestive of a frontal lobe impairment (Brown et al., 1992), this result has not been supported by other studies (Manschreck et al., 1990).

With these research limitations in mind, the objective of Experiment 1 was to evaluate AIMs and non-AIMs schizophrenic patients on a relatively broad range of neuropsychological tests designed to measure memory, problem solving, abstract reasoning, and visuoperceptual
abilities. By using a broad range of tests, it was hoped that Experiment 1 would help to clarify 1) whether cognitive impairment in AIMs schizophrenia is focal or generalized and 2) whether AIMs and non-AIMs schizophrenia show a different pattern of memory impairment. Further, Experiment 1 provided an opportunity to determine whether Brown et al.'s (1992) finding that schizophrenic patients with AIMs perform more poorly on tests associated with frontal lobe impairment can be replicated.

The second purpose of Experiment 1 was to assess whether the neuropsychological performance of AIMs schizophrenic patients resembles the reported pattern of cognitive impairment attributed to Huntington's disease. Based on the possibility that cognitive loss in both Huntington's disease and AIMs schizophrenia may evolve from a pathology of the caudate nucleus (Brown et al., 1992; Goldberg et al., 1990), it was proposed that the cognitive impairment characteristic of Huntington's disease would provide an useful guide for predicting the pattern of cognitive impairment present in AIMs schizophrenia. In consideration of the neuropsychology of Huntington's disease (see Chapter 5), it was proposed that AIMs schizophrenic patients would have greater deficits on test measuring verbal fluency, mental flexibility, conceptual reasoning, recall memory, and visuoperceptual abilities.

Additionally, expectations concerning the pattern of cognitive impairment of AIMs schizophrenic patients were influenced by suggestions that AIMs-related caudate nucleus pathology may disrupt the dorsolateral prefrontal circuit which connects the dorsolateral prefrontal cortex to
the dorsolateral portion of the caudate nucleus (Brown et al., 1992). Cummings (1993) proposed that in disorders of the basal ganglia, the disruption of the dorsolateral circuit produces a specific pattern of cognitive impairment which includes decreased verbal and design fluency, mental inflexibility, and poor recall memory (see Chapter 3). Although speculative, the disruption of the dorsolateral prefrontal cortex may provide the pathophysiological mechanism by which cortical function is lost in both AIMs schizophrenia (Brown et al., 1992) and Huntington's disease (Cummings, 1993).

Research Questions and Hypotheses

The specific research questions and hypotheses reflect an attempt to assimilate behavioural, neuropsychological, and neuroanatomical evidence which suggests that AIMs and non-AIMs schizophrenic patients may be differentiated on the basis of cognitive impairment.

1. Are the neuropsychological profiles of schizophrenic patients with and without AIMs distinguishable? In general, it was proposed that on tests which differentiated patient groups, AIMs schizophrenic patients would display greater cognitive deficits than non-AIMs schizophrenic patients. This prediction was based on neuropsychological evidence that AIMs in schizophrenia is associated with more pronounced cognitive deficits (Brown et al., 1992; Waddington et al., 1993;
2. Which cognitive measures best discriminate schizophrenic patients with and without AIMs? It was proposed that schizophrenic patients with AIMs would primarily have greater deficits on tests which measure verbal fluency, concept formation, and mental flexibility. This prediction was based on 1) Brown et al.'s (1992) report that more prominent deficits on tests associated with frontal lobe functions occur in AIMs schizophrenia, and 2) reports that frontal lobe impairment is a feature of Huntington’s disease (Brandt & Butters, 1986; Goldberg et al., 1990).

3. Do schizophrenic patients with and without AIMs have specific types of memory deficits? The investigation of memory deficits in AIMs schizophrenia has yielded inconsistent results. In one study, AIMs schizophrenia has been associated with impaired recall memory (Manschreck et al., 1990) while other studies have not reported recall deficits (Sorokin et al., 1988). Since the neuropsychological findings are inconsistent, the proposal that recall deficits would be more prominent in AIMs schizophrenia was based on the presence of recall deficits in Huntington’s disease (Brandt & Butters, 1986; Folstein, 1989).

4. Are visuoperceptual deficits more prominent in AIMs schizophrenia
than in non-AIMs schizophrenia? Based on the presence of visuospatial (Fedio et al., 1979) and visuoconstructional deficits (Folstein, 1989) in Huntington's disease, it was expected AIMs schizophrenic patients would have greater deficits on visuoperceptual tests which measure spatial judgments and constructional abilities.

Method

Subjects

The subjects in this study were 20 schizophrenic patients with AIMs, 20 schizophrenic patients without AIMs, and 20 non-psychiatric control subjects. Using DSM-III-R criteria, the diagnosis of schizophrenia was made by two psychiatrists within the last four years. Twenty subjects had paranoid schizophrenia, 17 subjects had undifferentiated schizophrenia and three subjects had disorganized schizophrenia. The presence of schizophrenia was confirmed, using DSM-III-R criteria, through reviewing file notes and a semi-structured interview conducted prior to testing. All schizophrenic patients were in a residual phase which is characterized by a decline of psychotic features (i.e., delusions and hallucinations). The psychiatric history and the level of neuroleptic dose of schizophrenic patients with and without AIMs are presented in the Results Section.

The presence of AIMs was assessed by the experimenter using the Abnormal Involuntary Movement Scale (Guy, 1976) which is described in the Instruments Section. Using an approach similar to that of Manschreck et al. (1990), a score of two or greater on any one scale of the
Abnormal Involuntary Movement Scale was considered evidence of AIMs. Schizophrenic patients with and without AIMs had mean scores of 3.78 and 0.20, respectively.

Schizophrenic patients were recruited from the Nova Scotia Hospital (N=20) and the Halifax County Regional Rehabilitation Centre (N=20). Patients from the Nova Scotia Hospital were outpatients with the exception of two inpatients. Outpatients typically resided in supervised group homes or lived independently in apartments. All patients from the Halifax County Regional Rehabilitation Centre were full time residents who were in a program designed to improve life and job skills. Of the 50 patients approached to take part in the study, four patients made the decision not to participate in the study. Once testing was initiated, no subjects withdrew from the study. All subjects received a 15 dollar incentive for participating in the study.

Inclusion in the study required schizophrenic patients to be able to give informed consent (see Appendix 2), to be cooperative, and to have been on neuroleptics for at least one year. Schizophrenic patients whose level of psychiatric symptoms interfered with testing (N=2), or who were diagnosed with mental retardation were excluded from the study (N=4). Schizophrenic patients with neurological disorders and/or vascular disease, as determined from file notes, were not recruited. One schizophrenic patient who had undergone a frontal lobotomy was excluded. In order to reduce the effects of age on test performance, subjects sixty years of age or older were not included in the study.
The twenty control subjects were matched to schizophrenic patients in terms of age and educational level. Schizophrenic patients with AIMs (17 males and 3 females), mean age of 33.8 years, had a mean educational level of 9.3 years. Schizophrenic patients without AIMs (14 males and 6 females), mean age 34.4 years, had a mean educational level of 9.4 years. Control subjects (11 males and 9 females), mean age 32.6 years, had a mean educational level of 10.0 years. The demographic information for patient and control groups are presented in the Results Section.

Fifteen control subjects, selected from Forsyth Adult Learning Centre (Dartmouth, Nova Scotia), were in a program devised to improve academic skills. Students with learning disabilities, as determined by school records, were not included in the study. The remaining control subjects were university students enrolled in a first year psychology course at Dalhousie University. University students received course credits while subjects from the Adult Learning Centre received a 15 dollar incentive for participating in the study.

**Instruments**

**Introduction.** The neuropsychological tests were chosen to evaluate a relatively broad range of cognitive functions (see Table 4). The tests that were selected provide information about 1) general intellectual ability, 2) language functions, 3) memory capacity, 4) visuospatial/constructional abilities, and 5) concept formation, mental flexibility, and verbal fluency. There were several reasons for assessing schizophrenic patients with and without AIMs on tests that
Table 4. Summary of Neuropsychological Tests Administered in Experiment 1.

<table>
<thead>
<tr>
<th>Name of Test</th>
<th>Basic Purpose</th>
<th>Primary Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mini-Mental Status Examination</td>
<td>-Detection of lowered cognitive ability indicative of dementia</td>
<td>Folstein, Folstein, and McHugh (1975)</td>
</tr>
<tr>
<td>Wechsler Adult Intelligence Scale-</td>
<td></td>
<td></td>
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<tr>
<td>Revised</td>
<td></td>
<td></td>
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<tr>
<td>Information</td>
<td>-Breadth of general knowledge</td>
<td>Wechsler (1981); Izak (1983); Spreen and Strauss (1991)</td>
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<tr>
<td>Digit Span</td>
<td>-Immediate auditory memory</td>
<td></td>
</tr>
<tr>
<td>Arithmetic</td>
<td>-Problem solving/arithmetic skills</td>
<td></td>
</tr>
<tr>
<td>Similarities</td>
<td>-Abstract reasoning</td>
<td></td>
</tr>
<tr>
<td>Vocabulary</td>
<td>-Verbal skills/word knowledge</td>
<td></td>
</tr>
<tr>
<td>Picture Completion</td>
<td>-Visual perceptual organization</td>
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<tr>
<td>Picture Arrangement</td>
<td>-Social judgment/sequential reasoning</td>
<td></td>
</tr>
<tr>
<td>Block Design</td>
<td>-Visuoconstructional ability</td>
<td></td>
</tr>
<tr>
<td>Digit Symbol</td>
<td>-Psychomotor ability</td>
<td></td>
</tr>
<tr>
<td>Boston Naming Test</td>
<td>-Word retrieval ability assessed in a confrontational naming context</td>
<td>Kaplan, Goodglass, and Weintraub (1978)</td>
</tr>
<tr>
<td>Semantic Verbal Fluency</td>
<td>-Word retrieval ability assessed in a controlled word association context</td>
<td>Goodglass and Kaplan (1972)</td>
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Table 4. Summary of Neuropsychological Tests Administered in Experiment 1 (continued).

<table>
<thead>
<tr>
<th>Name of Test</th>
<th>Basic Purpose</th>
<th>Primary Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FAS Verbal Fluency Test</td>
<td>-Word retrieval ability assessed in a controlled word association context.</td>
<td>Benton (1968)</td>
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<td></td>
<td>-Ability to organize and plan the spontaneous productions of words</td>
<td></td>
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<tr>
<td></td>
<td>-Ability to suppress the habitual tendency to search for words according to meaning</td>
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<td></td>
<td>-Ability to form concepts and shift cognitive sets.</td>
<td>Perret (1974)</td>
</tr>
<tr>
<td>Modified Card Sorting Test</td>
<td>-Ability to form concepts and shift cognitive sets.</td>
<td>Nelson (1976)</td>
</tr>
<tr>
<td>Wechsler Memory Scale</td>
<td>-Verbal recall memory</td>
<td>Wechsler and Stone (1973)</td>
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<tr>
<td>Logical Memory</td>
<td>-Verbal associate learning</td>
<td></td>
</tr>
<tr>
<td>Paired Associate</td>
<td>-Nonverbal recall memory</td>
<td></td>
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<tr>
<td>Visual Reproduction</td>
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<tr>
<td>Rey-Osterreith Complex Figure</td>
<td>-Nonverbal recall memory</td>
<td>Osterreith (1944)</td>
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<tr>
<td>Delayed Recall</td>
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<tr>
<td>Rey-Osterreith Complex Figure</td>
<td>-Visuospatial/constructional ability</td>
<td>Osterreith (1944)</td>
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<td>Copy</td>
<td></td>
<td>Taylor (1979)</td>
</tr>
<tr>
<td>Recognition Memory for Words</td>
<td>-Verbal recognition memory</td>
<td>Warrington (1984)</td>
</tr>
<tr>
<td>Judgment of Line Orientation Test</td>
<td>-Visuospatial ability</td>
<td>Benton, Varney and Hamsher (1978)</td>
</tr>
</tbody>
</table>
measure a variety of cognitive functions. First, most studies which have
examined cognitive differences between AIMs and non-AIMs schizophrenia,
have used a limited number of tests. Therefore, it is unclear whether
the cognitive deficits associated with AIMs schizophrenia (Manschreck et
al., 1990; Sorokin et al., 1988) reflect a generalized or a focal
cognitive disturbance. Second, the administration of a wide range of
tests is necessary for determining whether there are differences between
AIMs and non-AIMs schizophrenia in the areas of cognitive functioning
which have received little attention (e.g., language and visuoperceptual
ability) in previous studies. Third, while there have been reports of
significant differences between AIMs and non-AIMs schizophrenia, the
results of some of these studies have not been replicated (e.g., Brown
et al., 1992) while the results of other studies have been inconsistent
(Sorokin et al., 1988; Wolf et al., 1983). Therefore, by using a broad
range of tests in Experiment 1 it was hoped that a better understanding
of the cognitive abilities that are vulnerable to decline in AIMs
schizophrenia would be gained.

The Mini-Mental Status Examination (MMSE; Folstein, Folstein, &
McHugh, 1975) was administered with the purpose of excluding subjects
whose level of cognitive loss is indicative of dementia (see exclusion
criteria). The MMSE provides a quick screening of a variety of abilities
such as orientation, calculation, verbal recall, reading, writing,
naming, and copying. With a maximal score of 30, a cutoff score of 23/24
is suggestive of dementia (Grut, Fratiglioni, Viitanen, & Winblad,
The accuracy of the MMSE in detecting dementia has been investigated in a number of studies (Folstein et al., 1975; Grut et al., 1993; O’Connor, Pollitt, Hyde, Fellows, Miller, Brook, & Reiss, 1989). Grut et al. (1993), using a cutoff score of 23/24, determined that the MMSE has a 87% sensitivity and a 92% specificity in detecting dementia. However, O’Connor et al. (1989) reported that only 55% of their subjects who scored below 23 were found to be demented in follow-up assessments. This result suggests that the assessment of dementia in low scorers (< 23) on the MMSE must be confirmed through more detailed neuropsychological testing (O’Connor et al., 1989).

