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**Assessment of Attentional Deficits in Familial and Sporadic Schizophrenics
Using Event-Related Potentials and a Continuous Performance Task**

By Jemeen Horton

**Thesis Document submitted to the Faculty of Graduate Studies and Research in partial
fulfillment of the requirements for the degree of**

MASTERS OF SCIENCE

Department of Psychology, Carleton University

Ottawa, Ontario, Canada

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Acceptance of the thesis:

Assessment of Attentional Deficits in Familial and Sporadic Schizophrenics using Event-

Related Potentials and a Continuous Performance Task

submitted by

Jemeen Horton

in Partial fulfillment of the requirements for

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Chair
Thesis Supervisor
Thesis Co-Supervisor

Carleton University

August, 2000

ABSTRACT

The heterogeneous nature of schizophrenia has been well established. Considerable intra-group variability has been observed in a number of characteristic symptoms of schizophrenia including core deficits of attentional and information processing ability. The familial/sporadic strategy is one of many experimental approaches designed to subdivide the syndrome of schizophrenia. The objective of the present study was to examine the nature of attentional and information processing dysfunction in familial and sporadic schizophrenics. The P300 component of the event-related potential in 28 symptomatically stable, medicated, chronic schizophrenics (14 patients with a positive family history of schizophrenia) and 14 normal controls was examined during a degraded stimulus visual continuous performance task. No statistically significant differences were identified between the patient samples in behavioural performance or in P300 response. The familial patient group did however display prolonged P300 latency compared to healthy control subjects ($p < .05$). Prolonged P300 latency in familial schizophrenics is discussed in relation to stimulus evaluation time.

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TABLE OF CONTENTS

Thesis Acceptance Page.....	ii
Abstract.....	iii
Acknowledgments.....	iv
Table of Contents.....	v
List of tables.....	vi
List of figures.....	vii
List of Appendices.....	viii
Introduction.....	9
Hypotheses.....	42
Method.....	44
Results.....	48
Discussion.....	54
Tables.....	65
Figures.....	67
Appendices: A.....	76
B.....	77
References.....	78

LIST OF TABLES

Table 1: Follow-up independent t-tests for a group effect of reaction time

Table 2: Follow-up dependent t-tests for a time effect of reaction time.

Table 3: Follow-up dependent t-tests for reaction time across time blocks within patients groups.

Table 4: Follow-up dependent t-tests for reaction time across time blocks within the control group.

LIST OF FIGURES

Figure 1: Mean (+/- SE) DS-CPT reaction time (msec) values for familial schizophrenics, sporadic schizophrenics and controls over time blocks.

Figure 2: Mean (+/-) DS-CPT hit rate (%) values for familial schizophrenics, sporadic schizophrenics and controls over time blocks.

Figure 3: Mean (+/-) DS-CPT sensitivity (%) values for familial schizophrenics, sporadic schizophrenics and controls over time blocks.

Figure 4: Mean (+/-) DS-CPT false alarm rate (%) values for familial schizophrenics, sporadic schizophrenics and controls over time blocks.

Figure 5: Mean (+/-) DS-CPT β values (%) for familial schizophrenics, sporadic schizophrenics and controls over time blocks.

Figure 6: Grand averaged midline waveform comparisons of target and non-target elicited ERP waveforms within familial patients, sporadic patients and controls over DS-CPT time blocks.

Figure 7: Grand averaged midline target ERP waveforms of familial patients, sporadic patients and controls over DS-CPT time blocks.

Figure 8: Mean (+/- SE) P300 amplitude (μ v) values for familial patients, sporadic patients and controls over DS-CPT time blocks.

Figure 9: Mean (+/- SE) P300 latency (msec) values for familial patients, sporadic patients and controls over DS-CPT time blocks.

LIST OF APPENDICES

A: Informed Consent

B: Consent Form

INTRODUCTION

Schizophrenia: A heterogeneous disorder

Schizophrenia is a heterogeneous psychiatric illness marked by extreme disturbances in thought, perception, emotion and behavior. Thought processes are disorganized and often illogical, perceptions of themselves and the world are distorted and bizarre, emotion is withdrawn, and behaviors are irrational. Schizophrenics are thrown into a fantasy world plagued by hallucinations and delusions. Patients often report feelings of disassociation, feeling that the world is somehow different and perhaps almost surreal. Disturbances are often so severe that an affected person's social and occupational venues of daily life are markedly impaired.

The range of symptoms characterizing a diagnosis of schizophrenia is vast, and individual cases of schizophrenia often involve only a select number of a wide array of possible symptoms. The DSM-IV criteria for a diagnosis of schizophrenia has divided characteristic symptoms into two broad categories, positive and negative symptoms. Positive symptoms reflect an excess or distortion of normal functions including delusions, hallucinations, disorganized speech and catatonic behavior. Negative symptoms conversely, reflect a loss or diminished capacity of normal functions including flat affect, alogia (i.e. restrictions in the fluency and productivity of thought and speech) and avolition (i.e. lack of initiation in goal-directed behaviors) (American Psychiatric Association, 1994). For a clinical diagnosis of schizophrenia to be assigned, clinical symptoms must be present for a significant portion of time during a one-month period, with some signs of the disorder persisting over a period of at least six months and symptoms must be accompanied by marked social and/or occupational dysfunction.

DSM-IV has further identified subtypes of diagnosed schizophrenics into paranoid, disorganized, catatonic, undifferentiated and residual types. Paranoid type reflects a preoccupation with delusions and experiences of hallucinations. Catatonic type is assigned to a predominance of catatonic symptoms. Disorganized type is assigned to excessive disorganized speech and behaviour. Undifferentiated type reflects those individuals who experience active-phase symptoms but do not meet the criteria for paranoid, catatonic or disorganized type. When there is continuing evidence of disturbance but active phase symptoms are no longer present, residual type is assigned.

The variety of signs and symptoms that depict schizophrenia is both impressive and bewildering. Both clinical and experimental observations have reported marked heterogeneity in many aspects of psychopathology in individuals with schizophrenia (Carpenter & Kirkpatrick, 1988). As such, most researchers describe schizophrenia as a syndrome, made up of a group of disorders rather than a single disease entity (Kendell, 1975; McHugh & Slavney, 1983; Carpenter, 1987; Tsuang et al, 1991) and thus producing a variety of mental health outcomes (Lewis et al, 1987).

Since the early 1900's when Kraepelin and Bleurer coined the term "schizophrenia", the heterogeneous nature of schizophrenia has been considered a fundamental characteristic of the disorder. Bleurer (1950) asserted the importance in the heterogeneity of schizophrenia as he subtitled his book "The Group of Schizophrenics". Kraepelin (1919) in "Dementia Praecox and Paraphrenia" expressed that subdividing schizophrenia into homogenous subgroups would likely reveal etiological heterogeneity (Andreasen & Olsen, 1982), hence explaining the variable nature of schizophrenia. Recent investigators

Lewis et al (1987) suggest that schizophrenia be best described as a “final common pathway of a range of different processes”.

The heterogeneous nature of schizophrenia has led to various research strategies aimed at identifying and implementing specific-subtype experimental paradigms. If in fact subtypes of schizophrenia do exist with unique etiologies and pathophysiologies, identification of these groups will undoubtedly assist in achieving a more precise understanding of schizophrenia (Tsuang, Lyons & Faraone, 1990). The exploration and identification of subtypes with specific pathologies and etiologies may furnish opportunities to create subtype-specific interventions that may aid in the treatment and prevention of schizophrenia. Furthermore, it is important to note that the study of heterogeneous schizophrenic samples will provide ambiguous information if in fact schizophrenia is etiological heterogeneous. However, even if there is a unitary process underlying this disorder, studying more homogenous subtypes will not obscure identification of that single etiological factor.

Familial and Sporadic Schizophrenics

In fact, antecedents of recent experimental methods of subdivision of schizophrenia date back to traditional approaches of Kraepelin and Bleuler which emphasized cross-sectional phenomenology, purely on the basis of behavioural observations of symptom patterns. The Kraepelinian-Bleulerian divided schizophrenia into hebephrenic, catatonic, paranoid and simple subtypes, a classification that founded the basis for the DSM-III criterion (American Psychiatric Association, 1980). However more recently, investigators utilizing both behavioural and quantitative rating scales, have attempted to subtype the syndrome of schizophrenia on the basis of other variables such as premorbid

functioning (Strauss & Carpenter, 1972; Strauss, Koher & Klorman, 1977), predominant symptoms (Kraepelin, 1919), altered mood (Pope & Lipinski, 1978), paranoid versus nonparanoid (Magaro, 1974; Tsuang & Winokur, 1974), negative versus positive symptoms (Crow, 1980; Andreason & Olsen, 1982) as well as on the basis of biological variables such as ventricular brain ratio (VBR) (Goetz & Vankammen, 1986) and platelet monoamine oxidase activity (MAO) (Potkin et al, 1986).

Longitudinal research has further identified a variety of subtypes such as acute versus chronic (American Psychiatric Association, 1968), good versus poor prognosis (Vaillant, 1964) and long-term illness course (Carpenter & Kirkpatrick, 1988). A subtype of gender has also been used in numerous studies (Wilcox & Nasrallah, 1987; Pearlson et al, 1989; Foerster et al, 1991).

Subdivision of schizophrenia based on purely symptomatic and demographic observations will promote further insight into the variable course, presentation and outcome of schizophrenia however, these strategies provide little direct information concerning the direct origins of this syndrome (Lewis, Reveley, Reveley, Chitkara & Murray, 1987). However, subdivision of schizophrenia based on the presence or absence of a family history (i.e. familial/sporadic paradigm) has been presented by a number of researchers (Baron et al, 1982; Kendler & Hays, 1982; Shur, 1982; Lewis, Reveley, Reveley, Chitkara & Murray, 1987) as a potential means of uncovering both genetic and environmental factors fundamental to the pathogenesis of schizophrenia.

The Redundancy Formulation Model described by Asarnow & MacCrimmon (1978) lends support to the familial/sporadic schizophrenic paradigm. This model was composed of two broad categories of schizophrenia: high redundancy and low

redundancy patterns. These categories were developed with respect to course of illness, clinical symptomatology, attentional performance and prognosis. The high redundancy category included non-paranoid symptoms, poor premorbid sociosexual adjustment, less efficient cognitive performance, chronic and poor prognosis. This category was predominately associated with a positive family history of schizophrenia. Paranoid symptoms, healthier premorbid adjustment, better neuropsychological performance and a more favorable prognosis characterized the low redundancy group. This category was predominately associated with a negative family history of schizophrenia.