The Wechsler Adult Intelligence Scale-Revised (WAIS-R) was administered in order to 1) measure general intellectual ability of subjects, 2) exclude subjects whose level of intellectual functioning was within the mentally retarded range (see Subject Section), and 3) assess subjects in terms of a variety of cognitive abilities on tests of verbal and visuoperceptual functioning. In order to reduce the length of the assessment, an abbreviated WAIS-R was administered in which the Comprehension and Object Assembly subtests were excluded. These subtests were omitted because of their relatively lengthy administration times and, in the case of the Object Assembly subtest, because of its questionable reliability and its low association with overall mental ability (Lezak, 1983). The Verbal subtests consisted of Information, Digit Span, Vocabulary, Arithmetic, and Similarities. On the Information subtest, the subject is asked up to 29 factual questions which measure
breadth of knowledge rather than the ability to use or manipulate knowledge (Dean, 1983). The advantages of the Information subtest are that it is a good measure of general mental ability and that it is relatively resistant to the influences of brain damage (Lezak, 1983). A disadvantage of the subtest is that performance may be lowered by limited educational and/or cultural experiences (Dean, 1983). The Arithmetic subtest consists of 14 mathematical word problems which are presented orally. The subtest is discontinued when the subject makes four consecutive errors. The subject is asked to solve each problem without the use of pencil or paper. The 14 problems have time limits ranging from 15 to 120 seconds. For the last 4 questions bonus points are given for rapid responses. In deriving the correct solution, the subject is required to translate the word problem into the proper mathematical operation(s). In addition to arithmetic skills, this subtest is considered to measure concentration, immediate memory, and reasoning ability (Lezak, 1983). The Similarities subtest requires the subject to determine in what way two things (e.g., orange and banana) are alike. An abstract generalization earns a score of 2, while a concrete similarity earns a score of 1. This subtest is considered to be a good measure of general mental ability (Lezak, 1983). Successful performance requires the ability to form concepts (e.g., orange and banana are both fruits) and the ability to separate essential and nonessential information (Dean, 1983). An advantage of the Similarities subtest is that it is not affected by educational and/or cultural
limitations (Lezak, 1983; Zimmerman & Woo-Sam, 1973). The Vocabulary subtest measures word knowledge by asking the subject to provide definitions of words which are presented both visually and orally. Correct responses require both the recall of word meaning and the ability to express the meaning (Lezak, 1983). The Vocabulary subtest, which correlates most highly with the Full Scale IQ, has been identified as the single best measure of general mental ability (Lezak, 1983; McFie, 1975). Since good performance on this subtest is resistant to diffuse or bilateral brain damage, it is a good indicator of premorbid intelligence (Allison, Blatt, & Zimet, 1968). As with the Information subtest, successful performance may reflect enriched educational and/or cultural experiences. The Digit Span subtest consists of a Digits Forward subtest and a Digits Backward subtest. On the Digits Forward subtest, the subject is asked to repeat sequences of up to nine digits. The Digits Forward subtest is considered a measure of immediate auditory memory capacity (Golden, 1981), although poor performance may be caused by inattention and/or anxiety (Dean, 1983). On the Digits Backward subtest, the subject is required to repeat, in a reverse order, sequences of two to eight digits. The cognitive requirements of the Digit Backwards subtest goes beyond auditory memory in that effortful mental processing is needed to mentally manipulate the order of the digits. In normal subjects without brain injury, the Digits Forward subtest is typically higher than the Digits Backward subtest by approximately one digit (Costa, 1975).
The four Performance subtests employed were Picture Completion, Picture Arrangement, Block Design, and Digit Symbol. The Block Design subtest requires the subject to construct replicas of printed geometric designs from a set of either four or nine red and white blocks. The subject is asked to construct up to 10 different designs which become increasingly difficult with successive designs. The designs must be completed within time limits ranging between 60 to 120 seconds. The last seven designs receive bonus points for the rapid completion of the design. The Block Design subtest is considered to measure nonverbal reasoning ability (Zimmerman & Woo-Sam, 1973) in addition to perceptual organizational and constructional skills (Lezak, 1983). On the Picture Arrangement subtest, the subject is required to arrange a set of pictures, presented in a jumbled order, so that they tell a sensible story. The subject must arrange each of the 10 sets of pictures within time limits ranging between 60 and 120 seconds. This subtest requires the ability to develop plans of how sequential information is associated in cause and effect relationships. In addition to measuring planning and reasoning abilities, Picture Arrangement provides an indication the subject’s social knowledge. Poor performance may reflect socially inappropriate and/or bizarre thinking. Schizophrenic patients with impaired social judgment may have difficulty with successfully performing this test (Berger, Bernstein, Klein, Cohen, & Lucas, 1964). The Picture Completion subtest consists of 20 incomplete pictures of familiar objects or scenes. Within a 20 second time limit, the subject
is required to say or point to the missing element of the picture. The Picture Completion subtest measures the subjects's ability to distinguish essential and nonessential detail, and the ability to comprehend the meaning of details within the drawing (Lezak, 1983). In the Digit Symbol subtest, the subject is initially presented with a set of number-symbol pairs and is then presented with lines of numbers which are to be matched with the appropriate symbols. This subtest measures motor speed, sustained attention, visual-motor coordination, and visual associative memory (Golden, 1981).

The short form of the Boston Naming Test is sensitive to word retrieval difficulties that may occur in patients with suspected naming impairment (e.g., anomia) (Goodglass & Kaplan, 1972; Thompson & Heaton, 1989). This test requires the subject to name 30 drawings of familiar objects. When the subject is unable to give the name, a stimulus cue is given. If a correct answer is not obtained with a stimulus cue, a phonemic cue is used to prompt the correct answer. Landre et al. (1992) reported that schizophrenic patients with disturbed speech score within the impaired range on the Boston Naming Test. The Boston Naming Test has also been reported to be sensitive to word retrieval difficulties in Alzheimer's disease (Knesevich, LaBarge, & Edwards, 1986), Parkinson's disease (Matiso, Mayeaux, Rosen, & Fahn, 1982), and aphasia (Kohn & Goodglass, 1985).

On the Semantic Verbal Fluency Test, the subject is asked to name as many animals as possible in an one minute period (Goodglass & Kaplan,
In addition to measuring word retrieval ability, the Semantic Verbal Fluency Test is considered to measure the ability of the subject to access remote memory (Hart, Smith, & Swash, 1988). Performance on the Semantic Verbal Fluency Test is lowered in aphasic patients and in many brain-injured patients who are impaired in mental processing speed and in the ability to shift between different kinds of animals (e.g., domestic versus wild animals) (Goodglass & Kaplan, 1972).

The FAS Verbal Fluency Test measures the ability of the subject to spontaneously produce words belonging to specific orthographic categories (Spreen & Strauss, 1991). The subject is initially instructed to name within a one minute period as many word as possible starting with the letter "F". This task is then repeated for the letters "A" and "S". The score for the test is the total number of words for the three letters. Successful performance depends on the ability to develop strategies which permit a systematic search of words that are associated in a logical manner (Lezak, 1983). For example, the production of words beginning with "S" may be facilitated by thinking of "S" words with a common meaning (slim, skinny, and slight) (Lezak, 1983).

In Brown et al.‘s (1992) comparison of schizophrenic patients with and without AIMs, the Thurstone Word Fluency Test (Thurstone & Thurstone, 1962) was employed. This test involves writing as many words as possible beginning with the letter "s" in five minutes and then as many four-lettered words as possible starting with the letter "c" in four minutes. In Experiment 1, it was thought that the FAS Verbal
fluency test would be a less stressful measure of verbal fluency given that words are generated over a shorter period of time. A second advantage of the FAS verbal fluency test is that it has standardization samples from which age-related norms, which are useful in detecting clinical impairment, have been developed (Yeudall, Fromm, Reddon & Stefanyk, 1986).

Reduced FAS word production is reported to be present in patients with frontal lobe lesions more so than in patients with posterior lesions (Benton, 1968; Parks, Loewenstein, Dodrill, Baker, Yoshii, Chang, Emran, Apicella, Sheramata, & Duara, 1988; Pcrret, 1974). Benton (1968) reported significant differences among patients with right, left, and bilateral frontal lobe lesions. Specifically, more patients with left (70%, N=10) and bilateral (71%, N=7) frontal lobe lesions scored within the impaired range than patients with right frontal lobe lesions (38%, N=8). In a PET study by Parks et al. (1988), it was determined that poor verbal fluency is associated with left frontal lobe damage. Perret (1974) reported that patients with frontal lobe lesions have lower FAS word fluency than patients with posterior lesions. It was also reported by Perret (1974) that poorer verbal fluency performance is associated with left rather than right hemisphere damage. Further, Cavalli, Renzi, Fagliani and Vitale (1981) reported that patients with right hemisphere lesions are not impaired on FAS verbal fluency test as compared to normal control subjects.

The Modified Card Sorting Test (MCST; Nelson, 1976) was used to
assess the hypothesis that AIMs schizophrenic patients would have greater impairment on tests which measure abstract concept formation and mental flexibility. The MCST was chosen over the Wisconsin Card Sorting Test (WCST; Heaton, 1981) on the basis that the MCST has a shorter administration time and is less ambiguous in terms of card sorting criteria (Bondi, Monsch, Butters, Salmon, & Paulsen, 1993). These two advantages of the MCST are considered to make it simpler and less stressful than the WCST (Nelson, 1976). It was thought that the use of the MCST in Experiment 1 would facilitate the testing of schizophrenic patients whom may have been deterred by the complexity and length of the WCST.

The MCST requires the subject to sort a deck of 48 cards according to the shape, number, or colour of the item(s) on each card. After each card sort the subject is informed whether the response is correct. Initially, the subject is presented with four cards and asked to sort the remainder of the cards without being informed of the sorting rules. The first category selected by the subject is designated as being correct. After six consecutive correct sorts are made, the subject is told that the sorting rule has changed. The same procedure is used until the three categories are achieved. For the remainder of the test the subject must repeat the order which they chose for the first three categories. The test is completed when the subject achieves six categories or when all the 48 cards have been sorted.

Test performance was assessed by the number of perseverative
errors, the percent of perseverative errors, and the number of categories achieved. Poor performance on these measures reflects an inability to form concepts and to change response sets. A perseverative error occurs when a card is incorrectly sorted to the same attribute of the previous card; whereas non-perseverative errors occurs when the sort is incorrect, but does not share the same attribute as the previous card. The percent of perseverative errors is a ratio of perseverative errors to total number of errors multiplied by 100.

The sensitivity of the MCST to frontal lobe lesions was examined by Nelson (1976). In a sample composed of 25 frontal lobe patients and 28 non-frontal lobe patients, Nelson (1976) reported that patients with frontal lobe lesions made a greater percentage of perseverative errors and completed fewer categories than patients with posterior lesions. It was determined by Nelson (1976) that a percentage of perseverative errors of 50 or greater correctly classified approximately one third of the patients with frontal lobe lesions and misclassified five percent of the patients without frontal lobe lesions. The finding that approximately two-thirds of the patients with frontal lobe lesions did not perform within the impaired range suggests that Nelson’s (1976) cutoff score is limited in its sensitivity to frontal lobe pathology. More recently, Broek et al. (1993) reported that the MCST has poor sensitivity to frontal lobe pathology in that MCST performance did not discriminate between frontal and non-frontal lobe patients. The percentage of patients with bilateral frontal lobe lesions (44.4 %) and
patients with posterior lesions (41.65%) scoring above Nelson's (1976) impairment cutoff did not differ.

The specificity of the MCST to frontal lobe lesions has also been called into question (Bondi et al., 1993). Specifically, reports that MCST performance is lowered in patients with diffuse cerebral pathology (i.e., Alzheimer's dementia) and in patients with posterior lesions indicate that poor MCST performance is not specific to frontal lobe pathology (Bondi et al., 1993; Broek et al., 1993; Hart, Kwentus, Wade, & Taylor, 1988). In light of the questionable sensitivity and specificity of the MCST to frontal lobe pathology, caution must be used in attributing poor performance on the MCST to a frontal lobe pathology.

It should be noted that the sensitivity and specificity of the WCST have also been questioned on the basis of reports that poor WCST performance does not occur exclusively in patients with frontal lobe lesions (Anderson, Damasio, Jones, & Tranel, 1991; Hermann, Wyler, & Richey, 1988). However, it is important to emphasize that card sorting performance provides valuable information about the ability of the subject to form abstract concepts and shift cognitive sets, irrespective of the lesion site (Heaton, 1981).

Several studies have compared the memory performance of schizophrenic patients with and without AIMs (Mylobodsky et al., 1985; Sorokin et al., 1988). The results of these studies are not consistent. One study has reported that AIMs are associated with recognition and recall memory deficits (Sorokin et al., 1988) while another study has
reported that only recall memory deficits are associated with AIMs schizophrenia (Manschreck et al., 1990). Another study has reported an absence of memory deficits in AIMs schizophrenia (Wolf et al., 1983). In Experiment 1, schizophrenic patient groups were assessed on verbal and non-verbal tests of recall and recognition memory with the purpose of clarifying whether a specific pattern of memory deficits distinguishes schizophrenic patients with and without AIMs.

Three tests of memory were employed in Experiment 1: the Wechsler Memory Scale, the Recognition Memory Tests for Faces and Words (Warrington, 1984), and the Rey-Osterreith Complex Figure Delayed Recall (Taylor, 1979). The Wechsler Memory Scale (Form I), composed of seven tests, was administered to measure a broad range of visual and verbal memory abilities. The Wechsler Memory Scale exists in two forms. Form I was employed in Experiment 1 on the basis that the standardization of Form II is considered inadequate (Lezak, 1983) and, consequently, Form I rather than Form II is typically used for research purposes (Spreen & Strauss, 1991). The first test, Personal and Current Information, consists of six questions which ask the subject’s age and the identity of current political leaders. On the second test, Orientation, the subject is asked five questions about time and place. The first two tests provide an indication of mental status and are useful in the screening of subjects with dementia (Wechsler & Stone, 1973). The third test, Mental Control, measures attention and concentration by asking the subject to count backwards from 20, recite the alphabet, and count by
multiples of three. On the **Logical Memory** test, the subject is required to repeat two orally presented stories, each consisting of a few sentences. Its primary purpose is to measure immediate verbal recall memory. The fifth test, **Memory Span** is the same as the Digit Span test previously described. On the **Visual Reproduction** test, the subject is asked to draw from memory a set of four geometric drawings after viewing each drawing for ten seconds. The forth drawing consists of two designs, both of which the subject must draw from memory. This test is primarily a measure of immediate visual recall memory. The last test, **Associate Learning**, is a paired word-learning task composed of easy and difficult associations. The easy associations (e.g., apple-fruit) require the recall of over-learned associations while difficult associations (e.g., school-grocery) involve the learning and recall of novel information (Wechsler & Stone, 1973).

In order to measure verbal and nonverbal recognition memory, the **Recognition Memory Tests for Faces and Words** was administered. An advantage of this test is that it has been standardized across different age ranges; therefore, age-related norms have been determined (Warrington, 1984). For both words and faces, 50 items are presented individually for approximately three seconds. To ensure that the test material is attended to, the subject is asked to state whether each item is pleasurable. After the administration of the 50 items, each presented item is again shown with a distractor item. The subject is required to name or point to the item that was originally presented.
The Rey-Osterreith Complex Figure (Taylor, 1979) is administered in two stages. In the copy stage, the subject is initially presented with a Rey-Osterreith Complex Figure with the instruction to copy the drawing as carefully as possible. After a 45 minute delay (delayed stage), interpolated with other tests, the subject is asked without warning to reproduce the drawing as carefully and as completely as possible. The delayed reproduction of the Rey-Osterreith Complex Figure is a measure of non-verbal recall memory (Lezak, 1983). The copy of the Rey-Osterreith Complex Figure measures planning and problem solving strategies as well as visuoperceptual organizational and constructional skills (Spreen & Strauss, 1991). Scoring of the Rey-Osterreith Complex Figure is described by Lezak (1983). Briefly, the 18 elements of the Complex Figure are scored in terms of the accuracy and the placement of the elements. With a maximum score of 36 points, each element receives a score ranging from .5 to 2 points. In addition to the objective scoring criteria, qualitative interpretation is based on the manner by which the Rey-Osterreith Complex Figure is reproduced. A distinction in the types of copying errors has been made between patients with anterior and posterior lesions (Kolb & Whishaw, 1990; Lezak, 1983). Errors that involve the failure to develop systematic planning strategies are typical of frontal lobe impairment while distorted reproductions with poor spatial organization are associated with posterior lesions (Spreen & Strauss, 1991). Poor performance in recalling the figure is associated with right rather than left temporal lobe lesions (Taylor, 1979).
The last category of tests addressed the hypothesis that visuoperceptual deficits are more prominent in AIMs schizophrenia than in non-AIMs schizophrenia. This hypothesis was primarily based on the possibility that Huntington’s disease and AIMs schizophrenia have similar visuoperceptual deficits (see rationale of Experiment 1). The two aspects of visual perception investigated were visuospatial and visuoconstructional perception. Visuospatial perception refers to the process of judging the spatial characteristic of a visual stimulus (Benton, 1985). Deficits in visuospatial perception involve difficulties in locating points in space and in determining directional and distance relationships (Benton, 1985). Visuoconstructional ability refers to the process of organizing elements of an object so that they form correct spatial relationships (Benton, 1985). Assembling objects from component parts or drawing a design are examples of tasks involving visuoconstructional abilities. The copy of the Complex Rey-Osterrieth Figure (Rey, 1941; Osterrieth, 1944), and the Block Design test from the WAIS-R were used to assess visuoconstructional abilities. These tests were previously described in this section.

The Judgment of Line Orientation Test (Benton, Varney, & Hamsher, 1978) was administered in order to measure visuospatial ability (Benton, 1985; Benton et al., 1978; Benton, Hamsher, Varney, & Spreen, 1983). In addition to a relatively brief administration time (approximately 10 minutes), the Judgment of Line Orientation Test has the advantage of a standardized sample from which age-related norms have been developed. On
this test, the subject is presented with items composed of two lines with different angular orientations. The subject is required to judge the angle of orientation of both lines by matching them with an array of 11 lines arranged in orientations ranging between 0 and 180 degrees. The test consists of the 30 items, which are preceded by five practice items. In the standardization of the Judgment of Line Orientation Test, Benton et al. (1978) determined that 95 percent of the 137 normal control subjects received a score of 19 or greater. Based on standardization data, scores ranging between 15-18 are considered to be indicative of moderate to mild deficits.

Poor performance on the Judgment of Line Orientation Test has been associated with brain damage (Benton et al., 1978). In a sample of patients with left (N=50) and right (N=50) hemisphere lesions, 46 percent of the right hemisphere patients scored in the defective range while only 10 percent of the left hemisphere patients had defective performances. In the right hemisphere patient group, 55 percent of the patients with posterior lesions (N=18) had defective scores while all of the patients with prefrontal lobe lesions (N=8) scored within the normal range. Sixty-three percent of an intermediate group (N=19) with more extensive lesions involving prefrontal and perirolandic (frontoparietal and anterior temporal) areas had defective performances (Benton et al., 1978).

Psychiatric Status. The Brief Psychiatric Rating Scale (Overall & Gordam, 1968) was used to assess the degree of psychiatric symptoms.
This scale consists of 16 items each of which measures a specific type of symptom. The items are rated on a one to seven scale where one indicates the absence of a symptom and seven indicates the presence of an extremely severe symptom. Included in the scale are symptoms indicative of positive symptoms (e.g., hallucinatory behaviour and unusual thought content) and negative symptoms (blunted affect, and emotional withdrawal).

Movements. The Abnormal Involuntary Movement Scale (Guy, 1976) assesses movement disturbances in a variety of areas such as facial and oral movements, trunk movements, and extremity movements. Each area of movement disturbance is rated on a one to four point scale. Included in the assessment procedure are overall judgment of the degree of incapacitation, the awareness of the subject of abnormal movements, and the severity of movements.

Procedure

Testing procedure. The testing session began with a presentation of the informed consent form which stressed 1) that subject information was confidential, 2) that participation was voluntary and 3) that participation was independent of treatment. The informed consent form was accompanied by further explanation of the rights of subjects to ensure that the informed consent form was fully understood. The results were not discussed with the subjects or the referral source, in order to ensure that information gathered would not be misinterpreted.
Once the informed consent was received, a semi-structured interview was conducted in which demographic information, mental status, and psychiatric history was obtained. The administration of the tests required approximately two hours to complete. Rest periods were provided hourly or when the subject requested a break from testing. An attempt was made to complete the test battery in a single day; however, for four subjects the tests were administered over a two day period. At the end of the testing session any questions arising from the study were addressed.

Data collection. The subjects were recruited and tested between September of 1990 and May 1992. The initial suitability of a subject with schizophrenia was determined through a meeting with the attending psychiatrist/psychologist (i.e., the psychiatrist/psychologist most familiar with a given patient), case conferences, and team meetings. In these meetings the patient was discussed in terms of the requirements of the study. The suitability of a patient was further assessed during a semi-structured interview with the patient in which both the the mental status and the willingness of the patient was determined. For all the patients, the neuropsychological battery was administered by the same experimenter. It was not possible to administer the tests blind to the three treatment conditions due to the overt nature of AIMs.

Results

General Considerations

A general problem with previous neuropsychological investigations
of AIMs and non-AIMs schizophrenia (e.g., Manschreck et al., 1990) is their reliance on univariate analysis that becomes statistically inappropriate when numerous comparisons are involved (Keppel, 1982). Specifically, the use of multiple comparisons, without the utilization of corrective procedures, increases the probability of a making Type I error; the false rejection of the null hypothesis that a significant difference does not exist between treatment conditions. The result of making Type I errors, referred to as familywise error rate, is the heightened probability of incorrectly detecting significant differences between treatment conditions.

A second difficulty with univariate analysis of multiple comparisons is that the relationship among the dependent measures is not usually examined. Although orthogonal comparisons is a statistical requirement of univariate analysis, this requirement is often violated, especially when measures are repeatedly derived from the same subjects (Hair, Anderson, Tatham, & Grablowsky, 1979). As with the accumulation of familywise error, the inability to analyze interrelationships among variables may lead to systematic biases which confound the interpretability of the data. In certain instances, when dependent measures are correlated and familywise error accumulates, the use of multivariate and univariate techniques may produce divergent statistical implications (Green, 1978). For example, while univariate analysis may indicate that treatment conditions do not differ in terms of a set of dependent measures, multivariate analysis may suggest that an overall
difference does exist. Alternatively, as a result of familywise error, univariate analysis may identify a number of significant treatment differences which may be found to be non-significant with a multivariate analysis.

In an effort to avoid the problems associated with familywise error and the interdependence of dependent measures, a variety of multivariate and univariate statistical techniques were employed in the present experiment. The multivariate analysis employed consisted of two statistically complimentary procedures, multivariate analysis of variance (MANOVA) and multiple discriminant analysis.

MANOVA, which is a logical extension of univariate analysis of variance (ANOVA), is statistically suited to the simultaneous analysis of multiple measures derived from one or more treatment conditions. Instead of examining individual dependent measures, MANOVA transforms dependent measures to composite scores based on variance-covariance matrices of the variables. These composite scores are referred to as group centroids or vectors, and represent the extent to which treatment conditions differ in terms of variance and covariance of the dependent measures. The tests, which assess the significance of differences between treatment conditions (e.g. Wilks' lambda), examine the distinctiveness of the group centroids derived from the variance/covariance matrices.

When two or more treatment conditions are considered, discriminant analysis is used to identify the pattern of distinctiveness among the
conditions (Hair et al., 1979). Discriminant analysis is also used, as a method of post hoc analysis, to determine the contribution of each individual dependent measure to the distinctiveness of the treatment conditions. As in MANOVA, the specific objective of discriminant analysis is to determine whether the levels of a treatment condition are distinct in terms of a set of dependent measures. To estimate the distinctiveness of a treatment condition linear combinations of variables are formed in such a way so as to maximize the variance between-groups while minimizing within-group variance. That is, by mathematically combining variables the dimensions which separate the groups are identified. The linear combinations of dependent measures are referred to as discriminant functions.

The significance of a discriminant function is determined by examining the discriminant scores of individuals in the different treatment conditions. A discriminant score is calculated for each individual case based on the weight assigned to each variable and the score of the individual case on each variable. The mean discriminant score of all individuals in a treatment condition defines the group centroid. Statistical tests of the significance of a function are based upon the divergence of the group centroids. The Wilks' lambda statistic may be used to determine the significance of the separation between the centroids associated with a specific function. The validation of a significant function may be obtained by the implementation of classification procedures which compare predicted group membership with
the actual group membership. The process of correctly classifying the individuals used to derive a discriminant function provides a further indication of the discriminating ability of the function. The classification procedures are essential to the interpretation of a significant function in that with sufficiently large sample sizes a significant function may be produced even though the group centroids are equal.

When only two treatment conditions are compared, one discriminant function is computed. However, when more than two treatment conditions exist, it may be necessary to compute a variety of functions with the maximum number being one less than the number of treatment conditions. A discriminant function may be conceptualized as an axis in geometric space in which group centroids are maximally separated. When further discriminant functions are warranted, separation of the groups occurs in an orthogonal direction as compared to the previous functions. As with multiple regression, the function may be characterized or named on the basis of the variables which make the greatest contribution to that function.

The determination of which variables to include in the analysis may be based on both direct and step wise procedures. In the direct method, discriminant analysis is based upon the simultaneous entry of all dependent measures. This method is appropriate when a global assessment of all the variables is desired. The step wise method entails the entry of variables individually until a function with adequate discriminating
power is achieved. The entry order of variables is determined by the size of the multivariate F-ratio for each variable. Once a variable is selected, the next variable entered is the one which is able to maximally enhance the ratio of between-group and within-group variances. The variables which are entered in the initial stages of analysis may be removed if they no longer provide significant discriminating power. The advantage of the step wise procedure is that a greater separation of groups may be achieved when variables which do not enhance the distinctiveness of the groups are not included in the analysis. Therefore, step wise procedures often require fewer variables to determine whether treatment groups are significantly distinguishable.

In the formation of a discriminant function, each measure is assigned a coefficient which indicates its contribution to the function. When a coefficient is standardized so it has a mean of zero and a standard deviation of one, it provides a measure of the significance of the variable to the function. Standardized discriminant function coefficients are analogous to beta weights of multiple regression and, therefore, must be used cautiously. Specifically, standardized discriminant function coefficients are difficult to accurately interpret in that when many variables are included in the analysis, the relative contribution of each variable is unstable (Dillon, 1984) due to possible intercorrelations among variables. For example, if a correlation between two variables exists, the value of the coefficient may be diminished by the division of the coefficient between the two variables. A more
A reliable measure of the discriminating value of a variable is the structured coefficient which is derived from the correlation of the variables with the function. Structured coefficients account for the shared variance between the variables and the function; consequently, they are more stable than standardized discriminant function coefficients.

The use of multivariate statistics was supplemented with parametric and non-parametric statistics. Analysis of variance (ANOVA) was used to examine demographic information and test instruments. Familywise error rate was corrected with the Modified Bonferroni test procedure (Keppel, 1982) which reduces the rejection interval of the null hypothesis and, thereby, reduces the probability of making Type I errors. The Bonferroni correction yielded an adjusted alpha of .001 based on original alpha of .05. The acceptance, however, of such a stringent alpha would increase the likelihood of making Type II errors involving the incorrect acceptance of the null hypothesis. Therefore, as a compromise between Type I and Type II errors the alpha level was set at .005. The Tukey test, which also corrects for familywise error, was used in post hoc comparisons involving the three subject groups. To examine non-parametric data, Chi-square analysis was employed. To further examine the relationship between medication and test variables, multiple correlations were conducted.
Demographic and Clinical Treatment Factors.

Univariate ANOVAs did not identify significant differences among the three subject groups in term of age ($F(2, 57)=0.16, NS$), and level of education ($F(2,57)=0.31, NS$). Chi-square analysis also indicated that significant differences did not exist in the distribution of sex ($\chi^2(2, N=60)=4.23, NS$) and handedness ($\chi^2(2, N=60)=0.022), NS$) among the three subject groups. The majority of subjects, however, were right handed (81.7%). The means and standard deviations for these variables are presented in Table 5.