As some diagnosed cases of schizophrenia have shown to involve heredity factors, the incidence of schizophrenia is often mistakenly believed to be caused primarily through familial transmission of the illness. Although many family, twin and adoption studies have unequivocally demonstrated that genetic factors play a vital role in the etiology of approximately 10 to 15% of diagnosed cases of schizophrenia (Walker & Shaye, 1982), purely genetic models cannot sufficiently explain the distribution of schizophrenia within affected families and within the general population (Lewis, Reveley, Reveley, Chitkara & Murray, 1987). Genetic research contends that a substantial number of schizophrenic cases are the result of a “phenocopies”; cases of the disorder that resemble the genetic form but are due to non-genetic environmental causes. Thus, it seems acceptable to speculate that the minority cases of schizophrenics with genetic loading differ fundamentally from sporadic cases with respect to causality clinical symptomatology and illness course. Consequently from a practical research perspective, it is possible that most experimental samples likely include a minority of subjects with a genetic loading whom differ fundamentally from other, non-familial schizophrenics. This lack of

homogeneity induces problems with respect to generalizability of the results and interpretation of experimental findings.

In sum, to better understand the genetic implications of familial psychopathology comparison of biological, symptomalogical and performance characteristics of familial versus sporadic schizophrenics is required (Walker & Shaye, 1982). To test the hypothesis of the importance of genetic factors in some cases and environmental factors in others, the classification of patients based on the presence or absence of a family history has been suggested as a stepping stone in elucidate potential etiological factors of schizophrenia. Furthermore, O'Donohue (1985) claims that the familial/sporadic distinction has been used in a number of disorders whose epidemiology is similar to that of schizophrenia, such as epilepsy.

A review paper by Lyons et al (1989) cites a large number of studies reporting significant differences between familial and sporadic schizophrenics. Interesting profiles of predominant signs and symptom severity on various clinical and biological parameters in familial and sporadic schizophrenics have been generated that otherwise may not have been recognized.

For example, familiar schizophrenics have demonstrated various neurological impairments including increased neurological "hard" signs of localization of corticospinal, cerebellar and extrapyramidal abnormalities (i.e. slow/clumsy movements, balance abnormalities and asymmetrical reflex hyperactivity) (Woods, Kinney & Yurgelun-Todd, 1991). Further, Walker and Shaye (1982) reported that positive family history schizophrenics exhibit higher levels of overall neuropsychological impairment, making significantly more errors on the continuous performance task (CPT: a task of

sustained attention) than both sporadic schizophrenics and controls. Furthermore, Kendler & Hays (1982) reported that familial schizophrenics displayed more indicators of global thought disorder at the beginning and peak of their illness (56% within the familiar group versus 18% within the sporadic group). Positive family history schizophrenics have also demonstrated significantly greater intra-group variability involving cognitive skills such as abstraction, problem solving and motor control than negative family history schizophrenics (Sautter et al, 1995). Lastly, it has been reported that familial schizophrenics have a less favorable short-term course of illness (Sautter & McDermott, 1994) and in general, a worse prognosis (McCabe et al, 1971; Winoken et al, 1974; Tsuang & Winokur, 1974).

A higher prevalence of obstetric complications (Lewis & Murray, 1987) and head injuries (Kinney & Jacobsen, 1978) has been reported in sporadic cases of schizophrenia. Structural cerebral abnormalities (Lewis & Murray, 1987) including CT scan abnormalities (i.e. ventricular enlargement) (Cambell et al, 1979; Farmer et al, 1985; Pearlson et al, 1989) have been more often identified in sporadic schizophrenics than in familial cases. Furthermore, it has been observed that when schizophrenia is accompanied by a preexisting cerebral abnormality such as epilepsy (Slater et al, 1963) or trauma (Achte et al, 1969), a positive family history of schizophrenia is seldom reported. More electroencephalographic (EEG) abnormalities have been identified in sporadic schizophrenics, with 72% of sporadic versus 43% of familial schizophrenic patients demonstrating EEG abnormalities (Kendler & Hays, 1982). Moreover, the number of schizophrenics developing tardive dyskinesia is more common in the sporadic cases (Bartels et al, 1985). Shur et al (1982) reported that a larger number of sporadic

schizophrenics are born during the winter months. Birth during the winter months has been reported to be a possible environmental risk factor associated with the development of schizophrenia. Moreover ventricular enlargement, which has been documented more often in sporadic cases, is far more common in schizophrenics born during the winter months (Zipursky & Schulz, 1987). In regards to clinical symptomatology, Jonsson & Jonsson (1992) reported a higher prevalence of paranoid symptomatology in sporadic schizophrenics. Interestingly, investigations have reported that the incidence of mental illness in relatives of paranoid schizophrenics is quite low as compared to the incidence rates of mental illness occurring in relatives of schizophrenics with other predominant symptomatology (Larsson & Nyman, 1973; Kendler & Davies, 1981). With respect to cognitive impairment, Sautter et al (1994, 1995) reported that sporadic cases are associated with a pattern of less severe, generalized deficits. Furthermore, it has been reported that sporadic schizophrenics respond better to drug treatment (Silverman et al, 1987).

It is important to note however, that the familial/sporadic schizophrenia paradigm has been criticized on the basis of methodological grounds (i.e. limitations of classification for non-familial and lack of statistical power) (Eaves et al, 1986; Kendler, 1987) and some investigations have failed to report any significant findings (Alm et al, 1984; Romani et al, 1986).

Cumulative findings of familial/sporadic studies depict interesting profiles of familial and sporadic schizophrenics as distinct entities. Lyons et al (1989) suggest that “a byproduct of this strategy may be the elucidation of which brain abnormalities or dysfunctions are more influenced by genetic factors and which are more influenced by

environmental factors". In terms of attentional and information processing, the bulk of evidence suggests that familial schizophrenic pathology is associated with severe, focal neuropsychological impairment irrespective of any structural damage. Thus, one may postulate that the high incidence of neuropsychological impairment evident in schizophrenia may be primarily associated with genetic transmission of the illness and could therefore serve as a fundamental vulnerability indicator for classifying familial schizophrenic cases from other subgroups of schizophrenia.

Sporadic schizophrenic on the contrary, demonstrate far less severe, more generalized profile of neuropsychological abnormalities however these cases are characterized by a larger incidence of environmental insults. Thus structural abnormalities may serve as a marker of this subgroup of schizophrenics.

In sum, it appears that characteristics of both familial and sporadic schizophrenics are not representative of a "unitary" concept of schizophrenia. In light of the plethora of significant differences reported among familial and sporadic schizophrenics, this strategy has shown to be a viable approach for subgrouping schizophrenic patients for the purpose of elucidating mechanisms mediating symptomatology, its course and its response to treatment.

Schizophrenia-Linked Attention and Information Processing Abnormalities

The existence of cognitive dysfunction in schizophrenia is one of the most consistent findings in contemporary schizophrenia literature. More specifically, schizophrenia-linked attentional and information processing deficit symptoms have been repeatedly well documented in the literature and are considered to be fundamental to the underlying

etiology of psychotic symptoms (George & Neufeld, 1985; Braff, 1993; Nuechterlein & Dawson, 1984; Granholm et al, 1996; Rund, 1998).

Disturbances in cognition have long been accepted as one of the most distinguishing features of schizophrenia. Emil Kraepelin's definition of "dementia praecox" (i.e. original term for schizophrenia) described "the weakening of judgement, of mental activity and of creative ability..." and "a certain unsteadiness of attention". (Kraepelin, 1919). Kraepelin postulated that disorganized thought processes observed in schizophrenic patients was directly related to attentional dysfunctions. Two types of attention abnormalities in schizophrenia were described by Kraepelin: a disorder of active attention, where the patient "loses both inclination and ability on their own initiative to keep their attention fixed for any length of time" and a disorder of passive attention, in which there is an "irresistible attraction of the attention to causal external impression". Kraepelin's use of terms, active and passive attention, are similar to modern day definitions of sustained and selective attention (Green, 1998).

The importance of schizophrenia-linked attentional deficits was further highlighted by Eugen Bleuler (1976) when he documented that schizophrenic patients were "incapable of holding the train of thought in the proper channels" and where "acute attention is lacking". Bleuler (1950) hypothesized that deficiencies in attentional processes were fundamental to the formation of psychotic symptoms, characteristic of schizophrenia. The predominant role that both Kraepelin and Bleuler gave to attentional impairments in the schizophrenia syndrome has had a wide spread pervasive influence in the direction of cognitive based schizophrenic research.

The constructs of attention and information processing are widely used in a variety of settings. The notion of attention seems very simplistic to understand but much difficulty has arisen from trying to operationally define this construct. Despite these difficulties, attention has been broadly described as a non-specific, limited capacity resource that is directed to events (Gjerde, 1983). It facilitates focused concentration on particular (i.e. relevant) stimuli while inhibiting other non-relevant sensory events, thus preventing susceptibility to distractions from extraneous, non-relevant stimuli. Moreover, attention is a very basic, elementary cognitive function that precedes higher cognitive abilities such as memory, learning and problem solving. An early pioneer in the area of attention William James (1950), noted that the process of attention is, on some level, known to everyone as the “taking possession of the mind... of one out of what seems to be several objects or trains of thought”. Kahneman (1973) created a model of attention illustrating that an individual can direct their processing capacity in a flexible and voluntary way by devoting all of one’s capacity to one task or dividing it up among various tasks simultaneously. Furthermore, distribution of resources can be spontaneously redirected. Attention is different than alertness in that alertness is a more basic state of consciousness where an individual is responsive to any stimuli lacking particular focus on a relevant event (Nuechterlein & Dawson, 1984). Alertness does not necessarily imply attentiveness. Further, the ability to attend to a specific event(s) is controlled and voluntary in nature, as opposed to involuntary and automatic. One’s ability to sustain attention is limited and demands on it will vary according to various tasks (i.e. difficulty level). There are three generally accepted aspects of attention: selective, sustained and switching.

Attention and information processing are highly interrelated and models of one intricately involve the other. Information processing as attention has also been broadly conceptualized, described as a process of transmission and interpretation of sensory stimuli by the central nervous system where stimuli are given meaning that is contextually appropriate. This process has been characterized as a series of “information processing stages” involved in relating sensory stimuli to the central nervous system. Initially, early information processing theorists devised serial models that described a series of events that occurred to encode stimuli in such a fashion as to enable processing of sensory stimuli and to establish contextual meaning. Sternberg (1966, 1967, 1969) devised an information processing model derived from choice reaction time studies of memory scanning that included four sequential stages necessary between incoming stimulus and subsequent response of the individual. These four stages were stimulus encoding, serial comparison, binary decision and response translation and organization. It has been argued however, that these four stages are rigid and inflexible and are only of particular relevance for tasks involving only single simple stimulus (Nuechterlein & Dawson, 1984).

Subsequent information processing models emphasized flexibility in processing, rejecting strict, fixed sequence of stages. Donald Broadbent’s “Filter Theory” (1971, 1982), that has been frequently applied to cognitive deficits in schizophrenia, conceptualized information processing into three types of cognitive operations. The first cognitive process “Stimulus-set” (i.e. filtering) describes the process of selecting a particular channel of information characterized by some simple physical attribute (e.g. sex of voice, spatial location of stimulus). This process enhances entry of stimulus input

into the limited capacity where relevant and non-relevant are differentiated by a single sensory factor. Secondly “categorizing” the second type of cognitive function occurs during attentiveness and refers to the process of selecting only characteristics of relevant stimuli while inhibiting categories of irrelevant stimuli thus processing only those of contextual relevance. Categorization develops slowly but with learning, it becomes much more efficient (Nuechterlein & Dawson, 1984). Lastly, “pigeonholing” (i.e. response set) occurs by which a particular bias is placed to the categories produced in the limited capacity stage (i.e. attentiveness) so that a particular categorical input will be triggered with less sensory input than usually necessary. Pigeonholing allocates more or smaller numbers of “states of evidence” to each category state.

A relatively different approach to description of information processing has been adopted by Neisser (1967) who contends that two types of interactive processes are involved in sensory processing. The preattentive process is responsible for arranging sensory input into a global manner very rapidly. This process is followed by focal attention where a slower, more detailed analysis of sensory input occurs. According to this model, selective processing of sensory input varies as a function of the degree to which sensory inputs are processed, thus stimuli receiving focal attention are more likely to reach awareness (Nuechterlein & Dawson, 1984).

Despite the lack of clear consensus as to the precise nature of schizophrenia linked cognitive deficits (Kreman et al, 1994; Murray, 1994; Rund, 1998), it has been well established that schizophrenics possess a reduction in their available attentional resources affecting their ability to correctly attend to and evaluate stimuli (Hemsley, 1975). It has been further suggested that schizophrenics experience a heightened awareness to

irrelevant stimuli, resulting in deficient processing of relevant stimuli, thus producing inappropriate responses and behaviours. In light of this defective “filtering system” of sensory input, it has been hypothesized that profound emotional and behavioural disturbances (i.e. delusions and hallucinations and other psychotic behaviors) displayed by schizophrenics are a direct consequence of sensory stimuli overload generated by a deficient sensory filtering system (Nuechterlein et al, 1992). This hypothesis is further supported by McGhie and Chapman (1961) who argue that sensory filtering deficiencies in the central processing system induce an overload of sensory input, rendering an individual susceptible to an overload of sensory stimuli, consequently creating a breakdown of the person’s perceptual and sensory integration ability and in due course, generating psychotic behaviours.

Application of Broadbent’s filter theory to attentional deficits in schizophrenia proposes that schizophrenics experience deficiency in pigeonholing processes (Hemsley & Richardson, 1980; Schwartz, 1978). Individuals with schizophrenia appear to suffer from defective “pigeon-holing” mechanisms leaving them inherently prone to be more “open” to the surrounding environment (leading to distortions in perception and reasoning). However, schizophrenics do not appear to experience “filtering” deficiencies, perhaps due to the reasoning that pigeonholing requires more active processing of information (Hemsley, 1975, Hemsley & Richardson, 1980; Schwartz, 1978). Further views on the nature of the cognitive impairment in schizophrenia from Frith (1979) proposes that the basic cognitive schizophrenia dysfunction emanates from awareness of automatic processes that are normally carried below the level of consciousness.

Early investigations of Attentional and Information-Processing Deficits in Schizophrenia

The earliest schizophrenia linked attentional impairment experimental investigations involved smooth-pursuit eye movement (SPEM) studies. Smooth-pursuit eye movement studies performed at the turn of this century by Diefendorf and Dodge (1908) showed that schizophrenics demonstrated deficient eye tracking abilities. Dierdorf and Dodge observed that schizophrenic patients made step-like ocular movements as they attempted to maintain focus on objects, thus preventing them from following moving targets continuously as normal persons do. Furthermore, more recent smooth pursuit eye movement studies have identified a higher frequency of SPEM abnormalities in first degree relatives than in the general population (Holzman et al, 1974; Matthysse et al, 1986; Levy et al, 1993).

Reaction Time Studies

Around the 1950's, behavioural reaction time (RT) studies were widely used to further explore the nature of schizophrenia-linked attentional abnormalities. The basic form of RT studies utilized uniform (i.e. regular) and varied time intervals between the warning signal of the upcoming stimulus and signals to respond to the stimulus (Zahn & Rosenthal, 1965). Subjects responded to the visual or auditory stimuli as quickly as possible with either a simple button press or a lift. RT methodology was proposed to measure the basic ability to maintain concentration in order to process basic stimuli and execute appropriate motor responses (Nuechterlein & Dawson, 1984).

Marcus (1973) applied a simple RT paradigm of varied preparatory intervals (i.e. irregular duration) to adult schizophrenic patients, offspring of schizophrenic mothers and to multiple comparison groups. Results showed that the adult schizophrenics and at-

risk children (between the ages of nine and eleven) displayed significantly slower reaction time response as compared to their respective control groups. This pattern of RT slowing has been repeatedly demonstrated by Huston, Shakow and Riggs, (1937) and by Rodnick and Shakow (1940).

Investigators Rodnick and Shakow measured cross over reaction time (RTX), an index of behavioural response differences to random presentations of a sequence of regular and irregular preparatory intervals. Investigators observed that normal control subjects responded faster to regular preparatory intervals than to irregular preparatory intervals. Rodnick and Shakow observed that reaction time crossover performance in control subjects improved during regular preparatory intervals (i.e. same length) whereas schizophrenic performance progressively deteriorated during regular preparatory intervals. It was also reported that schizophrenics responded faster to very short regular preparatory intervals, but with longer preparatory intervals, patients responded quicker to irregular intervals than to regular ones. (Rodnick & Shakow, 1940; Steffy & Galbraith 1974), a pattern known to demarcate schizophrenic patients (Nuechterlein & Dawson, 1984). Cross over reaction time in schizophrenia was hypothesized to reflect an excessively greater sensitivity to the lengths of the preceeding preparatory interval (PPI) than controls (Chapman, 1979), possibly reflecting a dysfunction in maintaining appropriate attentional functioning throughout the task.

Cross-over RT response has not only been demonstrated in both chronic and remitted patients (Bellissimo & Steffy, 1972: 1975; Strauss, Bohannon, Kaminsky & Kharabi, 1979) but also in schizotypal personalities (Simons, MacMillian & Ireland, 1982) and in children of schizophrenic parents who show RTX pattern (DeAmicis & Cromwell, 1979).

Furthermore, more recent reaction time studies have also observed “cross over “ abnormalities in relatives of schizophrenics (Cromwell et al, 1979).

Zubin (1976) investigated “cross modal” RT, the ability to switch attention from one sensory modality to another (i.e. primarily visual to auditory modalities and visa-versa). The tasks involved either presenting the warning signal and the response stimuli in the same modality (i.e. both signals either visual or auditory) or presenting the warning signal to the auditory modality and the response stimuli to the visual modality or visa-versa. Schizophrenic patients displayed poorer performance compared to controls in their ability to switch their attention to the appropriate modality, indicating that patients were “stuck” in their attentional set, unable to selectively shift their attention from one modality to another (Braff, 1993).

Robust reaction time findings set the stage for further, more advanced behavioural techniques in the assessment of schizophrenia-linked attentional deficits. Reaction time methodology predominately measures processes involving maintenance in readiness to respond to stimuli over time. However more recently, modern behavioural techniques not only measure maintenance in response readiness but also measure ability to sustain focused attention over a period of time (i.e. vigilance).

Continuous Performance Task

In the search of an objective measure to identify schizophrenic cognitive vulnerability, the continuous performance task (CPT) is most highly preferred and is presently considered a benchmark task in assessing schizophrenia-linked attentional deficits (VanDes Bosh, 1996).

The CPT was originally developed by Rosvold et al (1956) to detect attentional deficits in brain damaged patients, however more recently several modified versions of this task have been widely used to investigate putative attentional abnormalities in a range of psychopathological disorders including schizophrenia. Investigations utilizing various versions of the CPT have reported robust findings in the assessment of schizophrenia-linked attention deficits, elucidating sustained attentional and information processing deficits in schizophrenics (Chapman, 1979) and among high-groups and schizotypal populations (Cornblatt & Kleip, 1994). In comparison to the simple reaction time model, the CPT emphasizes time-related changes of task performance involving selection of specific target stimuli for immediate response from a series of target and non-target stimuli (Nuechterlein & Dawson, 1984).

The CPT is a family of attentional tasks involving a quasi-random presentation of a sequence of target and non-target stimuli, usually for a period of approximately ten minutes or longer (Van den Bosch, Rombouts & Van Asma, 1996). Stimuli are presented briefly (40-200 ms) at intervals of 1 to 2 seconds and subjects are asked to respond to targets presented in a random stimulus sequence. Most CPT versions involve visual stimuli (Cornblatt & Keilp, 1994) and variations of the task have included target stimuli that are single letters or numbers (Rosvold et al, 1956), playing cards (Erlenmeyer-Kimling & Cornblatt, 1987) and perceptually degraded numbers (Nuechterlein, 1983; Nuechterlien, Parasuraman & Juang, 1983). All CPT versions demand integration of perceptual, cognitive and motor function, however each version differ in terms of demand on attentional and information-processing resources (Van den Bosch, et al, 1996).

Several cognitive processes are believed to contribute to CPT performance. However more specifically, CPT performance is considered reflective of attentional ability, primarily an experimental measure of sustained attention (i.e. vigilance) and visual-motor functioning (Walker & Shaye, 1982). The CPT has two basic forms.

The Original Version of the CPT

The traditional version of the CPT consisted of a series of single letters that were presented visually for a duration of approximately ten minutes (Rosvold et al, 1956). The classic CPT was made up of two individual tasks, the X and the AX tests (Cornblatt & Kelip, 1994). The X test required detection of a single target letter (i.e. letter X). The AX test also included a memory load, however requiring response to a target letter only when a particular letter preceded the target (i.e. response to the letter X when followed by the letter A). Performance of the basic CPT was quantified using behavioural indices of hits (i.e. correct response to a target stimulus), false alarms (i.e. incorrect response to a non-target stimulus) and reaction time.

X/AX CPT studies reported that schizophrenics perform poorly on CPT compared to controls and to other clinical groups (Mirsky & Kornetsky, 1964; Orzach & Kornetsky, 1966; Orzach et al, 1967; Orzach & Kornetsky, 1971), and compared to their own performance on other types of cognitive and behavioural measures (i.e. digit symbol substitution test) (Orzach & Kornetsky, 1971; Cornblatt & Kelip, 1994).

Investigators predicted that observations of deficits in sustained attentional ability as evidenced by slower reaction time, increased rates of hits and more false alarms was a trait marker of schizophrenia in that deficits were identified in remitted patients as well as those who were actively symptomatic (Wohlberg & Kornetsky, 1973).

Once initial findings of CPT attentional dysfunction in schizophrenic patients were reported, numerous questions were raised including whether observed deficits were reflective of specific attentional factors such as perceptual sensitivity or whether deficits were indicative of non-specific attentional processes of motivation level and fatigue. Furthermore, researchers became increasingly aware of the importance of identifying “trait” indicators of schizophrenia (Goldin et al, 1986; Cloninger, 1987; Cornblatt & Keefe, 1991; Erlenmeyer-Kimling & Cornblatt, 1992) to determine whether these deficits are fundamental to schizophrenia or a secondary manifestation of the illness. Thus, focus shifted from schizophrenic samples to those individuals at high risk for schizophrenia. Since classic CPT versions are relatively easy and involve little memory load, researchers were not successful in identifying possible, subtle attentional deficits in high risk individuals (Cohler et al, 1977; Asarnow & MacCrimmon, 1978; Nuechterlien, 1993). In contrast to these negative findings, more difficult CPT versions that produce high moment to moment processing loads have identified perceptual sensitivity deficits in individuals at high risk for developing schizophrenia.