Schizophrenic patients with and without AIMs were compared on clinical and treatment characteristics which have a potential to influence the performance on neuropsychological tests (see Table 6). There was not a significant difference in the daily neuroleptic exposure (chlorpromazine equivalence), assessed over a one year period, between AIMs ($M=444.0$ mg/day) and non-AIMs ($M=363.8$ mg/day) schizophrenic patients ($F(1, 38)=0.56, NS$). The age at first hospitalization of AIMs ($M=22.0$ years) and non-AIMs ($M=19.5$ years) schizophrenic patients did not significantly differ ($F(1, 38)=1.72, NS$). The number of hospital admissions of AIMs ($M=8.9$) and non-AIMs ($M=11.0$) schizophrenic patients not differ significantly ($F(1, 38)=0.75, NS$). The duration of hospitalization of AIMs ($M=12.3$ months) and non-AIMs ($M=15.1$ months) schizophrenic patients did not significantly differ ($F(1, 38)=.64, NS$).

A mean was obtained for each subject on the 18 items of the Brief Psychiatric Rating Scale in order to obtain a overall index of
Table 5
Demographic Characteristics of Schizophrenic Patients With and Without Abnormal Involuntary Movements (AIMs) and Control Subjects

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>AIMs Schizophrenic Patients (n=20)</th>
<th>Non-AIMS Schizophrenic Patients (n=20)</th>
<th>Control Subjects (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
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<tr>
<td>Mean</td>
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<td>34.4</td>
<td>32.6</td>
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<tr>
<td>SD</td>
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<td>11.9</td>
<td>9.1</td>
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<tr>
<td>Education (years)</td>
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<td>Mean</td>
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<td>9.4</td>
<td>10.0</td>
</tr>
<tr>
<td>SD</td>
<td>4.2</td>
<td>2.9</td>
<td>2.0</td>
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<td>16</td>
<td>17</td>
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<tr>
<td>Left</td>
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Table 6  
Means, Standard Deviations, F-Values, and F-Probabilities for Psychiatric History Variables of Schizophrenic Subjects With and Without Abnormal Involuntary Movements (AIMs)

<table>
<thead>
<tr>
<th>Variables</th>
<th>AIMs (n=20)</th>
<th>Non-AIMs (n=20)</th>
<th>F-Values</th>
<th>F-Prob.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorpromazine equivalence (mean mg/day)</td>
<td>444.0</td>
<td>363.8</td>
<td>0.56</td>
<td>.459</td>
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<tr>
<td>Age at first Hospitalization</td>
<td>22.0</td>
<td>19.5</td>
<td>1.72</td>
<td>.197</td>
</tr>
<tr>
<td>Number of Admissions</td>
<td>8.9</td>
<td>11.0</td>
<td>0.75</td>
<td>.391</td>
</tr>
<tr>
<td>Total Length of Hospitalizations (months)</td>
<td>12.3</td>
<td>15.1</td>
<td>0.64</td>
<td>.429</td>
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</table>
psychiatric well being. The level of psychiatric impairment, derived from the Brief Psychiatric Rating Scale, was not significantly different between AIMs (M=14.65) and non-AIMs (M=16.30) schizophrenic patient groups (F(1, 38)= 0.80, NS). The rating of schizophrenic patients on the Brief Psychiatric Rating Scale indicates a mild level of psychiatric symptoms.

Based on the lack of difference with respect to the number of hospital admission and duration of hospitalization, it appears that both schizophrenic patient groups have experienced a similar pattern of institutionalization. The lack of difference on the Brief Psychiatric Rating Scale suggests that the schizophrenic patient groups cannot be differentiated on their general level of psychopathology.

A considerable range of chlorpromazine exposure existed (12 mg/day to 1400 mg/day). In order to examine whether a relationship exists between neuroleptic exposure and performance on the test battery, multiple correlations were conducted. The results of this analysis, which are presented in Table 7, show that neuroleptic exposure is not significantly correlated with any of the test results. These non-significant correlations suggest that differences in neuroleptic exposure had little influence on the test performance of schizophrenic patients. Also, the possibility that neuroleptics differentially affected AIMs and non-AIMs schizophrenic patients is diminished by a lack of a group difference with respect to the level of neuroleptic exposure.
Table 7.
Multiple Correlations between level of Mean Daily Neuroleptic Exposure (Chlorpromazine Equivalence) and Test Results

<table>
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<th>Neuroleptic Exposure</th>
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<th>Significance</th>
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<td>Wechsler Adult Intelligence Scale-Revised</td>
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<tr>
<td>Full Scale</td>
<td>-0.001</td>
<td>0.997</td>
<td></td>
</tr>
<tr>
<td>Performance Scale</td>
<td>0.133</td>
<td>0.412</td>
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</tr>
<tr>
<td>Verbal Scale</td>
<td>-0.061</td>
<td>0.709</td>
<td></td>
</tr>
<tr>
<td>Information</td>
<td>0.024</td>
<td>0.884</td>
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</tr>
<tr>
<td>Digit Span</td>
<td>-0.164</td>
<td>0.311</td>
<td></td>
</tr>
<tr>
<td>Arithmetic</td>
<td>0.106</td>
<td>0.538</td>
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</tr>
<tr>
<td>Similarities</td>
<td>-0.125</td>
<td>0.442</td>
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<tr>
<td>Vocabulary</td>
<td>0.138</td>
<td>0.394</td>
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</tr>
<tr>
<td>Picture Completion</td>
<td>-0.153</td>
<td>0.352</td>
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<tr>
<td>Picture Arrangement</td>
<td>0.021</td>
<td>0.900</td>
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<td>Block Design</td>
<td>0.174</td>
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<tr>
<td>Digit Symbol</td>
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<td>0.400</td>
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<td>Wechsler Memory Scale</td>
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<tr>
<td>Memory Quotient</td>
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<td>0.998</td>
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</tr>
<tr>
<td>Orientation</td>
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<td>0.517</td>
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<tr>
<td>Information</td>
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<td>0.416</td>
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<tr>
<td>Logical Memory</td>
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<td>Paired Associate</td>
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<td>Visual Reproduction</td>
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<td>Rey-Osterreith Complex Figure Delayed Recall</td>
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<td>Recognition Memory Test for Faces</td>
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<td>0.646</td>
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<tr>
<td>Recognition Memory Test for Words</td>
<td>0.123</td>
<td>0.450</td>
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</tr>
<tr>
<td>Judgment of Line Orientation Test</td>
<td>0.209</td>
<td>0.196</td>
<td></td>
</tr>
<tr>
<td>Modified Card Sorting Test</td>
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<tr>
<td>Perseverative errors</td>
<td>0.154</td>
<td>0.342</td>
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<tr>
<td>Percent of Perseverative Errors</td>
<td>0.263</td>
<td>0.101</td>
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<tr>
<td>Categories Achieved</td>
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<td>-0.023</td>
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<tr>
<td>Semantic Verbal Fluency Test</td>
<td>-0.001</td>
<td>0.995</td>
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</table>
MMSE and WAIS-R.

The three treatment groups differed on the MMSE ($F(2, 57) = 6.61, p < 0.005$). AIMs schizophrenic patients ($M=27.15$) and non-AIMs schizophrenic patients ($M=27.25$) scored significantly lower (Tukey-HSD critical $I=3.42, p < .05$) than control subjects ($M=29.10$) while a significant difference did not occur between schizophrenic patient groups. The performance of the schizophrenic patient groups was not in the impaired range and, therefore, this difference is not a source of concern.

In terms of WAIS-R results, there is little clinical variation (less than 10 scaled point difference) between Performance and Verbal Scales for each subject group. Figures 4 and 5 report means and confidence intervals of Verbal and Performance Scales. There is also little clinical difference in variation (i.e., less than three scaled point difference between any two subtests) among the subtests for the three subject groups. Statistical analysis showed that the three subjects groups were similar in intellectual functioning without significant differences on the WAIS-R Full Scale ($F(2,57)=1.97$, NS), Performance Scale ($F(2, 57)=3.68$, NS) or Verbal Scale ($F(2,57)=0.42$, NS). The mean Full Scale WAIS-R performance of each subject group was within the average range of intellectual functioning (90 to 109) with no subject scoring below the low average range (80 to 89) of intellectual functioning.

Only minimal differences existed among the three subject groups on the WAIS-R subtests. The only significant difference was detected on
Figure 3. Means and 95% confidence intervals for Full, Verbal, and Performance Scales of Wechsler Adult Intelligence Scale-Revised.
Figure 4. Means and 95% confident intervals for Verbal (above) and Performance (below) Tests of Wechsler Adult Intelligence Test Revised.
Digit Symbol ($F(2, 57)=5.76, p < .005$) in which AIMs schizophrenic patients ($M=8.36$) performed significantly lower than control subjects ($M=10.20$) (Tukey HSD critical $t=3.40, p < .05$). In summary, the performance between and within subject groups in terms of 1) the average Full Scale results, 2) the consistency between Verbal and Performance Scales, and 3) the lack of variation among the WAIS-R subtests indicates that significant differences on the neuropsychological battery were not an artifact of skewed intellectual impairment.

Research Hypotheses

Univariate Analysis. To a certain extent, the results of the univariate analysis indicated a differentiation between the control group and the two schizophrenic patient groups. See Table 8 for the means and standard deviations and Table 9 for the levels of significance of ANOVAs. In the majority of the tests in which a significant difference was found, post hoc analysis indicated that the difference in test performance existed between the control group and both groups of schizophrenic patients. Specifically, the tests in this category primarily provided an index of verbal fluency (FAS and Semantic Verbal Fluency Tests) and memory (Memory Quotient, Visual Reproduction, Verbal Associate Learning, and Rey-Osterreith Complex Figure Delayed Recall).

In a second category of test results, only schizophrenic patients with AIMs performed below control subjects. Control subjects performed significantly better than AIMs schizophrenic patients on the Mental
Table 8
Means and Standard Deviations (SD) of the Three Subject Groups on the Test Battery.

<table>
<thead>
<tr>
<th>Tests</th>
<th>AIMS Schizophrenic Patients (N=20)</th>
<th>Non-AIMS Schizophrenic Patients (N=20)</th>
<th>Control Subjects (N=20)</th>
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<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
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<td>91.85</td>
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<tr>
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Table 9.
F Values and F-Probabilities of ANOVAs Comparing Control Subjects with Schizophrenic Patients With and Without Abnormal Involuntary Movements (AIMs)

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<tr>
<th>Variables</th>
<th>F-Values</th>
<th>F-Probabilities</th>
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<td>.000 *@</td>
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<td>Perseverative errors</td>
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<tr>
<td>Percent of Perseverative Errors</td>
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<td>.000 *</td>
</tr>
<tr>
<td>Categories Achieved</td>
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<td>.000 *</td>
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</tr>
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<td>FAS Verbal Fluency Test</td>
<td>16.25</td>
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<td><strong>Semantic Verbal Fluency Test</strong></td>
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<td>Boston Naming Test</td>
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<td>.000 **#</td>
</tr>
<tr>
<td><strong>Boston Naming Test</strong></td>
<td>10.43</td>
<td>.001 *</td>
</tr>
</tbody>
</table>

* AIMs and control subjects significantly different
# Both Non-AIMs and AIMs schizophrenic patients significantly different from control subjects
@ AIMs and Non-AIMs schizophrenic patients significantly different
Control Test of WMS, the MCST (categories achieved, number of perseverative errors, and percentage of perseverative errors), and the Boston Naming Test.

Direct evidence of a neuropsychological difference between AIMs and non-AIMs schizophrenic groups was provided only by the Judgment of Line Orientation Test \( (F(2, 57) = 7.78, p < .005) \). Specifically, AIMs schizophrenic patients performed significantly lower than non AIMs schizophrenic patients (Tukey-HSD critical \( I_{-3.40}, p < .05 \)).

**Multivariate Analysis.**

In general, the results of the multivariate analysis indicated a differentiation between the control group and the two schizophrenic patient groups. As an initial step in the analysis, a MANOVA was conducted to determine whether the three subject groups are differentiated by their pattern of performance on the test battery. An examination of all the tests in the battery identified a significant separation of the group centroids \( (\text{Wilks' lambda} (34, 80) = 0.25, p < .001) \). Thus, the three subject groups are distinguishable by their pattern of performance on the test battery. The importance of the discriminant function was indicated by an eigenvalue of 2.42 which explained 93.42 percent of the total variance associated with the scores on the various tests of the battery. The associated power of the Wilks' lambda test of significance was 0.99 suggesting that there is a relatively low probability of making a Type II error.

In the next step of the examination of group differences, a
multiple discriminant analysis was conducted to identify the pattern of differentiation among the three groups. At this stage of analysis, the test variables were entered in a direct fashion in order to determine the relative importance of all the tests in the differentiation of the three subject groups. While two discriminant functions were statistically possible in the three group comparison, only one of the functions was significant (Wilks' lambda (34, 80) = 0.25, p < .001). As with the initial MANOVA, this function had a eigenvalue of 2.40 which accounted for 93.4 percent of the variance. The canonical correlation of .84 indicates that 70.56 percent of the variance of the tests variables is explained by the difference among the subject groups. The non-significant second function (Wilks' lambda (16, 80), p < .05) accounted for only 6.65 percent of the variance associated with the tests battery and, therefore, has little importance to the separation of the three groups.

The finding that only one of the functions was significant suggests that the differentiation involves a single division among the three groups. An examination of the scatterplot (displayed in Figure 5) of the first and second functions indicates that the differentiation is characterized by a separation on the first function between schizophrenic patients (with and without AIMs) and the control subjects. That is, the group centroid difference of 0.748 between AIMs and non-AIMs schizophrenic patients is relatively minor compared to the significant group centroid differences between control subjects and AIMs.
Figure 5. Three-group scatter plot of the first discriminant analysis depicting group centroids of AIMs (C1), non-AIMs (C2), and control (C3) subjects.
schizophrenic patients (3.74), and control subjects and non-AIMs schizophrenia patients (2.99). While not significant, the second discriminant function appeared to differentiate schizophrenic patients with AIMs from both the control and non-AIMs schizophrenic subjects.

The classification analysis supports the importance of the first discriminant function in its separation of the three groups. The overall number of subjects correctly classified was 85 percent indicating that the discriminant function is capable of classifying the majority of the subjects regardless of actual group membership. As displayed in Table 10, while 100 percent of the control subjects were correctly classified, a lower classification success was obtained for the schizophrenic patients with AIMs (70 percent) and the schizophrenic patients without AIMs (85 percent). It appears, therefore, that the first discriminant function reflects a degree of overlap between schizophrenic patients with and without AIMs while the control subjects were identified as a distinct group.

The structured coefficients were used to determine the relative significance of the tests to the discriminant function. The five most important discriminating variables and their structured correlations are Semantic Verbal Fluency Test, 0.519; FAS Verbal Fluency test, 0.484; Memory Quotient (WMS), 0.470; Verbal Associate Learning subtest (WMS) 0.411, MCST (perseverative error number) 0.378. The structured correlations of the remaining variables are listed in Table 11.
Table 10. Classification Results of the First Discriminant Analysis

<table>
<thead>
<tr>
<th>Actual Group Membership</th>
<th>Predicted Group Membership</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AIMs</td>
</tr>
<tr>
<td></td>
<td>Non-AIMs</td>
</tr>
<tr>
<td></td>
<td>Controls Subjects</td>
</tr>
<tr>
<td>AIMs Schizophrenics</td>
<td>70 %</td>
</tr>
<tr>
<td>Patients</td>
<td>20 %</td>
</tr>
<tr>
<td>10 %</td>
<td></td>
</tr>
<tr>
<td>Non-AIMs Schizophrenic</td>
<td>15 %</td>
</tr>
<tr>
<td>Patients</td>
<td>85 %</td>
</tr>
<tr>
<td>0 %</td>
<td></td>
</tr>
<tr>
<td>Control Subjects</td>
<td>0 %</td>
</tr>
<tr>
<td>0 %</td>
<td></td>
</tr>
<tr>
<td>100 %</td>
<td></td>
</tr>
</tbody>
</table>
Table 11.
Structured Correlations of Test Variables for Function 1 and Function 2
of the First Discriminant Analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Function 1</th>
<th>Function 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wechsler Adult Intelligence Scale-Revised</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full Scale</td>
<td>0.16409</td>
<td>-0.15926</td>
</tr>
<tr>
<td>Performance Scale</td>
<td>0.21676</td>
<td>-0.28778</td>
</tr>
<tr>
<td>Verbal Scale</td>
<td>0.07754</td>
<td>-0.02568</td>
</tr>
<tr>
<td>Wechsler Memory Scale</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Memory Quotient</td>
<td>0.46590</td>
<td>-0.16602</td>
</tr>
<tr>
<td>Logical Memory</td>
<td>0.27565</td>
<td>-0.17401</td>
</tr>
<tr>
<td>Paired Associate</td>
<td>0.41103</td>
<td>-0.16895</td>
</tr>
<tr>
<td>Visual Reproduction</td>
<td>0.31181</td>
<td>-0.17407</td>
</tr>
<tr>
<td>Mental Control</td>
<td>0.13765</td>
<td>-0.04321</td>
</tr>
<tr>
<td>Rey-Osterreith Complex Figure Copy</td>
<td>0.05506</td>
<td>0.21927</td>
</tr>
<tr>
<td>Rey-Osterreith Complex Figure Delayed Recall</td>
<td>0.22737</td>
<td>0.13568</td>
</tr>
<tr>
<td>Recognition Memory Test for Faces</td>
<td>0.20194</td>
<td>0.25448</td>
</tr>
<tr>
<td>Recognition Memory Test for Words</td>
<td>0.10897</td>
<td>-0.26307</td>
</tr>
<tr>
<td>Judgement of Line Orientation Test</td>
<td>0.32032</td>
<td>0.38213</td>
</tr>
<tr>
<td>Modified Card Sorting Test</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perseverative errors</td>
<td>0.37388</td>
<td>-0.07295</td>
</tr>
<tr>
<td>Percent of Perseverative Errors</td>
<td>-0.30964</td>
<td>-0.03891</td>
</tr>
<tr>
<td>Categories Achieved</td>
<td>0.37067</td>
<td>-0.17436</td>
</tr>
<tr>
<td>FAS Verbal Fluency Test</td>
<td>0.48382</td>
<td>-0.17277</td>
</tr>
<tr>
<td>Semantic Verbal Fluency Test</td>
<td>0.51942</td>
<td>-0.04523</td>
</tr>
<tr>
<td>Boston Naming Test</td>
<td>0.14591</td>
<td>0.03871</td>
</tr>
</tbody>
</table>
Differentiation of Schizophrenic Subject Groups. The possibility of a secondary separation between AIMs and non-AIMs schizophrenic patients provided impetus for the next stage of analysis involving the examination of only the two schizophrenic patient groups. A probable consequence of the predominant differentiation of control subjects from the two schizophrenic groups is that more subtle differentiation of AIMs and non-AIMs schizophrenic groups may have remained statistically unimportant. In order to more carefully examine potential differences between AIMs and non-AIMs schizophrenic groups, a second discriminant analysis was conducted to determine whether these two groups may be differentiated when the performance of the control subjects is not considered. The variables in the second discriminant analysis were entered in a stepwise manner in an effort to examine group difference in terms of only the tests with the greatest discriminating ability. The inclusion of variables with minimal discriminating ability may actually obscure group differences which would otherwise be identified with the inclusion of only the variables which have the greatest amount of discriminating power (Klecka, 1975).

The discriminant analysis produced a significant function (Wilks' lambda = 0.63, p < 0.005). The canonical correlation of .61 indicates that 37.2 percent of variance associated with the tests is attributable to the difference between the two schizophrenic subject groups. The importance of the discrimination function is supported by the classification results. Specifically, 77.5% of all subjects were
correctly classified with 75 percent of non-AIMs schizophrenic patients and 80 percent of AIMS schizophrenic patients being correctly classified.

The variables that contributed to the discriminant equation were 1) Judgment of Line Orientation Test, 2) categories on the MCST, 3) Mental Control of WMS, and 4) Semantic Verbal Fluency Test. These tests provided a significant level of discrimination. The relative importance of the tests entered in the step wise procedure, as indicated by the structured coefficients, are Mental Control (0.57), Judgment of Line Orientation Test (0.53), Semantic Verbal Fluency (0.50) and Categories achieved on MCST (0.46).

Discussion

The neuropsychological performances of the three subject groups differed in specific areas of cognitive functioning. As indicated by multivariate analysis, schizophrenic patients with and without AIMs were differentiated on certain neuropsychological measures of verbal fluency (Semantic Verbal Fluency Test), visuospatial ability (Judgment of Line Orientation Test), and concept formation (categories achieved on the MCST). Univariate analysis revealed that AIMs schizophrenic patients performed significantly more poorly than non-AIMs schizophrenic patients on only the Judgment of Line Orientation Test. The neuropsychological performances of schizophrenic patients (both AIMs and non-AIMs) and control subjects will be discussed first, in order to present the overall cognitive profile of the schizophrenic patient group. This
discussion provides the context for presenting the areas of cognitive functioning that differentiated AIMs and non-AIMs schizophrenic patients. The implications of Experiment 1 are discussed in further detail in the General Discussion Section at the end of Experiment 2.

Schizophrenic and Control Groups. In Experiment 1, univariate analysis indicated that both of the schizophrenic patient groups had significantly poorer performance than that of the control subject group on measures of verbal fluency (FAS and Semantic Verbal Fluency Tests), memory (Visual Reproductions and Paired Associate Learning subtests of the WMS, and Rey-Osterreith Complex Figure Delayed Recall). The results of the multivariate analysis also differentiated schizophrenic patients and control subjects on measures of verbal fluency (FAS and Semantic Verbal Fluency Tests), memory (Paired Associate Learning subtest of the WMS) and, additionally, problem solving (MCST; categories achieved and number of perseverative errors).

An important aspect of the differentiation of the schizophrenic patients and the control subjects was the significantly lower performance of schizophrenic patients on tests of recall memory (Rey-Osterreith Complex Figure Delayed Recall as well as the Visual Reproductions and Paired Associate Learning subtests of the WMS). In contrast, schizophrenic patients and control subjects did not significantly differ on the Recognition Memory Test for Faces and Words.

The finding that schizophrenic patients had poorer performance on recall than recognition memory tests is consistent with other studies.
which have reported that schizophrenic patients are impaired on recall, but not on recognition memory tests (Beatty, Jocic, Monson, & Staton, 1993; Kolb & Whishaw, 1983; Goldberg & Weinberger, 1988; Koh et al., 1978). Reports that recognition memory is normal and that impaired recall is improved with retrieval cues (Sengel & Lovallo, 1983) suggests that poor recall memory in schizophrenia stems from a retrieval deficit rather than an inability to encode or store information (Beatty et al., 1993).

The results of both the univariate and multivariate analyses indicated that schizophrenic patients generated significantly fewer words than control subjects on both the FAS and Semantic Verbal Fluency Tests. While poor performance on the Semantic Verbal Fluency Test is suggestive of a word retrieval deficit (Goodglass & Kaplan, 1972; Hart et al., 1988), poor performance on the FAS Verbal Fluency Test indicates an impaired ability to effectively search for words in an organized, systematic manner (Lezak, 1983). The lower verbal fluency performance of schizophrenic patients is consistent with previous studies which have examined verbal and non-verbal fluency (e.g., Design Fluency Tests; Jones-Gotman & Milner, 1977) in schizophrenia (Beatty et al., 1993; Gruzelier et al., 1988; Kolb & Whishaw, 1983; Liddle & Morris, 1991).

In another area of cognitive functioning, both the number of perseverative errors and the categories achieved on the MCST made an important contribution to the differentiation of schizophrenic patients and control subjects. The MCST results suggest that schizophrenic
patients had a greater difficulty than control subjects in abstracting the correct sorting principle, shifting mental sets, and using feedback information to alter incorrect response strategies. The results of the MCST are in agreement with previous studies reporting that poor performance on card sorting tests is prominent in schizophrenia (Berman et al., 1988; Braff et al., 1991; Kolb & Whishaw, 1983; Liddle & Morris, 1991; Weinberger et al., 1986). As discussed in the General Discussion Section (page 177), the poor performance of schizophrenic patients on card sorting tests as well as verbal fluency tests is generally considered as evidence of a frontal lobe dysfunction (Kolb & Whishaw, 1983; Liddle & Morris, 1991; Weinberger et al., 1986). This interpretation is primarily based on evidence that card sorting tests (i.e., WCST) and verbal fluency tests (i.e., FAS Verbal Fluency test) are sensitive to lesions of the frontal lobe (Beatty et al., 1993).

In terms of the overall test battery, the matching of subjects on important demographic characteristics reduced the possibility that the lower performance of schizophrenic patients reflected differences in age and education. Further, since schizophrenic patients were equivalent to control subjects on the WAIS-R, it is improbable that the poorer performance of schizophrenic patients on tests of memory, verbal fluency, and problem solving is attributable to generalized cognitive deterioration.

Schizophrenic Patient Groups. The first research question was concerned with whether the neuropsychological performances of
schizophrenic patients with and without AIMs may be differentiated. It was determined that the second discriminant analysis, which was based on the two schizophrenic patient groups, distinguished AIMs and non-AIMs schizophrenic patients. The discriminating ability of the discriminant function was reflected in the classification results in which 75 percent of the non-AIMs schizophrenic patients and 80 percent of the AIMs schizophrenic patients were classified correctly. However, the classification results of the discriminant analysis should be interpreted with caution. The classification rate achieved may have been inflated because the same subjects were used to both derive the function and to test its predictive accuracy (Huberty, 1984). The cross-validation of the discriminant function on an independent sample of AIMs and non-AIMs schizophrenic patients would have provided a more accurate indication of its ability to correctly classify subjects (Green, 1978).

In the discriminant analysis, schizophrenic patients with and without AIMs were differentiated on measures of concept formation, (categories achieved on the MCST), visuospatial ability (Judgment of Line Orientation Test), verbal fluency (Semantic Verbal Fluency Test) and attention and concentration (Mental Control subtest of the WMS). In terms of univariate analysis, AIMs schizophrenic patients performed significantly lower than non-AIMs schizophrenic patients only on the Judgment of Line Orientation Test. As assessed by the mean performance, only schizophrenic patients with AIMs performed more poorly than control
subjects on some tests of concept formation and mental flexibility (categories achieved and percentage of perseverative errors on the MCST), attention and concentration (Mental Control subtest of the WMS), and word naming ability (Boston Naming Test).

The second research question addressed the possibility that AIMs schizophrenic patients would have greater impairment on tests that measure verbal fluency, mental flexibility, and concept formation. As indicated by univariate analysis, schizophrenic patients with and without AIMs did not significantly differ on the FAS Verbal Fluency Test or the MCST (categories achieved, percent of perseverative errors, and number of perseverative errors). These results are in contrast to Brown et al. (1992) who attributed the poorer performance of AIMs schizophrenic patients on verbal fluency and card sorting tests to a frontal lobe dysfunction that may be mediated by the basal ganglia pathology that underlies AIMs (see Chapter 5).

The failure of Experiment 1 to replicate the findings of Brown et al. (1992) may be explained by differences in the schizophrenic patient samples employed in the two studies. In Experiment 1, younger (mean age 33.8 years) AIMs schizophrenic patients with intact intellectual abilities and mild levels of AIMs (mean AIMs rating 3.8) were tested. In comparison, Brown et al. (1992) employed older (mean age 58.1 years) AIMs schizophrenic patients who were described as being extremely deteriorated, and as having a high degree of movement abnormalities (mean AIMs rating 9.6). It is conceivable that AIMs-related cognitive
impairment is more prominent in older AIMs schizophrenic patients who may have more severe movement disturbances. This view is supported by the fact that AIMs-related cognitive impairment is typically reported in studies using older (mean age > 50 years) AIMs schizophrenic patients (Myslobodsky et al., 1985; Waddington et al., 1986), but not in studies employing younger AIMs schizophrenic patients (Gureje, 1988; Kolakowska et al., 1986). Additionally, reports that the severity of AIMs in schizophrenia is positively correlated with cognitive impairment and behavioural deficits (Davis et al., 1992; Wade et al., 1987), suggest that cognitive impairment would be greater in older schizophrenic patients who frequently have more severe movement disturbances (Gerlach & Casey, 1988).