Modified Versions of the CPT

Modern versions of the CPT have added various types of visual and/or auditory distractions to the basic version of the CPT to increase the tests’ cognitive demand on attentional and information processing resources (Stammeyer, 1961; Wohlberg & Kornetsky, 1973). The most common modified versions of the basic CPT used in schizophrenia research are the degraded stimulus CPT (DS-CPT) developed by Nuechterlien (1983) and the identical pairs version (CPT-IP) created by researchers of the

New York high-risk project (Cornblatt & Erlenmeyer-Kimling, 1985; Erlenmeyer-Kimling & Cornblatt, 1992).

In the DS-CPT, the basic X procedure is maintained (i.e. subject required to respond to single target letter/digit among a series of letters/digits) however the presentation of the stimuli is blurred, therefore making the stimuli more difficult to see. The DS-CPT produces a high processing load on attention by oppressing early aspects of stimulus encoding and perceptual analysis (Nuechterlein, 1991; Cornblatt & Kelip, 1994).

Modern CPT versions use traditional indices of hits, false alarms and reaction time as well as more modern measures of A' (A prime) and β . The signal detection analysis (Rutschman et al, 1977) combines hits and false alarm rates into non-parametric indices of A' and β . A' is a measure of perceptual sensitivity: a subject's ability to discriminate target (i.e. signal) stimuli from non-target stimuli (i.e. noise), indicative of specific attentional factors. β is an index of a subjects' tendency either to over-respond or under-respond to stimuli. This index is considered as a measure of state disposition, motivation and expectancy (Cornblatt & Kelip, 1994), characteristic of non-specific attentional processes. A high A' score reflects a more competent, non-deficient processing ability whereas a high β indicates a cautious response tendency (i.e. sacrifice hits to make fewer errors) and a low β reflects a more liberal response disposition (i.e. maximizing hits but making more errors) (Cornblatt & Kelip, 1994). Schizophrenic CPT performance is typically characterized by slower reaction time, fewer hits, more false alarms and lower A' than controls. However despite exhibiting poorer behavioural performance compared to controls at task onset and throughout task performance, observations do not indicate

that schizophrenic performance declines more rapidly than that of controls during conditions of vigilance (Nuechterlein & Dawson, 1984; Nuechterlein, 1983, 1985).

Versions of the CPT where a relatively high demand on attentional and information processing resources is generated through the use of degraded stimuli or sequential targets have identified deficits in actively symptomatic schizophrenic patients (Asarnow & MacCrimmon, 1978; Walker, 1981), relatively remitted and acutely disturbed schizophrenic patients (Wohlberg & Kornetsky, 1973; Asarnow & MacCrimmon, 1978) and in well recovered single-hospitalization schizophrenic patients (Cornblatt & Kelip, 1994). CPT deficits have also been identified before onset of clinically psychotic symptoms and persist even in a state free of major clinical symptoms (Nuechterlein et al, 1986). Furthermore, CPT impairment appears independent of the effects of medications as Wohleberg & Kornetsky (1973) and Asarnow & MacCrimmon (1978) have reported impairment in non-medicated schizophrenic patients.

In contrast to X/AX studies, more difficult CPTs have identified attentional deficits in individuals at risk for schizophrenia on the basis of parental schizophrenia (Nuechterlein, 1983; Cornblatt & Erlenmeyer-Kimling, 1985). These studies have observed patterns of CPT deficits in unaffected offspring that are similar to those demonstrated by their schizophrenic parent. CPT deficits in first-degree relatives of schizophrenics (Nuechterlein & Dawson, 1984; Mirsky et al, 1992) and in schizotypal personality disorders (Nuechterlein, Edell & West, 1985) have also been identified.

Thus, it appears that when the appropriate CPT version is employed (i.e. those that produce a high momentary demand on attentional resources) subtle deficits in individuals at high risk for schizophrenia are identified. Easier versions of the CPT which failed to

recognize deficits in high-risk populations suggests that more severe attentional and information processing deficits are present after initial onset of clinical symptoms.

Identification of attentional dysfunction in active and remitted schizophrenics, as well as in high risk individuals and reports of the independence of medication effects suggests an intrinsic deficit of sustained attention in tasks involving high levels of encoding and processing ability rather than reflecting a transient byproduct of the illness (i.e. secondary effect of psychotic symptoms and/or medications). However as experimental observations have reported that schizophrenic performance at task onset does not appear to decline more rapidly than controls performance during conditions of vigilance, schizophrenia-linked attentional deficits seem best described as a deficit of lower perceptual sensitivity (i.e. impaired signal/noise discrimination) rather than differential sensitivity over time. (Nuechterlein, 1983; Nuechterlein & Dawson, 1984). Put another way, attentional deficits in schizophrenia appear better described as a deficit in high moment to moment demands on attentional capacity, rather than as a deficit of sustained attention decrement per se. Importantly, since there are few reports of differences in β (response bias) between patients and controls, extraneous, non-specific attentional factors likely do not account for observations of attentional impairment (Cornblatt & Kelip, 1994).

Event-Related Potentials

Event-related potentials are often utilized in the study of attention and information processing. Given that human ability to cognitively process information occurs within the brain, it seems appropriate to explore in vivo neurophysiological concomitants to promote further understanding into the nature of attention and sensory information

processing. Event-related potentials (ERPs) aid in the investigation of active brain functions during cognitive tasks as they can be recorded concomitantly with behavioural task performance. Thus, ERPs may provide a means to reveal supposed neurophysiological mechanisms underlying attentional deficits in schizophrenia (Baribeau 1986; McCarley et al, 1991).

In comparison to behavioural measures (i.e. measures of reaction time, hits & false alarms), ERPs provide a more complete description of brain functioning during cognition as they reflect brain activity elicited at various stages in sensory information processing (i.e. earlier versus later ERP components). For example, short-latency ERPs are believed to offer an index of neuronal activity occurring at the earliest stages of sensory nerve stimulation, reflecting activity at relay stages in the ascending pathways (Hillyard, 1993). Furthermore in the study of attention, ERPs are advantageous in that they provide a measure of stimulus response in the absence of any requirement that the subject actively attend to or behaviourally respond to the stimuli. Finally, high temporal resolution (in the range of milliseconds) of ERPs, provides insight into the absolute and relative timing of neural based cognitive processes that are difficult to abstract from purely behavioural measures (Mangun & Hillyard, 1987).

ERPs are voltage changes in brief segments (< 1 sec) of electroencephalographic (EEG) activity that are time locked to the presentation of a sensory stimulus. These time-locked voltage variations reflect the brain's activity in response to sensory input. As voltage variations evoked by the individual stimuli are notably small in contrast to background EEG activity, signal averaging is a commonly used technique to extract the signal (i.e. time-locked ERP) from the noise (i.e. background EEG). Signal averaging

enhances the signal-to-noise ratio by averaging values of identical time points across multiple segments of ERPs. As background EEG varies randomly, when averaged it will sum to zero. The residual waveform represents non-random, stimulus-locked neural activity elicited by the brain.

As the ERP waveform is reflective of activity produced by the brain in response to sensory input, individual positive and negative voltage components of the ERP are often described in terms of their functionality in cognitive information processing stages. The functional approach to describe ERPs classifies ERP components into two general categories: exogenous and endogenous components.

The amplitudes (μV) and latencies (msec) of the early components of the ERP, generating a poststimulus latency of < 100 millisecond, are mostly functions of the physical properties of the stimulus, variables such as modality, intensity and rate (i.e. inter-stimulus interval) (Friedman & Squires-Wheeler, 1994) and thus are termed “exogenous”. These short latency ERP components are reflective of early brainstem/midbrain processes involving transmission and arrival of sensory information from the peripheral sensory system to the cortex (McCarley et al, 1991). Exogenous ERP components are the least sensitive ERP components to internal psychological variables such as attention and memory as their characteristics (i.e. amplitude and latency) remain fairly constant across various types of cognitive information processing (Roth, 1977).

Later latency (< 100 msec) ERP component (amplitude/latencies) are deemed to be endogenous in nature in that they are relatively independent of the physical parameters of stimuli (Pritchard et al, 1986; McCarley et al, 1991) but are highly influenced by cognitive and psychological variables such as attention, task complexity, decision making

and probability. Experimental manipulations have demonstrated that endogenous ERP components are directly modulated by the characterization (i.e. significance) and/or interpretation of the stimulus as established by the task or by the perception of the subject (Sutton et al, 1965).

The P300-ERP

The long latency P300 component has received particular interest in information processing research (Baribeau-Braun et al., 1983; Pfefferbaum et al., 1984; Pritchard, 1986; Friedman & Squires-Wheeler, 1994) in that it has been described as a correlate of elementary cognitive information processing, also possibly involving aspects of attention (Morstyn et al., 1983). The P300 component is a positive wave usually occurring at approximately 300 milliseconds after presentation of a rare, significant stimulus. It is believed that the amplitude and latency of the P300 are indicative of awareness and/or allocation of attentional resources to relevant signals in carrying out a task and a measure of stimuli evaluation time, respectively (Picton, 1992; Braff, 1993).

P300 is traditionally measured at the midline sites where P300 amplitude has been consistently found to be maximal, particularly at the parietal region (Pritchard, 1986; McCarley et al, 1989). Depth recordings (Halgren et al, 1995), neurologic lesion evidence (Knight, 1996; Knight et al, 1989) and functional MRI activation (magnetic resonance imaging) (Menon et al, 1997; Turetsky et al, 1998) have identified multiple cerebral structures postulated to contribute to the generation of the P300 waveform. The most prevalent structure involved in P300 generation appears to be the temporal lobes (Strik et al, 1994) with some additional contribution from the frontal lobe (Wood &

McCarthy, 1985), inferior parietal lobe (Smith et al, 1990), the amygdala and the hippocampus and brainstem (McCarley et al, 1989).

The P300 is generated when attention is actively directed to discriminate between different stimuli. P300 has shown to be most reliably elicited in an “oddball” type paradigms where low probability stimuli occur randomly in a sequence of high probability events. A large number of psychological constructs such as attention, decision making, processing demands and subjective probability (Pritchard, 1986) have been suggested to account for variations in P300 amplitude and latency that have been observed in a wide range of experimental procedures. At the present time the precise functional role of the P300 remains unclear (Shelley et al, 1996), however a number of researchers have attempted to provide a theoretical account of P300 generation. For example, Posner (1975) related the P300 to “channel-limited information processing”, in that the P300 reflects the engagement and allocation of limited attentional resources to task relevant stimuli. This attentional link is most notably depicted in selective attention and dual-task paradigm studies where P300 amplitude has been consistently found to be attenuated to non-attended target stimuli (vs. attended target stimuli) and to be smaller when processing target events during dual versus single task demands (Parasuraman, 1980). Donchin (1979) further conceptualized the P300 as a “physiological correlate of updating of a cognitive hypothesis”, suggesting that P300 reflects a change in the mental model of the environment generated by working memory. Moreover, Baribeau (1986) described the P300 as illustrating the activation of a large number of perceptual operations, all contributing to the “decisional strategy” required for response to relevant stimuli.