The third research question was concerned with whether AIMs and non-AIMs schizophrenic patients would be differentiated on memory tests. The prediction that recall memory deficits would be more evident than recognition memory deficits in AIMs schizophrenia was not supported in Experiment 1. Schizophrenic patients with and without AIMs did not differ on either recall or recognition memory tests. Specifically, neither univariate nor multivariate analyses differentiated schizophrenic patient groups in terms of the WMS subtests, the Rey Osterreith Complex Figure Delayed Recall, and the Recognition Memory Test for Faces and Words.

In previous studies, reports of greater memory deficits in AIMs schizophrenia have been inconsistent (Sorokin et al., 1988; Wolf et al.,
The results of Experiment 1 are in agreement with Wolf et al.'s (1983) study which failed to differentiate schizophrenic patients with and without AIMs on the basis of the WMS. However, the results of Experiment 1 are in conflict with Sorokin et al. (1988) who reported that AIMs schizophrenic patients had poorer performance than non-AIMs schizophrenic patients on a non-verbal recall memory test (Benton Visual Retention Test). However, Sorokin et al.'s (1988) finding that AIMs schizophrenic patients are impaired on the Benton Visual Retention Test may be questioned on the basis that schizophrenic patients were not equated in terms of intellectual abilities. Because poor performance on the Benton Visual Retention Test is associated with lower intellectual abilities (Benton, 1974), the degree to which Sorokin et al.'s (1988) results reflect group differences in intellectual abilities was not determined.

The fourth research question dealt with whether visuoperceptual deficits are more prominent in AIMs than in non-AIMs schizophrenia. Both univariate and multivariate analyses indicated that the performance of schizophrenic patients with AIMs on the Judgment of Line Orientation Test was significantly lower than that of schizophrenic patients without AIMs. Moreover, the mean performance of only the AIMs schizophrenic patients on the Judgment of Line Orientation Test fell within Benton et al.'s (1978) criterion for impairment (total score ≤ 18). The impairment of the AIMs schizophrenic patient group on the Judgment of Line Orientation Test is further indicated by the finding that a higher
The proportion of AIMs schizophrenic patients (60 percent) than non-AIMs schizophrenic patients (15 percent) scored within the impaired range. The results of the Judgment of Line Orientation Test suggest that AIMs in schizophrenia are associated with a visuospatial deficit. The assessment of a visuospatial deficit in AIMs schizophrenia has not been reported previously and, therefore, replication in future studies is required to validate this finding.

The relatively high discriminating ability of the Semantic Verbal Fluency Test was not predicted. The contribution that the Semantic Verbal Fluency Test made to the second discriminant function suggests that AIMs schizophrenic patients had a greater difficulty in generating words that are confined by a semantic category. Poor performance on the Semantic Verbal Fluency may indicate a word finding difficulty that is characteristic of anomia (Goodglass & Kaplan, 1972). Additionally, a deficit in language functioning is suggested by the finding that only AIMs schizophrenic patients performed significantly lower than control subjects on the Boston Naming Test, a test that is sensitive to naming deficits (Goodglass & Kaplan, 1972; Lezak, 1983). The observation that schizophrenic patients frequently made word substitution errors (e.g., atlas for globe) indicates that their errors represent an inability to correctly name a given object, rather than a perceptual deficit (e.g., the misidentification of the side of the harmonica as a row of windows on a bus; Lezak, 1983). In general, the results of the Semantic Verbal Fluency Test and the Boston Naming Test are consistent with reports that
the disturbed speech of schizophrenic patients reflects, in part, aphasic-like disturbances (Cadet, Rickler, & Weinberger, 1986; Landre et al., 1992).

Another unexpected finding was that the Mental Control subtest of the WMS contributed to the differentiation of the schizophrenic patient groups. This result appears to reflect the lower scores of AIMs schizophrenic patients on tasks requiring the rapid performance of over-learned mental exercises (e.g., reciting the alphabet). The differentiation of the schizophrenic groups may be a result of the increased distractability of the AIMs schizophrenic patients causing the occurrence of more frequent errors and slowed performance time. Alternatively, poor performance on the Mental Control Test, in which bonus points are given for quick performance, may actually reflect slowed cognitive processes of AIMs schizophrenic patients.

The second purpose of Experiment 1 was to investigate the extent to which the cognitive profile of AIMs schizophrenia resembles previous reports of cognitive impairment in Huntington's disease. The poorer performance of schizophrenic patients with AIMs on the Judgment of Line Orientation Test may indicate a visuospatial deficit that resembles visuospatial discrimination and directional judgment deficits that occur in Huntington's disease (Fedio et al., 1979). However, because Huntington's disease patients have not been tested on the Judgment of Line Orientation Test in previous studies, the possibility that AIMs schizophrenic patients and Huntington's disease patients have a similar
impairment involving visuospatial ability must be considered to be speculative.

Evidence that the neuropsychological profile of AIMs schizophrenia resembles that of Huntington’s disease was not obtained in terms of recall memory or problem-solving. While Huntington’s disease patients typically have poor recall memory in the context of normal recognition memory (Brandt & Butters, 1986), schizophrenic patients with and without AIMs were not differentiated on either recall or recognition memory tests. Additionally, schizophrenic patients with and without AIMs did not significantly differ on tests that assess problem-solving ability (MCST, Rey-Osterreith Complex Figure Copy, Block Design subtest of WAIS-R).

The comparison of the neuropsychological profiles of patients with AIMs schizophrenia and Huntington’s disease should be considered in the context that the schizophrenic patients in Experiment 1 and the Huntington’s disease patients employed in previous studies may differ in characteristics (e.g., education, psychiatric symptoms, and mental deterioration) that could potentially alter the performance of neuropsychological tests. Thus, the comparison of schizophrenic patients and Huntington’s disease patients who have been matched on demographic and psychiatric variables, would provide a more accurate assessment of the neuropsychological similarities and differences between these two patient groups.

As discussed in Chapter 5, recent neuropsychological studies have
emphasized that deficits in problem solving and mental flexibility are prominent in both AIMs schizophrenia (Brown et al., 1992; Waddington et al., 1993; Wade et al., 1987) and Huntington's disease (Weinberger et al., 1988). To investigate problem solving abilities of patients with Huntington's disease and schizophrenia (AIMs and non-AIMs), simplified and standard versions of the MCST were administered in Experiment 2. In previous studies, the extent to which schizophrenic patients were impaired on card sorting tests has been investigated by providing detailed instructions which explain sorting and shifting rules (Goldberg et al., 1987; Stuss, Benson, Kaplan, Weir, Naeser, Lieberman, & Ferrill, 1983). In Experiment 2, the purpose of administering the MCST with detailed instructions was to determine whether schizophrenic patients with and without AIMs and Huntington's disease patients have a similar degree of impairment on the MCST.
Experiment 2 was undertaken to directly investigate the MCST performances of patients with Huntington’s disease and schizophrenia (AIMs and non-AIMs). The purpose of this comparison was to determine the extent to which these patient groups are impaired on the MCST by examining whether improvement occurs when card sorting and shifting rules are explained. It was proposed that patients with Huntington’s disease and AIMs schizophrenia would have a similar level of impairment on the MCST on the basis that deficits in problem solving, conceptual reasoning and mental flexibility in both of these patient groups may evolve from a pathology of the basal ganglia (Brown et al., 1992; Goldberg et al., 1990; Waddington et al., 1993).

The poor performance of schizophrenic patients on card sorting tests (i.e., WCST and MCST) is frequently interpreted to support the hypothesis of a frontal lobe dysfunction in schizophrenia (Liddle & Morris, 1991; Weinberger, 1988). In recent studies, the WCST has been employed with the purpose of determining whether the poor performance of schizophrenic patients reflects behavioural deficits (e.g., inattention), rather than a cognitive dysfunction (Goldberg et al., 1987; Goldman et al., 1992). Stuss et al. (1983) administered the WCST to prefrontal leucotomized schizophrenic patients and normal control subjects with standard WCST instructions initially and then with instructions which explained card sorting and shifting rules. Although the performance of the control subjects improved with detailed
instructions, the poorer performance of schizophrenic patients was not altered. This result was interpreted as indicating that the WCST impairment of schizophrenic patients was not due to a poor understanding of the requirements of the test. Similarly, Goldberg et al. (1987) reported that the impaired WCST performance of chronic schizophrenic patients was not improved when instructions that explained card sorting and shifting rules were provided. The lack of improvement on the WCST was substantiated on all test measures (i.e., percent of perseverative errors, percent of correct responses, and number of categories achieved). The lack of improvement by schizophrenic patients was interpreted by Goldberg et al., (1987) as evidence of a frontal lobe deficit.

In contrast, Goldman et al. (1992) reported that schizophrenic patients improved on the WCST when they were informed of the card sorting and shifting rules. However, the finding that schizophrenic patients did not improve on the number of categories achieved, suggests that the detailed instructions did not alter the ability of the schizophrenic patients to abstract the correct sorting principles. It should be noted that Goldman et al. (1992) observed WCST improvement in schizophrenic patients with mild cognitive impairment, as determined by a mental status examination. In comparison, Goldberg et al. (1987) tested chronic schizophrenic patients who had a high probability of being cognitively impaired.

While it has been reported that the WCST performance of schizophrenic
patients with mild psychiatric symptomatology improves when detailed instructions are provided (Goldman et al., 1992), the question of whether schizophrenic patients with and without AIMs differ in their ability to improve on card sorting tests has not been investigated previously. Because AIMs in schizophrenia have been associated with deficits in problem-solving and mental flexibility (Brown et al., 1992; Waddington et al., 1993; Wade et al., 1987), it was expected that AIMs schizophrenic patients would have a greater difficulty than non-AIMs schizophrenic patients in using detailed instructions to improve their MCST performance.

In order to examine the MCST performances of schizophrenic patients with and without AIMs and Huntington's disease patients, the MCST was administered in Experiment 2 on three occasions. Initially, the MCST was administered with standard instructions (Nelson, 1976). On the second MCST administration, detailed instructions which explained the categories and sorting principles were provided. The purpose of second administration was to determine whether knowledge of how to perform the test would lead to improved performance. The third administration was given with the standard instructions in order to determine whether improved performance may be sustained with the discontinuation of the detailed instructions.

Method

Subjects

Seventy subjects were assessed: 20 schizophrenic patients with AIMs,
20 schizophrenic patients without AIMs, 10 Huntington's disease patients, and 20 normal control subjects. The schizophrenic and control subjects were drawn from the subject groups of Experiment 1. The diagnosis of Huntington's disease was made by a neurologist based upon a positive family history and the presence of involuntary choreiform movements. Additionally, diagnosis of Huntington's disease was supported by Predictive Genetic Testing which was administered by the Atlantic Research Centre (Halifax, Nova Scotia). Inclusion in the study required subjects to be able to give informed consent (see Appendix 2) and to be cooperative. Subjects with neurological disorders (other than Huntington's disease) and/or vascular disease, as determined from file notes, were not recruited.

Materials

The WAIS-R was administered to assess intellectual functioning (see Experiment 1). The MCST was initially administered with the standard instructions as described by Nelson (1976). Subjects then performed the MCST with instructions which specified the three sorting categories and category shifting rules. The third administration was accompanied with the standard instructions of the first administration. The MCST administrations were separated by one-half hour periods. During these periods other tests from the protocol of Experiment 1 were administered.

Procedure

After informed consent was obtained, subjects were interviewed in order to obtain demographic information. Following the interview, the
three MCST presentations were administered along with the tests used in Experiment 1. The assessment procedure required approximately 1 1/2 hours. The subjects were then debriefed as to the purpose of the study.

**Design and Statistical Analysis**

Experiment 2 had a 4 (subject groups) x 3 (instructions) mixed factorial design. The four levels of the between-subject factor, subject groups, consisted of Huntington’s disease patients, schizophrenic patients with AIMs, schizophrenic patients without AIMs, and control subjects. The three administrations of the instructions (i.e., standard instructions, detailed instructions, and standard instructions) composed the three levels of the within subject factor.

In order to examine the influence that the instructions had on the MCST performance of the four subject groups, analysis of variance (ANOVA) was conducted on the three dependent measures (number of categories achieved, number of perseverative errors, and the percentage of perseverative errors). To correct for familywise Type I error a Bonferroni adjustment placed the cut off alpha level at 0.01 for ANOVA’s. Interaction contrast analysis was used to examine significant interactions. Additionally, in the case of significant interactions the change in MCST performance over the three presentations was examined for each subject group. The Tukey Test was used to analyze post hoc comparisons of differences between levels of the treatment conditions.
Results

Demographic Information

The four subject groups differed in age ($F(3, 65)=6.24, p < .001$). Huntington's disease subjects ($M=48.66$) were significantly older than schizophrenic patients with AIMs ($M=34.35$), schizophrenic patients without AIMs ($M=30.60$), and control subjects ($M=32.65$) (Tukey HSD critical $\alpha = 3.73, p < .05$). The subjects groups did not differ in the number of years of education ($F(3, 65)=2.76, \text{NS}$) or intelligence as measured by the Full Scale of the WAIS-R ($F(3, 65)=1.27, \text{NS}$).

Categories Achieved

The 4 x 3 mixed design ANOVA conducted on the number of categories achieved identified a main effect for subject groups ($F(3,65)=10.62, p < .001$). As displayed in Figure 6, the number of categories achieved by schizophrenic patients with AIMs ($M=3.45$) was fewer than the number achieved by control subjects ($M=5.70$) (Tukey critical $\alpha = 2.12, p < .05$). The number of categories achieved by non-AIMs schizophrenic patients ($M=5.01$) did not significantly differ from AIMs schizophrenic patients (Tukey critical $\alpha = 2.12, \text{NS}$). There was a main effect for instructions ($F(2, 64)=15.19, p < .001$) in which the number of categories achieved ($M=5.09$) on the third presentation was significantly higher than the first and second presentations (Tukey critical $\alpha = 0.66, p < .05$). There was not a significant difference between the first and second presentations (Tukey critical $\alpha = 0.66, \text{NS}$). The interaction was also not significant ($F(6, 130)=2.76, \text{NS}$).
Figure 6. Mean number of categories achieved by the subject groups on the Modified Card Sorting Test as a function of the three administrations.
Number of Perseverative Errors

The results of the 4 x 3 ANOVA conducted on the number of perseverative errors made revealed a main effect for subject groups ($F(3,65)=9.49$, $p < .001$). Schizophrenic patients with AIMs ($M=11.98$) made significantly more perseverative errors than control subjects ($M=1.27$) (Tukey critical $I=10.74$, $p < .05$). Schizophrenic patients with and without ($M=4.70$) AIMs did not significantly differ in terms of the number of perseverative errors (Tukey critical $I=10.74$, NS). The main effect for instructions was significant ($F(2, 130)=21.30$, $p < .01$). Fewer perseverative errors were made on the third presentation ($M=8.94$) than on the second presentation ($M=5.70$) and the first presentation ($M=4.33$) (Tukey critical $I=2.71$, $p < .05$).