Perhaps the most comprehensive theory of the functional role of the P300 is that of Johnson (1986) who proposed a “triarchic model” of P300 amplitude. Johnson reduced many of the psychological constructs to explain variations in P300 amplitude into three main factors: two independent factors, subjective probability and stimulus meaning modulated by a third factor, information transmission.

An inverse relationship has been repeatedly documented between P300 amplitude and subjective probability in various types of task conditions (Johnson & Kopell, 1980) and with virtually any kind of stimuli (Johnson, 1986). Subjective probability reflects the degree of unexpectedness that a particular stimulus will be presented. In a typical paradigm, a random series of events are presented and subjects are required to respond to one of them (Duncan-Johnson & Duncan, 1977). The rarer the event is, the larger the P300 amplitude is elicited. In addition to sensitivity to the overall frequency of the stimuli presented, P300 is also modulated by sequential expectancies of the stimuli. The repetition of specific stimuli (i.e. BB) elicits smaller P300 amplitudes than non-repeated stimuli (i.e. BA) (Squires et al, 1976).

The second dimension of Johnson’s model, stimulus meaning includes variations in P300 amplitude attributed to three variables: task complexity, stimulus complexity and stimulus value. The variables are all related to the broad concept of task demand (Johnson, 1986). The bulk of evidence shows that P300 amplitude increases are positively related to the degree of task complexity. For example, Chesney and Donchin (1979) reported larger P300 amplitudes when stimuli had to be predicted than when the same stimuli were counted. Moreover, even larger P300 amplitudes were generated when reaction time response was required than when the same stimuli were counted or

predicted. P300 is further modulated by the degree of complexity associated with the stimulus. Stimuli with more relevant features and/or more intricate patterns require more cognitive processing, thus evoking larger P300 amplitudes (Johnson, 1986). The last variable on this dimension, stimulus value refers to the significance of the stimuli as perceived by the subject. High value stimuli, such as stimuli with monetary payoffs promote larger P300 amplitudes than low value stimuli (Steinhauer, 1981; Tueting & Sutton, 1973).

The third dimension of Johnson's triarchic P300 model, information transmission refers to the proportion of information received by the subject relative to the total amount of information inherent in the stimuli (Johnson, 1986). This information transmission component of Johnson's model is especially important in that P300 contribution of the other two components is directly regulated by the extent to which information contained in a stimulus is successfully transmitted to the subject. According to Johnson, information contained in the stimulus can be lost through either equivocation or inattentiveness. Equivocation is loss of information due to subjective uncertainty about a correct response to a particular stimulus. The greater the equivocation, the lower the P300 amplitude (Johnson, 1986). Loss of information also occurs through lack of attention on behalf of the subject. If sufficient information is not extracted from the stimulus due either to equivocation or inattentiveness, amplitude contributions of both subjective probability and stimulus meaning dimensions will be directly decreased, resulting in a lower P300 amplitude than would have been elicited had the subject received sufficient information from the stimulus (Johnson, 1986).

The latency of the P300 waveform is commonly used as an index of the time required in processing task relevant, low probability sensory stimuli. P300 latency ranges from 300 to 700 milliseconds poststimulus depending on the complexity of the task. Experimental measures of P300 latency are often generated concurrently with measures of reaction time. The latency variability of the P300 is determined by the ease of which the rarer of the two events can be classified, the more difficult the event is to categorize, the longer the latency is (Kutas et al, 1977).

P300 latency is largely determined by in vivo processes leading up to stimulus classification and is relatively independent of processes involving response selection. Support for the independence of P300 latency and reaction time comes from several sources including the effects of response bias, stimulus discriminability and stimulus response compatibility studies.

The effects of response bias have been examined in a study involving two choice reaction time conditions, speed and accuracy. Kutas and Donchin (1976) reported that in speed conditions, correlations between P300 latency and reaction time were smaller than in accuracy conditions. Further support for the independence of P300 latency and reaction time is provided by studies involving manipulation of both stimulus discriminability and response compatibility within the same paradigm. McCarthy and Donchin (1981) varied stimulus discriminability by presenting the word "right" or "left" embedded in either a matrix of letters or numbers. P300 latency and reaction time measures were longer when the words were embedded in the matrix of letters. These investigators suggested that processes related to the discriminability of the target stimuli influenced both P300 latency and reaction time. Response selection conditions were

manipulated by requiring a response that was either incompatible or compatible with the meaning of the target stimuli. Investigators, McCarthy and Donchin reported that reaction time measures were longer for incompatible response whereas measures of P300 latency were not affected by response selection manipulations. Thus, both stimulus discrimination and response selection influenced reaction time, however P300 latency was affected only by stimulus discrimination. Further to this, Smid et al (1992) reported that reaction time not P300 latency was significantly influenced by manipulations of response selection difficulty, although both measures increased relative to the difficulty level of stimulus evaluation.

Thus, the bulk of evidence suggests that P300 latency indexes speed of stimulus evaluation independent of overt response selection processes.

With respect to the effect of vigilance on the P300 waveform, experimental manipulations have evoked no change in P300 amplitude over time when subjects discriminate target from non-target stimuli (Pritchard, Brandt, Shappell, O'Dell & Barrett, 1986; Tueting & Levitt, 1979) except when behavioural task performance decreases concurrently. However, when P300-like potentials are elicited through simple repetition of a stimulus, P300 amplitude diminishes in both visual (Courchesne, 1978; Kok & Looren de Jong, 1980) and auditory (Woods & Elmasian, 1986) modalities.

The P300-ERP in Schizophrenia

Numerous P300 investigations have reported marked abnormalities in schizophrenia with the use of various ERP paradigms (Levitt, Sutton & Zubin, 1973; Roth, Pfefferbaum, Horvath, Berger & Kopell, 1980). The vast majority of investigations have utilized auditory P300 paradigms, mainly the "oddball discrimination task" whereby a subject

must either respond to (i.e. RT response) or count an infrequent tone that is randomly presented in a series of frequent tones. Reduction in auditory P300 is one of the most robust biological finding in schizophrenia (Levit et al, 1973; Roth et al, 1980; Steinhauer & Zubin, 1982; Baribeau-Braum et al, 1983; McCarley, Faux, Shenton, Nestor & Adams, 1991; Strik et al, 1994). A less consistent finding of prolonged latency has been reported in some studies (Roxborough et al, 1993; Blackwood et al, 1991; Romani et al, 1986) but not in others (Pfefferbaum et al 1984; Ford et al 1994). Midline P300 abnormalities however, have not only been observed in schizophrenics but also in other clinical populations such as alcoholics and major affective disorders (Blackwood et al, 1987; Patterson, Williams, McLean, Smith & Scaeffler, 1987; Pfefferbaum, Ford, White & Mathalon, 1991; Pfefferbaum, Wenegrat, Ford, Roth & Kopell, 1984).

Auditory P300 cerebral asymmetries in schizophrenia have also been demonstrated (Jahob & Beckmann, 1986; Posner et al, 1988; Faux et al., 1990; Shenton et al, 1992; Strik et al., 1993) with a greater reduction of left hemisphere activity, specifically over left temporal areas (O'Donnell et al, 1993) resulting in a corresponding increase in right hemisphere activity (Morstyn et al., 1983; McCarley et al., 1991; Strik et al, 1994). Left posterior superior temporal gyrus volume reductions have been correlated with reduced P300 (McCarley et al, 1989; 1993).

P300 abnormalities have shown to be independent of the effects of conventional neuroleptics as abnormal P300 has been observed in drug free schizophrenics (Blackwood et al, 1987), patients withdrawn from medication (Faux et al, 1993; Ford et al, 1994; Pfefferbaum et al, 1989) and in never medicated patients (Hirayasu et al, 1998) and also when medications effects are statistically controlled for with the analysis of

covariance (Baribeau-Braun et al, 1983). Furthermore, non-significant correlations between medication dosage and P300 amplitude have also been reported (Roth & Cannon, 1972; Levit et al, 1973; Roth et al, 1980). Asymmetrical P300 amplitude also appear independent of conventional neuroleptics in that lateralized P300 deficits have been observed in off-medication schizophrenic patients (Faux et al, 1993), in first-episode schizophrenics patients (Salisbury et al, 1994) and in never medicated schizotypal subjects (Salisbury, Voglmaier, Seidman & McCarley, 1996).

Abnormal P300 response has been proposed to reflect a trait characteristic of schizophrenia as abnormalities have been observed in children (Friedman, Vaughan, Erlenmeyer-Kimling, 1982), in first-degree relatives (Saitoh, Niwa, Hiramatsu, Kameyama, Rymar, Itoh, 1984; Blackwood et al, 1991) and in individual with schizotypal personality (Kutcher, Blackwood, St.Clair, Gaskell & Muir, 1987). Further, P300 deficits have shown to be stable over time (Sklare & Lynn, 1984) and have been observed regardless of clinical state (Blackwood, St.Clair & Kutcher, 1986). Moreover, Kidogami et al (1992) reported non-significant correlations between low P300 response and clinical symptoms further supporting the contention that abnormal P300 is likely represents a trait marker of schizophrenia rather than secondary by product of the disorder.

Although most P300 investigations have utilized an auditory odd-ball paradigm (Wagner et al., 1989), a reduced visual P300 amplitude was found by Pass et al (1980) in schizophrenic inpatients and by Brechler and Begleiter (1983) in non-medicated patients. However, in a mixed visual-auditory paradigm, Pfefferbaum et al (1984) reported reduced P300 amplitude in schizophrenics in response to auditory stimuli but observed

normal P300 amplitude with visual stimuli at central and parietal sites. Moreover, Duncan et al (1988) also reported normal visual P300 response in medicated schizophrenics. Furthermore, there is evidence that visual P300 but not auditory may be state dependent in that P300 enlargement has been reported to increase following clinical improvement as Duncan (1988) and Heinz and Emser (1987) reported normalization of visual P300 amplitude following symptom stabilization in acutely psychotic subjects.

Given that P300 amplitude/latency measures provide the investigator with noninvasive physiologic probes of mental processes, it is of interest to combine P300 measures with CPT assessments in an attempt to relate behavioural markers of attentional deficit in schizophrenia with in vivo brain markers. Two such studies have provided conflicting data in that one reported reduced visual P300 amplitude (Pass et al., 1980) and one reported normal visual P300 amplitudes (Wagner et al., 1989) in schizophrenics who concomitantly exhibited deficient CPT task performance on basic X/AX CPT versions. A more recent study by Knott et al (1999) showed both reduced P300 and CPT performance in a visual DS-CPT paradigm.

Objectives and Hypotheses

The primary objective of the present study, utilizing simultaneous monitoring of P300 and DS-CPT behavioural responses was to investigate whether schizophrenic patients with a family history demonstrate greater attentional deficits than those patients without a family history of schizophrenia. As the bulk of research indicates that positive family history patients demonstrate higher levels of overall cognitive impairment, it is expected that familial schizophrenics will show greater deficiencies on the DS-CPT and will elicit

longer latencies and exhibit a greater overall reduction in amplitude of the P300 as compared to sporadic schizophrenics and to normal control subjects.

As previous studies utilizing visual CPT-ERP paradigms have reported attenuated P300 amplitude and prolonged P300 latency in non-subgrouped samples of schizophrenic patients, a secondary objective of this study was to replicate previous findings. In this study, control subjects were examined for twice as long as the patient groups to assess whether normal performance over an extended time period would approach deficit levels expected to be observed in patients groups.

METHOD

Subjects

Twenty-eight ambulatory, community-dwelling outpatients from the Schizophrenia Clinic of the Royal Ottawa Hospital (14 with a positive history of schizophrenia and 14 with a negative family history of schizophrenia) as well as 14 normal control subjects participated in this study. Informed consent was needed to participate in this study. Only patients who met DSM-IV diagnostic criteria for chronic schizophrenia and who were clinically judged to be in a non-acute, stable phase of their illness, over a minimum of 4 weeks prior to study enrollment were included in this study. Lifetime diagnoses for all first-degree relatives using the family history method was obtained with the Family History-Research Diagnostic Criteria (FH-RDC) (Andreasen et al, 1986). All patients were receiving antipsychotic medication (i.e. chlorpromazine) and adjunct medications such as anticholinergics, antidepressants and anxiolytics. As much as possible the two patient groups and control subjects were matched on age (ages ranging between 20-40 years old) and sex. Fourteen non-patient volunteers selected from hospital staff who were not receiving any medications and who did not have a history of psychiatric illness participated in this study as normal controls. Subjects from both patient and normal control groups were excluded on the basis of major head injuries, serious medical problems, neurological disorders and alcohol or substance abuse/dependencies.

Study Procedure

Subjects attended the laboratory for one orientation session and one test session. During the orientation session, subjects were introduced to the ERP recording procedures and were required to practice on the DS-CPT. A minimum performance level of 60%

correct target detection (i.e. hits) was necessary for study inclusion. Testing was carried out in the morning following overnight abstinence of aspirin, antihistamines, herbal drugs, alcohol, caffeine-containing substances and cigarettes. Testing was carried out in a sound, attenuated, electrically shielded, dimly lit chamber with the subjects seated one meter from a 14-inch computer monitor on which the CPT stimuli were presented.

DS-CPT Paradigm

The DS-CPT paradigm utilized was similar to that employed by Nestor et al. (1990). Ten single digits (0-9) were presented in a random sequence for 100 ms intervals. Digits were presented in the center of the monitor and were subtended an angle of 0.6 degrees horizontally and 0.9 degrees vertically. Luminance of stimuli was held constant throughout testing. As with Nestor et al. (1990) the stimuli were degraded so that 30% of the pixels in a 36 x 40 array were removed from the digit images. Removal of the pixels was accomplished through reversing the black/white settings of these pixels (Nuechterlein et al, 1986). A total of approximately 500 stimuli were presented to patients at 1200 ms intervals over a period of 11.5 minutes. As controls were tested for twice as long as the patients, approximately 1000 stimuli were presented to controls over 23 minute time period. All subjects were instructed to keep their eyes focused on the center of the monitor and to press a mouse key (with the index finger of the dominant hand) only when the designated target digit was presented. The target digit was presented with a probability of approximately .25 thereby resulting in approximately 120 target and 350 nontarget stimuli presented to patients and 240 targets and 700 nontargets presented to controls.

DS-CPT Measures

Behavioural performance indices included number of correct responses to target stimuli (i.e. hit rate: HR), reaction times (RT) for correct responses, and number of behavioural responses to nontarget stimuli (i.e. false alarms: FA). Responses were considered correct if they occurred within a 100 to 1100 ms post-target time window. Also employed was Grier's (1971) signal detection procedure of combining hits and false alarms into nonparametric indices of sensitivity (A') and response bias (beta: β). As with Nestor et al (1990), the behavioural performance indices were examined for change over time by dividing examination time into equal consecutive time, generating 3 time blocks for patients groups and 6 time blocks for controls.

ERP Recordings

EEG was recorded (with linked ear reference) from 3 standard 10-20 system scalp sites (F_z , C_z , P_z) using a tin electrodes. Vertical electro-oculographic (VEOG) activity was recorded with electrodes placed on supra and infra orbital ridges of the left eye while horizontal (HEOG) was monitored with electrodes attached to the outer canthi of both eyes. All electrode impedances were kept below 5 k Ohms. EEG was recorded with a bandpass filter of 0.1 – 40.0 Hz and analog-to-digital sampling was carried out on-line at 1.5 ms intervals for a 900 ms sweep duration beginning 100 ms before stimulus onset. Digital data was stored on a disk for later off-line ERP processing and analysis.

ERP Measures

A computer program excluded individual sweeps from any site displaying EEG voltage in excess of $\pm 50 \mu V$ from further analyses and a minimum of 15 artifact-free correctly detected target stimulus sweeps per time block was required to retain a subject's

ERP data in the final analysis. Amplitude and latency measures were extracted for each Fz, Cz and Pz P300, which were defined as the maximum peak positive voltage (measured manually in relation to the average pre-stimulus voltage using a computer cursor) between 250-600 ms post-stimulus.

Statistical Analysis

Behavioural performance measures of RTs, hits (% of total), FAs (% of total), A' and β indices, were separately subjected to 3 (group) x 3 (time block), split-plot analysis of variance (ANOVA) procedures. Amplitudes and latencies of ERPs were analyzed separately with 3 (group) x 2 (stimulus) x 3 (site) x 3 (time block) split-plot ANOVAs. An additional 3 (group) x 3 (site) x 3 (time block) split-plot ANOVA was carried out on ERP amplitude "difference" values whereby peak digital voltage values of non target ERP positive waves were subtracted from peak digital voltage values of target ERP positive waves. Data obtained from controls was divided into 6 consecutive time blocks and the patient's data was divided into 3 consecutive time blocks. As the control subjects were tested for twice as long as the patients, each of the analyses described above were performed twice, first with the patients performance at 3 time blocks compared to the first 3 time blocks of the control group then again with the patients performance compared to the last 3 time blocks of the control group. Greenhouse-Geisser corrected p-values were used to protect against type 1 errors. Interactions were followed up with either dependent or independent t-tests.

Pearson Product Moment Correlation (Pearson's r) statistic was used to assess the relationship between performance/ERP measures and medication (using chlorpromazine equivalence dosage levels).

RESULTS

All statistical analyses were performed using SPSS (i.e. Statistical Package for Social Sciences). Analysis of Variance (ANOVA) was used to obtain overall effects, which were then followed up using t-tests. Between group effects and interactions were followed up using independent t-tests and within group effects were followed up using dependent t-tests.

Performance

Reaction time:

As illustrated by Figure 1, reaction time analyses revealed a significant group effect in the first [$F(2,38)=6.49, p<.004$] and second [$F(2,38)=4.19, p<.023$] analysis. Follow-ups of both analyses (see table 1) revealed that familial and sporadic schizophrenic patients responded more slowly than controls.

A significant time effect of reaction time performance was observed in the first [$F(2,76)=29.76, p<.000$] and second [$F(2,76)=21.33, p<.000$] analysis. Follow-up analysis (see table 2) revealed a significant decline in reaction time response across time blocks.

Follow-ups of a group x time interaction in the first analysis [$F(4,76)=3.01, p<.023$] showed significantly slower reaction time response in the familial patient group compared to controls at block 1 [$t(25)=4.09, p<.000$], block 2 [$t(25)=4.59, p<.000$] and block 3 [$t(25)=5.06, p<.000$] and in the sporadic patient group compared to controls at block 1 [$t(26)=2.39, p<.024$], block 2 [$t(26)=2.61, p<.015$] and block 3 [$t(26)=2.70, p<.012$].

A group x time interaction was also observed in the second analysis [$F(4,76)=5.23, p<.001$]. Follow-up t-tests revealed significantly slower reaction time response in the familial patient group compared to controls at block 4 [$t(25)=2.88, p<.008$], block 5 [$t(25)=3.48, p<.025$] and block 6 [$t(25)=4.60, p<.000$] and with sporadic patients responding more slowly than controls only at block 6 [$t(26)=2.37, p<.026$].

No statistically significant differences in reaction time performance were observed between the familial and sporadic patient groups for either analysis.

Hits:

Analyses of hits revealed a main effect of time for the first [$F(2,76)=3.52, p<.034$] and second analysis [$F(2,76)=7.72, p<.001$] with follow-up t-tests showing a significant drop in hit rate from block 1 to block 3 [$t(40)=2.09, p<.043$], block 4 to block 6 [$t(40)=3.11, p<.003$] and block 5 to block 6 [$t(40)=3.09, p<.004$] (see Figure 2).

A Prime:

A main effect of time in sensitivity (A') was observed in the first [$F(2,76)=3.94, p<.024$] and second [$F(2,76)=3.18, p<.047$] analysis as shown in Figure 3. Follow-up t-tests revealed a decline in sensitivity from block 1 to block 3 [$t(40)=2.21, p<.033$] and from block 4 to block 5 [$t(40)=2.15, p<.043$].

False Alarms and β :

Analyses of false alarms (Figures 4) and β (Figure 5) did not yield any significant effects within or between groups.

Within group analysis for reaction time performance:

As a main effect of group for reaction time was observed in the original analyses, in addition to between group follow-up t-tests already presented, analysis of reaction time within each group was performed to examine performance across time blocks. Within the familial and sporadic patient groups, dependent t-tests revealed a significant increase in reaction time performance across time blocks in both patient groups (see table 3). Dependent t-tests also revealed a significant increase in reaction time speed across time blocks within the control group (see table 4).

P300

Group-averaged ERPs waveforms are displayed in two separate formats. In Figure 6, target and non-target group averaged ERP waveforms are compared in familial patients, sporadic patients and in controls at three midline sites. Group-averaged target ERP waveforms are compared in familial patients, sporadic patients and controls at three midline sites in Figure 7.

P300 Amplitude:

Figure 8 illustrates mean P300 amplitude ($\pm$ s.e.) (μ v) values across DS-CPT time blocks for familial patients, sporadic patients and controls. No significant differences in P300 amplitude were observed between the three groups.

Follow-ups of a significant stimulus x time x group interaction [$F(4,72)=3.209, p<.020$] in the first analysis showed a significant increase in P300 target amplitude at block 2 compared to block 1 [$t(12)=-3.936, p<.002$] within the sporadic patient group. There were no significant between groups differences observed within this three-way interaction.

Follow-ups of a stimulus x time x group interaction [$F(4,70)=3.816, p<.007$] in the second analysis revealed larger P300 target amplitude in the control group compared to the sporadic patient group at block 6 [$t(23)=2.179, p<.040$]. Again, no significant between group differences were observed within this three-way interaction.