The interaction was also significant ($F(6, 130)=3.18$, $p < .001$). An examination of the interaction contrast effects indicated that AIMs schizophrenic patients improved more than the control subjects in terms of number of perseverative errors made on the second and third set of instructions ($F(1,38)=14.01$, $p < .001$). As displayed in Figure 7, it appears that control subjects may have reached a ceiling effect with a mean number of perseverative errors of 0.45 and 0.50 on the second and third presentations, respectively. AIMs schizophrenic patients made fewer perseverative errors on the third presentation ($M=8.85$) as compared to the second presentation ($M=12.85$).

The examination of performance across the three presentations detected changes in the number of perseverative errors for AIMs.
Figure 7. Mean number of perseverative errors made by subject groups on the Modified Card Sorting Test as a function of the three administrations.
schizophrenic patients ($F(2, 18)=8.07, p < .01$), non-AIMs schizophrenic patients ($F(2, 18) = 10.47, p < .01$) and control subjects ($F(2, 18)=4.89, p < .01$). The performance of the MCST significantly improved on the second presentation for the control subjects (Tukey critical $I=1.66, p < .05$) and non-AIMs schizophrenic patients (Tukey critical $I=2.67, p < .05$) while AIMs schizophrenic patients improved on the third presentation (Tukey critical $I=3.48, p < .05$). An improvement in the performance of Huntington's disease patients was not observed ($F(2, 7)=1.27, NS$).

**Percent of Perseverative Errors**

The 4 x 3 ANOVA for percent of perseverative errors yielded a significant main effect for subject groups ($F(3, 65)=13.96, p < .001$) in which AIMs schizophrenic patients ($M=54.11$) had a significantly greater percent of perseverative errors than control subjects ($M=13.95$) (Tukey critical $I=32.63, p < .05$) (see Figure 8). The percent of perseverative errors made by non-AIMs schizophrenic patients ($M=34.65$) did not significantly differ from AIMs schizophrenic patients (Tukey critical $I=32.63, NS$). The percentage of subjects within Nelson's impairment range (percent of perseverative errors > 50) is reported in Table 12. The main effect for instructions was significant ($F(2, 130)=11.11, p < .001$). The percent of perseverative errors was greater on the first presentation ($M=40.85$) than the third presentation ($M=28.34$). The interaction between subjects groups and instructions for the percent of perseverative errors was not significant ($F(6,130)=2.04, p > .01$).
Figure 8. Mean percent of perseverative errors made by subject groups on the Modified Card Sorting Test as a function of the three administrations.
Table 12.  
Percentage of subjects performing within Nelson's criterion for impairment (percent of perseverative errors > 50) on the MCST.

<table>
<thead>
<tr>
<th>Subject Groups</th>
<th>First</th>
<th>Second</th>
<th>Third</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-AIMs Schizophrenic Patients (N=20)</td>
<td>40%</td>
<td>15%</td>
<td>15%</td>
</tr>
<tr>
<td>AIMs Schizophrenic Patients (N=20)</td>
<td>70%</td>
<td>75%</td>
<td>50%</td>
</tr>
<tr>
<td>Control Subjects (N=20)</td>
<td>15%</td>
<td>5%</td>
<td>0%</td>
</tr>
<tr>
<td>Huntington's Disease Patients (N=10)</td>
<td>40%</td>
<td>40%</td>
<td>40%</td>
</tr>
</tbody>
</table>
Discussion

The results of Experiment 2 indicate that schizophrenic patients were able to improve on the MCST (number of perseverative errors) when informed of the card sorting and shifting rules. Additionally, schizophrenic patients without AIMs and control subjects improved on the second MCST administration while schizophrenic patients with AIMs did not improve until the third administration. The performance of Huntington’s disease patients remained stable over the three MCST administrations. This interaction between subject groups and the three MCST administrations was detected only for the number of perseverative errors dependent variable. Although the interactions for the number of categories achieved and the percent of perseverative errors were suggested by the results, they failed to reach our relatively conservative criterion for statistical significance ($p < .01$).

The absence of improvement in the Huntington’s disease group is consistent with reports that poor card sorting performance is a characteristic of Huntington’s disease patients (Brandt & Butters, 1986; Goldberg et al., 1990). The improvement of both groups of schizophrenic patients is in contrast to the MCST performance of the Huntington’s disease group. The results of Experiment 2, therefore, did not support the proposed similarity between patients with AIMs schizophrenia and Huntington’s disease. The finding that the Huntington’s disease group was not within the clinically impaired range indicates that their MCST performance does not necessarily reflect a deficit in problem-solving.
Rather, the difficulty that the Huntington’s disease group had in improving over the three presentations may indicate a poor ability to use instructional information to correct response strategies.

For the control subjects and the non-AIMs schizophrenic patients, significant improvement occurred in association with the more detailed instructions given on the second administration. In contrast, the AIMs schizophrenic patients did not display a significant improvement until the third administration; however, on average their performance remained within Nelson’s (1976) criterion for impairment. Moreover, on the third administration more AIMs schizophrenic patients (50%) scored in the impaired range than non-AIMs schizophrenic patients (15%).

The finding that the schizophrenic patients with AIMs did not improve until the third administration suggests that the detailed instructions did not immediately affect their performance on the second presentation. Further, while the performances of the schizophrenic patient groups were equivalent on the first presentation, significant differences were observed between these groups on the second and third presentations. These differences appear to be a result of the greater improvement of the non-AIMs schizophrenic patients.

The absence of improvement when more detailed instructions were administered may indicate that the AIMs schizophrenic patients had a greater degree of difficulty performing the MCST than non-AIMs schizophrenic patients and control subjects. Additionally, the impairment of the AIMs schizophrenic patients on the MCST is suggested
by the finding that the overall MCST performance of the AIMs schizophrenia group was significantly lower than that of the control subjects. The lower performance of the AIMs schizophrenic patients was consistent for the number of categories achieved, the number of perseverative errors, and the percent of perseverative errors.

The improvement of the non-AIMs schizophrenic patient group on the MCST is consistent with a number of studies which have reported that the card sorting performance of schizophrenic patients is improved by the use of more detailed instructions and/or monetary reinforcements (Goldman et al., 1992; Green, Satz, Ganzell, & Vaclav, 1992; Summerfelt Alphs, Funderburk, Strauss, & Wagman, 1991). The improvement of schizophrenic patients without AIMs suggests that their ability to abstract concepts and/or inhibit previous response tendencies was not impaired to the degree that it precluded the learning of the test.

The poorer MCST performance of AIMs schizophrenic patients is in agreement with Goldberg et al.'s (1987) study which reported that schizophrenic patients have difficulty in improving on their card sorting performance when sorting and shifting rules are explained. Because the MCST performance of the AIMs schizophrenic patients did not improve with the detailed instructions, their poorer performance cannot be attributed to a lack of knowledge of the three sorting criteria or the shifting rules. Rather, the difficulty that the schizophrenic patients with AIMs had in improving on the MCST may be related to a failure to use the information provided by the detailed instructions to
change their card sorting strategies.

The impairment of schizophrenic patients on card sorting tests has been reported to be more prominent in schizophrenic patients with chronic symptomatology (Braff et al., 1991; Gruzelier et al., 1988; Goldberg et al., 1987). However, given that the schizophrenic patient groups in the present research project did not differ on the Brief Psychiatric Rating Scale or other indicators of chronicity (e.g., length of illness and number of hospitalizations), the poorer MCST performance of the AIMs schizophrenic patients does not appear to be related to the presence of more chronic symptomatology.

A limitation of repeatedly administering the MCST or the WCST is that it does not address the possibility that poor card sorting performance may primarily reflect a low level of motivation to perform the test. Additionally, the repeated administration of the MCST/WCST may negatively alter card sorting performance by contributing to fatigue and boredom factors. Summerfelt et al. (1991) addressed the role that motivation has on the WCST performance of schizophrenic patients. In their study, standard instructions were combined with a monetary reinforcement (i.e., 10 cents per correct response). The main result was that the performance of schizophrenic patients significantly improved (categories achieved) when the monetary reinforcement was presented. The implication of this finding is that poor WCST performance may be partially a consequence of low motivation. The WCST performance of the schizophrenic patients, however, remained in the impaired range,
possibly indicating that they were not able to learn the abstract sorting principles needed for the successful performance of the test (Goldberg et al., 1991).

In summary, the MCST performances of schizophrenic patients with and without AIMs did not resemble that of Huntington's disease patients. Although AIMs and non-AIMs schizophrenic patients improved on the MCST (number of perseverative errors), the performance of Huntington's disease patients remained stable when the detailed instructions were provided. Schizophrenic patients with AIMs appeared to have greater difficulties in using the detailed instruction to improve their performance on the MCST as indicated by their lack of improvement when sorting and shifting rules were explained on the second administration.

**General Discussion**

The results of the present research may be summarized by three key findings. First, schizophrenic patients (both AIMs and non-AIMs) and control subjects were differentiated by tests of verbal fluency (FAS Verbal Fluency Test), problem solving (MCST; categories achieved and number of perseverative errors) and recall memory (Rey-Osterreith Complex Figure Delayed Recall, Paired Associate Learning and Visual Reproductions subtests of WMS). Second, our hypothesis that AIMs schizophrenic patients would perform significantly more poorly than non-AIMs schizophrenic patients on tests that measure problem solving, verbal fluency (i.e., FAS Verbal Fluency Test) and recall memory was not supported. Third, the results of the present study do not support our
hypothesis that AIMs in schizophrenia would be associated with neuropsychological deficits that resemble that of Huntington's disease. As discussed, this lack of similarity between AIMs schizophrenia and Huntington's disease questions Cummings' (1993) proposal that AIMs in psychiatric disorders are associated with impaired verbal fluency, mental flexibility, problem solving, and recall memory.

The results of the present research are consistent with previous studies which have identified neuropsychological deficits on card sorting, verbal fluency, and recall memory tests (Beatty et al., 1993; Berman et al., 1988; Kolb & Whishaw, 1983; Liddle & Morris, 1991; Weinberger et al., 1986). The impairment of schizophrenic patients on tests of problem solving and verbal fluency has been interpreted as indicating a disturbance of frontal lobe functioning (Kolb & Whishaw, 1983; Moses, 1983; Taylor & Abrams, 1984; Weinberger et al., 1986). Additionally, Goldberg et al. (1988) proposed that a frontal lobe dysfunction underlies the recall memory deficits in schizophrenia on the basis that patients with frontal lobe lesions also have recall deficits in the presence of normal recognition memory. Alternatively, the recall memory deficits in schizophrenia may represent an amnesic-like disorder that arises from a temporal lobe dysfunction (Beatty et al., 1993; Kolb & Whishaw, 1983). This view is supported by the finding that temporal lobe pathology occurs in a certain proportion of schizophrenic patients (Crow, 1990).

In Experiment 1, the poorer MCST performance of schizophrenic
patients does not necessarily implicate a frontal lobe impairment given Broek et al.'s (1993) report that the MCST has a poor sensitivity to frontal lobe pathology. However, because schizophrenic patients appeared to have difficulty in initiating, planning, and altering responses on certain measures of verbal fluency, problem solving and recall memory, an impairment of executive functioning may underlie their poorer neuropsychological performance. On the FAS Verbal Fluency Test, poor performance of schizophrenic patients may have been related to an inability to initiate strategies that would have facilitated the retrieval of words belonging to specific letter categories. The poorer MCST performance of schizophrenic patients may indicate a difficulty in inhibiting previously established response sets and in formulating abstract concepts. The poorer performance of schizophrenic patients on recall tests is consistent with the proposal that recall memory impairment in schizophrenia reflects an incapacity to initiate effective retrieval strategies (Beatty et al., 1993). The advantage of conceptualizing schizophrenia in terms of impaired executive functioning is that it emphasizes that deficits in higher order abilities are mediated by integrated brain systems (Stuss, 1992). It is probable that this approach is more likely to be successful in explaining the neuropsychological variation in schizophrenia than conceptualizations which emphasize that schizophrenia arises from solely a disturbance of the frontal lobe (Robbins, 1990).

It is improbable that the neuropsychological performance of
schizophrenic patients with and without AIMs represents a generalized pattern of cognitive impairment. Specifically, both schizophrenic patient groups were intellectually at the average level, and were not impaired on measures of general cognitive functioning (Information and Vocabulary subtests of WAIS-R), concentration (Arithmetic subtest of WAIS-R), immediate learning and recognition memory (Digit Span subtest of WAIS-R and Recognition Memory for Faces and Words), reasoning abilities (Picture Arrangement), and constructional abilities (Block Design subtest of WAIS-R and Rey-Osterreith Complex Figure Copy).

Additionally, it is unlikely that the severity of psychiatric symptoms altered the performance of schizophrenic patients insofar as both patient groups were mildly impaired on the Brief Psychiatric Scale, an indicator of global psychopathology.

As previously indicated, schizophrenic patients with and without AIMs were differentiated on the Judgment of Line Orientation Test, the Semantic Verbal Fluency Test, and the MCST (categories achieved). Defective performance on the Judgment of Line Orientation Test results from an impaired ability to accurately assess angular relationships (Lezak, 1983), and has been found to occur in right hemisphere damaged patients with parietal lobe lesions (Benton, 1985; Benton et al., 1978). Given that pathophysiological measures were not employed in Experiment 1, it is unclear whether the impairment of schizophrenic patients with AIMs on the Judgment of Line Orientation Test reflects a parietal lobe dysfunction. Since parietal lobe damage is not considered to be more
prominent in AIMs than in non-AIMs schizophrenia (Lohr et al., 1986), it may be more parsimonious to consider the visuospatial impairment of AIMs schizophrenic patients in terms of the basal ganglia pathology that underlies AIMs. Although speculative, this hypothesis is in agreement with the proposal that visuospatial deficits in Huntington's disease arise from damage to the basal ganglia (Goldberg et al., 1990) and animal studies which have reported that lesions limited to the basal ganglia produce deficits in visuospatial differentiation and spatial orientation (Stern, 1983).

In another area of cognitive functioning, the performance of the AIMs schizophrenic patients on the Semantic Verbal Fluency Test may indicate the presence of a word finding difficulty (i.e., anomia) (Goodglass & Kaplan, 1972). As discussed in Chapter 4, recent studies have indicated that aphasic-like disturbances, which include word finding difficulties, underlie the disturbed speech that frequently characterizes schizophrenic patients (Cadet et al., 1986; Landre et al., 1992). Alternatively, it is has been proposed that poor performance on the Semantic Verbal fluency Test may reflect an impaired ability to access remote memory (Hart, Smith, & Swash, 1988). That is, the generation of words belonging to a specific semantic category may be facilitated by recalling category-related events from one's own past (Hart et al., 1988). The question of whether an impairment in remote memory is more prominent in AIMs than in non-AIMs schizophrenia has not been investigated previously; therefore, it would be premature to
conclude on the basis of present research that a remote memory deficit is present in AIMs schizophrenia.

In Experiment 1, the MCST (number of categories achieved) contributed to the discriminant function that differentiated schizophrenic patient groups. Additionally, AIMs schizophrenic patients appeared to have difficulty completing the MCST in Experiment 2 insofar as their performance, which was in the impaired range, did not improve on the second administration when detailed instructions were provided. However, the finding that the schizophrenic patient groups did not significantly differ on the MCST (categories achieved, number of perseverative errors and percent of perseverative errors) does not support the hypothesis that poor MCST performance would be more prominent in AIMs than in non-AIMs schizophrenic patients. Because card sorting deficits have been associated with AIMs in older, deteriorated schizophrenic patients (e.g., Brown et al., 1992), the absence of MCST differences between schizophrenic patient groups in Experiment 1 may reflect the fact that younger schizophrenic patients with average intellectual abilities were employed (see discussion of Experiment 1).

The question of whether the performance of the AIMs schizophrenic patients on the test battery was adversely affected by poor attention is raised by their poorer performance on the Mental Control subtest of WMS; a measure of attention and concentration (Wechsler & Stone, 1983). If an attentional deficit is more prominent in AIMs schizophrenic patients, it is conceivable that poor test performance may reflect an inability to
focus their attention on the cognitive requirements of the test at hand. However, the presence of an attentional deficit in AIMs schizophrenia was not supported by the finding that the schizophrenic patient groups were not differentiated on other tests that may be adversely affected by poor attention (e.g., Digit Span subtest of the WAIS-R) or concentration (e.g., Arithmetic subtest of the WAIS-R).

In addition to investigating the neuropsychological differences between AIMs and non-AIMs schizophrenia, the purpose of the present research was to assess whether the neuropsychological performance of AIMs schizophrenic patients resembles the reported pattern of cognitive impairment attributed to Huntington's disease. With the exception of visuospatial ability, the cognitive impairment of AIMs schizophrenic patients did not appear to resemble that of Huntington's disease patients. This lack of similarity in cognitive functioning questions Cummings' (1993) proposal that the disruption of the dorsolateral circuit, which connects the frontal lobe and the basal ganglia, produces a specific pattern of cognitive deficits characterized by impaired verbal fluency, problem solving, and recall memory. Although speculative, it is conceivable that the basal ganglia alterations associated with AIMs in schizophrenia are confined to the motor circuit which mediates only the programming and control of movement (Alexander et al., 1986). The exact pathophysiology of AIMs in schizophrenia is unknown (Granholm et al., 1992; Jeste & Caligiuri, 1993); however, the possibility that the dorsolateral circuit is not disrupted in AIMs
schizophrenia may explain the finding in the present study that deficits involving higher-order cognitive abilities were not more prominent in AIMs than in non-AIMs schizophrenia.

More generally, a difficulty in conceptualizing the cognitive impairment of AIMs schizophrenic patients in terms of a basal ganglia pathology is that both cortical and subcortical pathophysiological processes may underlie schizophrenia (Buchsbaum & Haier, 1987). That is, because the disruption of the frontal lobe and the basal ganglia is thought to produce a similar pattern of higher-order cognitive deficits (Cummings, 1993), it is not possible to determine on the basis of neuropsychological testing the relative contribution of cortical and subcortical brain areas to the mediation of cognitive loss in AIMs schizophrenia. Thus, reports that schizophrenic patients with AIMs are impaired on tests which measure problem solving and mental flexibility (Brown et al., 1992; Waddington et al., 1993) are not necessarily suggestive of a basal ganglia pathology on the basis that these deficits in schizophrenia may also represent a frontal lobe pathology. The use of neuroradiological measures in future studies would provide a method of determining the relationship between cognitive loss and basal ganglia pathology in AIMs schizophrenia. This approach in studies investigating Huntington's disease has provided evidence that the subcortical disruption of the dorsolateral circuit underlies the cognitive impairment that is characteristic of Huntington's disease (Goldberg et al., 1990; Weinberger et al., 1988).
PM-1 3½"x4" PHOTOGRAPHIC MICROCOPY TARGET
NBS 1010a ANSI/ISO #2 EQUIVALENT

PRECISIONSM RESOLUTION TARGETS
A number of methodological issues, which are important to the interpretation of the results of Experiments 1 and 2, should be addressed. First, differences between schizophrenic patients with and without AIMs may reflect, to a certain degree, group differences in depressive symptoms. On the basis that depressive symptoms can be prominent in schizophrenia (Hirsch, Jolley, & Barnes, 1990), it is conceivable that the cognitive performance of schizophrenic patients was lowered by a loss motivation to perform a given test. In future investigations, it would be advantageous to rate the severity of depressive symptoms in order to minimize emotional factors that may alter test performance.

Second, because Experiment 1 had a cross-sectional design, it is not clear whether the neuropsychological impairment of AIMs schizophrenic patients predates the onset of AIMs. Therefore, if schizophrenic patients had cognitive impairment before the development of AIMs, it is possible that cognitive loss in AIMs schizophrenia is unrelated to the basal ganglia pathology that underlies AIMs. An advantage of a prospective design is that it would be possible to investigate the temporal relationship between the onset of AIMs and cognitive impairment in schizophrenia (Brown et al., 1992). Further, if AIMs are predated by a specific pattern of cognitive impairment, prospective studies would be valuable in identifying possible "cognitive markers" in schizophrenic patients who may be susceptible to developing AIMs.
Third, in studies involving the repeated administration of card sorting tests, the presence of poor card sorting performance which is not reversible is considered evidence of a frontal lobe deficit (Goldberg et al., 1987). A weakness of this approach is that hypotheses concerning frontal lobe deficits in schizophrenia must be formulated in terms of accepting a null hypothesis.

An advantage of the present research over previous studies was the employment of a relatively broad range of tests that assessed a number of areas of cognitive functioning. However, the test battery employed was in no way exhaustive. For example, differences between AIMs and non-AIMs schizophrenia were not investigated in terms of either motor (e.g., apraxia) or sensory-perceptual functions. Additionally, it is possible that certain tests, such as the MCST and the WMS, are not sufficiently sensitive to detect subtle cognitive deficits that may characterize AIMs schizophrenia. It may, therefore, be valuable for future studies to use the WCST (rather than the MCST) on the basis that the WCST is considered to be a more sensitive measure of frontal lobe deficits (Braff et al., 1991; Broek et al., 1993) that may underlie schizophrenia (Goldberg et al., 1987; Liddle & Morris, 1991; Weinberger et al., 1988). Additionally, because behavioural and cognitive deficits in schizophrenia may be related to a loss of executive functioning (Goldberg & Costa, 1987), it would be important to use tests which place a premium on planning and problem solving. For example, the Tinkertoy Test (Lezak, 1982), which assesses the initiation, planning, and
structuring of purposeful behaviour, is considered to provide a measure
executive capacity (Lezak, 1983).

The criticisms of the WMS are well documented (Lezak, 1983; Spreen
& Strauss, 1991; Erikson & Scott, 1977); they include 1) an over
emphasis of verbal memory processes, 2) the inclusion of non memory
measures (e.g., personal orientation), and 3) questionable sensitivity
to specific memory difficulties. Memory deficits in schizophrenia may be
more accurately assessed by the California Verbal Learning Test (Delis,
Kramer, Kaplan, & Ober, 1983), which measures both short- and long-term
recall and recognition memory, in conjunction with the Rey-Osterreith
Complex Figure Delayed Recall.

On the basis that a word naming deficit (as suggested by the Boston
Naming Test) may be more prominent in AIMs than in non-AIMs
schizophrenia, future studies need to investigate the degree to which
possible language impairment in AIMs schizophrenia resembles aphasic
language disturbances. In studies that have compared AIMs and non AIMs
schizophrenic patients, language functions have not been assessed in
terms of a comprehensive language examination (Waddington et al., 1993).

The finding in Experiment 1 that visuospatial ability may be
impaired in AIMs schizophrenia needs to be validated in future studies.
The Huntington’s disease comparison may be pursued by employing tests of
spatial cognition that been shown to be defective in patients with
Huntington’s disease. These may include tests visuospatial
discrimination, directional sense, and egocentric spatial perception
(Brand & Butters, 1986; see Chapter 5).

In conclusion, schizophrenic patients (both AIMs and non-AIMs) and control subjects were differentiated by tests of verbal fluency, problem solving and recall memory. However, the present research did not support the hypothesis that deficits involving higher-order cognitive functions are more prominent in AIMs than in non-AIMs schizophrenia. Additionally, with the exception of visuospatial ability, the neuropsychological performance of the AIMs schizophrenic patients did not resemble previous reports of neuropsychological impairment in Huntington's disease patients. Much more research is needed to clarify whether AIMs in schizophrenia are associated with a specific pattern of cognitive impairment. Finally, because of the possibility that cognitive impairment in AIMs schizophrenia may reflect a basal ganglia pathology (Brown et al., 1992; Cohen & Cohen, 1993), it would be especially valuable for future studies to employ biological measures (i.e., the use of neuroradiological techniques) in order to establish whether pathological changes to cortical and/or subcortical structures correlate with impaired cognitive functioning.
Appendix 1

Title: Movement Disturbances Associated with Schizophrenia and Huntington’s Disease.

Abnormal Involuntary Movements (AIMs): Choreiform and athetoid movements (see below) mainly affecting limbs and orofacial muscles. AIMs is used in present research project to refer to the same movement anomalies which occur in tardive dyskinesia. The difference between AIMs and tardive dyskinesia is that the former is not necessarily associated with neuroleptic exposure.

Akathisia: Increased movement activity (restlessness) involving such activity as rocking back and forth, foot tapping and pacing.

Athetoid Movements. Slow, withering involuntary movements which have a rhythmic pattern. Athetoid movements primarily affect distal muscle groups.

Bradykinesia: A marked slowness in initiating and performing voluntary movements.

Catatonic Stupor. A decrease in motor activity resulting in minimal expression of all voluntary movements.

Choreiform Movements. Short and abrupt involuntary movements which may affect limbs, truck, and facial muscles.

Echopraxia. The imitation of movement patterns of other individuals.

Grimacing. The involuntary movement of facial muscles in irregular contortions.

Mannerisms. The inappropriate performance of repeated goal directed movements (e.g. hand shaking).

Negativism. A reduction of voluntary movements marked by a loss of motivation to perform movement patterns when instructed.

Rigidity. Increased muscle tone of specific muscle groups (e.g., jaw).

Tardive Dyskinesia. Choreiform and athetoid movements mainly affecting limbs and orofacial muscles. Tardive dyskinesia is typically considered to be associated with exposure to neuroleptic medication.

Tics. Repetitive, jerky movements primarily involving small groups of muscles in the face.
SUBJECT'S NAME: ____________________________

INVESTIGATORS: D. Colquhoun and Dr. J. Connolly

PROJECT TITLE: Cognitive processes associated with abnormal involuntary movements in schizophrenia

INTRODUCTION
You are invited to take part in a research project. It is important for you to read and understand several general principles that apply to all who take part in this study.

1. Taking part in the study is entirely voluntary.
2. You may not personally benefit from taking part in the study, but knowledge may be gained that will benefit others.
3. A 15 dollar incentive will be provided to all participants in the study.
4. You may withdraw from the study at any time without loss of the 15 dollar incentive.
5. You may temporarily discontinue testing for any reason and, at your request testing will be resumed at a later date.

The nature of the study, the risks, inconveniences, and discomforts are discussed below. If you have any questions concerning participation in the study, you are urged to discuss them with the investigator who explains this to you.

NATURE OF STUDY
In this study you will be given a number of psychological tests in which you will either be asked to answer questions or to perform tasks. These tests will assess your strengths and weaknesses in a variety areas such as memory, problem solving, and perception. Some of the tests will be relatively easy while other tests will be difficult. Because some of the tests are difficult, no one is expected to make a perfect score on all the tests. It is, however, important for you to attempt to do your best on all the tests so that the results will give a true picture of your abilities.

The tests will require approximately 2 hours to complete. Whenever you feel tired, we will take a break between tasks. When the results of the study are reported in a scientific journal or at a meeting, your identity will be withheld. If you have any concerns after taking part in the study, you may telephone the investigators, David Colquhoun (494-6539) or Dr. John Connolly (494-2531) for more information.

I have read the explanation about this study and have been given the opportunity to discuss it and ask questions. I hereby consent to take part in the study.

Signature ____________________________ Date ____________

Signature of Investigator ____________________________ Date ____________
References


Kolb, B. & Whishaw, I. Q. (1983). Performance of schizophrenic patients on tests sensitive to left or right frontal, temporal or parietal function in neurological patients. *Journal of Nervous and Mental Disorders, 171*, 435-443.