Follow-up t-tests of a site x stimulus interaction [$F(2,72)=8.865, p<.001$] in the first analysis revealed larger target P300 amplitudes than non-target P300 amplitudes at all 3 sites, Fz [$t(38)=7.340, p<.000$], Cz [$t(38)=6.657, p<.000$] and Pz [$t(38)=10.889, p<.000$].

Smaller target P300 amplitudes were observed at Fz compared to Cz [$t(38)=-3.778, p<.001$] and Pz [$t(38)=-5.33, p<.000$] midline sites. Non-target P300 amplitudes were also smaller at FZ compared to Cz [$t(38)=-4.523, p<.000$] and Pz [$t(38)=-2.582, p<.014$].

Follow-ups of a site x stimulus interaction in the second analysis [$F(2,70)=11.845, p<.000$] showed the same pattern as the first analysis with larger P300 target amplitudes than non-target P300 amplitudes at Fz [$t(37)=-4.357, p<.000$], Cz [$t(37)=7.303, p<.000$] and Pz [$t(37)=11.082, p<.000$]. Smaller target P300 amplitudes were found at Fz compared to Cz [$t(37)=-4.866, p<.000$] and Pz [$t(37)=-5.585, p<.000$]. P300 target amplitude at Pz was larger than Cz P300 target amplitude [$t(37)=-2.255, p<.030$].

A main effect of site was observed [$F(2,72)=19.185, p<.000$] in the first analysis with smaller P300 amplitude at Fz than Cz [$t(38)=-4.882, p<.000$] and Pz [$t(38)=-5.092, p<.000$] and with larger P300 amplitude at Pz than Cz, however this difference was not statistically significant ($p>.05$). A main effect of site was again observed in the second analysis [$F(2,70)=20.480, p<.000$], also revealing larger P300 amplitude at Pz than

Fz [$t(37)=-4.99, p<.000$] and larger P300 amplitude at Cz compared to Fz [$t(37)=-5.301, p<.000$].

A main effect of stimulus was observed in both the first [$F(1,36)=84.654, p<.000$] and second [$F(1,35)=78.588, p<.000$] analysis indicating larger target P300 amplitude than non-target P300 amplitude.

P300 Latency:

Mean P300 latency (msec) (+/- s.e) values for familial patients, sporadic patients and controls across DS-CPT time block is presented in Figure 9. A main effect of group for P300 latency was observed in the first analysis [$F(2,36)=3.735, p<.034$]. Follow-up t-tests revealed a prolonged P300 latency in the familial patient group compared to controls [$p<.029$].

A main effect of stimulus was also observed [$F(1,356)=8.242, p<.007$] showing longer target P300 latency than non-target P300 latency.

A time x stimulus interaction was observed [$F(2,70)=3.206, p<.049$] in the second analysis, with target P300 latency occurring later than non-target P300 latency at block 5 [$t(37)=2.969, p<.005$].

P300 Amplitude Difference Scores:

Analysis of P300 amplitude difference scores revealed a significant group x time 2-way interaction [$F(4,72)=2.668, p<.047$] in the first analysis. Follow-ups showed that within the sporadic patient group P300 amplitude difference scores were significantly smaller at block 1 compared to block 2 [$t(12)=-5.742, p<.000$].

A main effect of site was also observed [$F(2,72)=9.053, p<.001$] with larger P300 amplitude difference scores at Pz than Fz [$t(38)=-3.549, p<.001$] and Cz [$t(38)=-$

2.347, $p < .024$], and larger P300 amplitude difference scores at Cz than Fz [$t(38) = -2.056, p < .047$].

A main effect of site also observed in the second analysis [$F(2, 70) = 16.261, p < .000$], again revealing larger P300 amplitude difference values at Pz than Fz [$t(37) = -4.781, p < .000$] and Cz [$t(38) = -2.293, p < .028$] and with larger P300 amplitude difference scores at Cz than Fz [$t(38) = -3.581, p < .001$].

P300 Latency Difference Scores:

No statistically significant differences were observed in either analysis of P300 latency difference scores.

Correlations

The Pearson Product Moment Correlation analysis performed between 'chlorpromazine equivalent' dosage levels (CPZ-DL) and P300 latency measures and behavioural performance measures failed to yield any significant relationships in either patient group.

However, a few significant correlations were revealed between CPZ-DL and P300 amplitude in both patient groups.

In the familial patient group, an inverse correlation between CPZ-DL and P300 target amplitude was observed at site FZ at block 1 ($r = -.579, p < .05$). Inverse correlations were also revealed between CPZ-DL and non-target P300 amplitude at site FZ at block 2 ($r = -.706, p < .05$), FZ block 3 ($r = -.740, p < .05$) and CZ block 3 ($r = -.665, p < .05$).

In the sporadic patient group, a positive correlation between CPZ-DL and P300 non-target P300 amplitude was observed at site PZ at block 3 ($r = .661, p < .05$).

Discussion

The main focus of the present study was to determine whether schizophrenia-linked attentional deficits as measured by concurrent use of DS-CPT and P300 recordings were more severe in schizophrenic patients with a family history of the disorder compared to those patients without a family history. A secondary focus of this study was to lend further support to previous reports of impaired CPT performance and abnormal P300 response in non-subgrouped schizophrenics compared to controls using a visual ERP paradigm.

With respect to the main focus of this study, no statistically significant differences were identified between the familial and sporadic schizophrenic patient samples in their DS-CPT performance or in their P300 amplitude or latency measures. It was expected that the familial patient groups would display greater deficits in sustained attention evidenced by poorer CPT performance (i.e. slower reaction time, fewer hits, more false alarms) and longer P300 latency and an overall reduction in P300 amplitude than sporadic patients. The familial group did exhibit slower reaction time, smaller P300 amplitude and longer P300 latency than the sporadic group, however these differences did not reach significance levels ($p>05$).

Despite the lack of non-significant differences between the two patient samples, an interesting finding emerged in the analysis of patients groups compared to controls, the secondary objective of this study. It was hypothesized that both patient groups would demonstrate poorer DS-CPT performance and abnormal P300 response evidenced by prolonged P300 latency and a reduction in P300 amplitude compared to normal control subjects. Analysis of Variance revealed that the familial patient sample elicited a P300

latency that was significantly longer than that elicited by the control group. P300 latency in the sporadic patient group did not statistically differ from controls ($p > .05$).

The P300 is often referred to as a correlate of information processing and allocation of attentional resources. As the P300 is generated as a discriminative response to a specific, low probability event embedded within a series of high probability events, its generation must be preceded by sufficient evaluation of the stimuli. Categorization of the stimuli must be complete before the P300 waveform is emitted. Following this line of reasoning, the latency of the P300 waveform is used as an electrophysiological measure of the time required for stimulus evaluation independent of processes related to response selection and execution. The assertion that P300 latency is independent of response selection and execution is based on experimental observations that have demonstrated that P300 latency is sensitive to stimulus discriminability manipulations but not to manipulations of response bias or stimulus response compatibility.

Prolonged P300 latency evidenced in the familial group but not in the sporadic patient group appears to suggest that familial schizophrenics require more time to evaluate and categorize the DS-CPT task stimuli appropriately. Perhaps the familial patient sample perceived the task stimuli as more difficult to categorize as target or non-target (i.e. needed to allocate more attentional resources) than normal control subjects thus requiring more time for stimulus evaluation. This is supported by researchers Kutas et al (1977) who reported an inverse relationship between stimulus categorization and P300 latency, in that the more difficult a stimulus is to categorize, the longer the P300 latency is. Further, the familial group may have experienced a greater degree of uncertainty in deciphering whether they were correctly identifying the task relevant stimuli.

However as P300 amplitude and latency are interdependent, interpretation of prolonged P300 latency is difficult under the present circumstances as a significant difference between familial schizophrenics and controls occurred only in measures of P300 latency and not in P300 amplitude. Nevertheless, as P300 latency is believed to be an appropriate index of stimulus evaluation time, prolonged P300 latency suggests that there is a dysfunction in the time required to categorize task stimuli. Unfortunately a thorough review of the ERP-schizophrenia literature did not reveal any past studies examining P300 amplitude and latency in familial versus sporadic patients, thus the results of this study cannot be interpreted in light of previous findings.

In sum, taken together the finding of lower P300 amplitude and slower reaction time in familial patients compared to sporadic patients (although non-significant) and prolonged P300 latency in familial patients compare to controls, may lend some support to the initial hypothesis of this study that familial schizophrenics posses greater attentional and information processing dysfunction possibly leading to a greater, overall reduction in cognitive abilities.

Past studies utilizing the familial/sporadic strategy in the study of attention and other cognitive functions in schizophrenia have reported greater dysfunction in familial patients using various measures. However future research in this area requires further, well-defined, medication controlled studies at the behavioural and especially at the electrophysiological level to elucidate signs and symptoms of schizophrenia that are more influenced by genetic factors and those that are more influenced by environmental factors.

The secondary objective of this study was to replicate previous findings of poorer behavioural performance and abnormal P300 response in a visual ERP paradigm using non-divided schizophrenic samples compared to healthy control subjects. With respect to DS-CPT performance indices, the present study found that both patient groups displayed slower reaction time response compared to control subjects, a well documented finding (Nuechterlein, 1977; Rodnick & Shakow, 1940). Measures of reaction time in cognitive psychology are utilized to generate inferences related to the human information processing system. Slowed reaction time is interpreted to reflect deficiencies in time related processes of overt response to a sensory event. Slowed reaction time could be the result of various factors including inefficient direction of attentional resources, response uncertainty, response compatibility and stimulus discriminability.

Reaction time however, was the only behavioural index that significantly differentiated patients' performance from controls in this study. Slower reaction time in schizophrenia has been reported in number of studies using both non-CPT and CPT paradigms (Nuechterlein, Edell & West, 1985; Knott et al, 1999) although, most DS-CPT investigations have also observed significant differences in behavioural indices of hits, false alarms and A' prime (i.e. signal from noise discrimination) (Nuechterlein, 1983; Knott et al, 1999) between schizophrenic patients and controls which were not identified in the present study.

The vast majority of ERP research assessing attention and information processing deficits in schizophrenia has reported attenuated P300 amplitude. Abnormal P300 amplitude has been most reliably reported using auditory "odd-ball" ERP paradigms

(Ford et al, 1994) however abnormal P300 has also been demonstrated using visual ERP tasks (Pass et al, 1980; Knott et al, 1999).

As models of P300 amplitude are often couched within theories of attention and stimulus evaluation, abnormal P300 in schizophrenia has been interpreted to reflect among other possibilities, a reduction in limited capacity attentional resources. In addition, as minimal P300 amplitude differences between target and non-target CPT stimuli have been reported by Pass et al (1980) and Knott et al (1999) in schizophrenic patients, it has been suggested that in addition to the contention that schizophrenics possess a reduction in their available attentional resources, schizophrenics seem unable to appropriately direct their attentional resources to relevant, target stimuli.

The present study however did not find any significant differences in P300 amplitude between patient groups and controls. Moreover, this study found large differences between patient elicited P300 target and non-target P300 waveforms (primarily at parietal sites), in that P300 amplitude to the relevant task stimuli was consistently and appropriately larger than P300 amplitude to non-relevant task stimuli.

Reports of prolonged latency have also been documented in schizophrenia P300 research, however less reliably than reports of attenuated P300 amplitude. As P300 latency is believed to reflect the time required for evaluation and categorization of a stimulus (Donchin, 1979), prolonged P300 latency in schizophrenia is interpreted to reflect attentional deficits relating to speed of stimulus evaluation.

A large majority of studies to date have reported robust abnormalities in P300 amplitude response and CPT performance when comparing schizophrenic patients to healthy controls using either behavioural or ERP measures or a combination of the two.

However to the contrary, the results of the present study indicate little difference in performance between patients and controls.

However, an important distinction between these past studies and the present study is that the vast majority of subjects in these past studies were receiving conventional type anti-psychotic medication as their primary treatment for schizophrenia. Approximately eighty percent of patients in this sample (i.e. both familial and sporadic patient samples combined) were receiving atypical drugs as their primary treatment for schizophrenia (approximately 36% of patients were receiving risperidone, 27% were receiving olanzapine and 17% were receiving clozapine). The type of atypical anti-psychotic medication received by patients in either sample was relatively equivalent, however there were more sporadic patients who were receiving conventional neuroleptics.

Since the 1950's with the introduction of pharmacological treatment for schizophrenia, typical neuroleptics such as halperidol, stelazine and chlorpromazine have been the primary medications prescribed for clinical treatment. As a class, typical neuroleptics exert their pharmacologically effects as antagonists of dopamine 2 (D_2) post-synaptic receptors, working to block post-synaptic activity, thus reducing the amount of dopaminergic activity. The dopaminergic theory of schizophrenia proposes that schizophrenia is caused by excessive dopamine activity in certain synapses of the brain. Research has shown however that typical neuroleptics are primarily effective only in reducing positive symptoms (Sharma & Mockler, 1998; Meltzer & McGurk, 1999) and exert relatively little effect, if any in reducing negative symptoms or schizophrenia-linked cognitive deficits (Kane & Mayerhoff, 1989). Moreover, there is evidence that typical

neuroleptics in fact cause further impairment in some cognitive functions, particularly in motor function and memory (Heaton & Crowley, 1981; Earle-Boyer, et al, 1991).

With over forty years of treatment with conventional medications, abnormal cognitive functioning, a fundamental aspect of schizophrenia has seen little improvement. More recent research is now showing that the new class of anti-psychotic referred to as “atypicals” (received by 80% of this sample) are demonstrating efficacy in promoting areas of cognitive functioning known to be deficient in schizophrenia. Atypical anti-psychotic drugs are differentiated from conventional medications in that they share potent serotonin type 2A receptor (5-HT_{2A}) antagonist properties and exert relatively weaker dopamine receptors type 2 antagonist action relative to typical neuroleptics.

Clinical use of atypical type anti-psychotic medications began with the introduction of clozapine, then risperidone and olanzaepine. The research to date suggests that these agents, as a group appear to be superior to typical neuroleptic medications not only with regard to cognitive functioning (Sharma & Mockler, 1998) but also appear to reduce negative symptoms and disorganized behaviour (Meltzer & Stockmeier, 1992; Kane et al, 1998). Furthermore, atypical anti-psychotic medications have shown to be just as effective, if not more, in reducing positive symptoms (Breier et al, 1994; Umbricht et al, 1998) than halperidol and are more effective in treating treatment resistant schizophrenics (Hagger et al, 1993; Green et al, 1997). These newer drugs have also shown to produced fewer extra-pyramidal symptoms (EPS) compared to conventional medications (Meltzer, 1995). Reduction in the occurrence of EPS's is an important factor in cognition as the often large number of EPS's produced by conventional agents may have further promoted

impairment of cognitive functions requiring motor ability, such as reaction time performance (Meltzer & McGurk, 1999).

Reports available to date on the effect of atypicals on cognitive functioning seems to suggest that individually, these drugs exert differential effects on aspects of cognitive functioning.

Clozapine, the first atypical drug introduced into clinical practice, has shown to exert its' effects primarily in cognitive areas of attention, verbal fluency and executive functioning (Sharma & Mockler, 1998; Meltzer & McGurk, 1999). Improvement in attention following clozapine treatment has been observed in both treatment responsive (Lee et al, 1994; Grace et al, 1996) and treatment resistant (Hagger et al, 1993; Hoff et al, 1996) schizophrenics.

Working memory has shown the most improvement following risperidone treatment, in both treatment responsive (McGurk et al, 1996; Rossi et al, 1997; Meltzer & McGurk, 1999) and treatment resistant schizophrenics (Green et al, 1997). Furthermore, two studies (Stripp & Lussier, 1996; Kern et al, 1999) reported a 20% improvement in reaction time from baseline (i.e. halperidol controlled) following risperidone treatment.

As olanzapine has only recently been introduced into clinical practice, there is just one study looking at the effect of olanzapine on cognitive functions. Meltzer & McGurk (1999) studied 20 schizophrenic patient, 10 of who met the criteria for treatment resistant schizophrenia. Baseline performance on various neuropsychological tests was obtained while patients were receiving conventional neuroleptics. Cognitive testing was repeated following six weeks of olanzepine treatment. Improvement was reported on measure of

executive function, verbal learning and memory (i.e. word list), verbal fluency (i.e. word association) and reaction time.

Three studies to date have looked at the effect of clozapine on the auditory P300 component of the event-related potential. These investigators Schall et al (1995), Umbricht et al (1998), and Pallanti et al (1999) all reported significant increases in P300 amplitude following clozapine treatment compared to baseline conventional neuroleptic assessments. Clozapine induced P300 amplitude enhancement may reflect a “top-down” effect, in that improvement in limited capacity attentional resources may have subsequently produced an increase in P300 amplitude (Umbricht et al, 1998). This hypothesis is supported by observations that P300 amplitude is directly modulated by vigilance, as experimental demonstrations have shown that a break in vigilance decreases P300 amplitude and when attentiveness resumes, P300 amplitude increases (Johnson 1986). However, P300 amplitude increase following clozapine treatment may also reflect improved functioning of critical brain regions (for example, P300 generators) responsible for processing of relevant stimuli, thus secondarily producing larger P300 amplitude (Umbricht et al, 1998). Umbricht and colleagues (1999) also looked at the effect of risperidone on auditory ERPs using an open label, pilot study. Investigators reported a decrease in peak P300 latency following risperidone treatment with no significant effect on P300 amplitude.

The bulk of research so far suggests that atypical anti-psychotic treatment for schizophrenia is more efficacious in promoting cognitive functioning than conventional neuroleptics. However, the majority of these studies suffer from various methodological problems including small and vaguely defined samples, are open labeled and non-

randomized, and often lack suitable control groups. Future research with more methodologically sound paradigms are needed to promote further understanding of the effects of atypicals on measures of sustained attention at both the behavioural and electrophysiological levels. However, from the cumulative evidence reported so far, it is quite possible that future research will report improvement in measures of sustained attention in schizophrenia following treatment with atypical drugs as current research is showing improvement in other measures of attention and in other cognitive domains.

In this line of reasoning, it is quite possible that atypical drugs may have impacted on behavioural performance and P300 response observed in the present study and thus undoubtedly affected any potential significant differences that otherwise may have been observed between the familial and sporadic patient samples.

The major limitation of the present study was the lack of control over the type and dose of medication received by both the familial and sporadic patients. No prior attempts were made to differentiate the patient samples on medication type as the majority of the existing literature (patients receiving conventional neuroleptics) reported that schizophrenia-linked cognitive dysfunction is independent of the effects of medication.

For future research in this area, application of the familial/sporadic strategy in a baseline controlled, double blind, randomized drug study would better aid in identifying the mechanisms of attentional and overall cognitive dysfunction in familial and sporadic schizophrenia. For example, utilizing the DS-CPT concomitantly with P300 recordings where one group receives one atypical drug and the other group receives another atypical and a control group. Another possibility could be where one group receives an atypical such as olanzapine and the other group receives a conventional neuroleptic such as

halperidol. Moreover, assessment of differential effects of atypicals on schizophrenia-linked attentional deficits in controlled drug studies would also promote further understanding of the differential effects of clozapine, risperidone and olanzapine on cognitive functioning.

TABLES

Table 1

Follow-up independent t-tests for a group effect of reaction time.

	Familial vs. Controls	Sporadic vs. Controls	Familial vs. Sporadic
First Analysis	$p < .002$	$p < .009$	n/s
Second Analysis	$p < .009$	$p < .038$	n/s

Table 2

Follow-up dependent t-tests for a time effect of reaction time.

Block 1 vs. Block 2	$t(40) = -4.98, p < .000$
Block 1 vs. Block 3	$t(40) = -6.15, p < .000$
Block 2 vs. Block 3	$t(40) = -3.10, p < .004$
Block 4 vs. Block 5	$t(40) = -4.06, p < .000$
Block 4 vs. Block 6	$t(40) = -4.86, p < .000$
Block 5 vs. Block 6	$t(40) = -2.27, p < .029$

Table 3

Follow-up dependent t-tests for reaction time across time blocks within patient groups.

	Block 1 to block 2	block 1 to block 3	block 2 to block 3
Familial	$t(12) = -2.97, p < .012$	$t(12) = -5.93, p < .000$	$t(12) = -2.86, p < .014$
Sporadic	$t(13) = -2.58, p < .023$	$t(13) = -2.73, p < .017$	n/s

Table 4

Follow-ups dependent t-tests for reaction time across time blocks within the control group.

block 1 to block 2	$t(13) = -5.26, p < .000$
block 1 to block 3	$t(13) = -4.65, p < .000$
block 1 to block 4	$t(13) = -5.77, p < .000$
block 1 to block 5	$t(13) = -5.60, p < .000$
block 1 to block 6	$t(13) = -5.90, p < .000$
block 2 to block 3	n/s
block 2 to block 4	$t(13) = -2.47, p < .028$
block 2 to block 5	$t(13) = -3.23, p < .007$
block 2 to block 6	$t(13) = -3.06, p < .009$
block 3 to block 4	$t(13) = -2.20, p < .047$
block 3 to block 5	$t(13) = -3.26, p < .006$
block 3 to block 6	$t(13) = -4.24, p < .001$
block 4 to block 5	n/s
block 4 to block 6	n/s
Block 5 to block 6	n/s

Figure 1

Figure 2.

Figure 3.

Figure 4.

Figure 5.

Familial Schizophrenics

Sporadic Schizophrenics

Controls

— target
..... non-target

-100 0 1000
milliseconds
6
6 μV

Block 1

Block 2

Block 3

Block 4

Block 5

Block 6

— Familial Schizophrenics
- - - Sporadic Schizophrenics
... Controls

-100 0 1000
milliseconds
-6
6
 μV

Figure 8.

Figure 9.

Appendices A:

INFORMED CONSENT

Title of study: Event-Related Potentials and CPT in Familial and Sporadic Schizophrenics
(MA Thesis)

Principal Investigator: Jemeen Horton, BA Hons (PSY)

Supervisors: Verner Knott, Ph.D and Brian Tansley, Ph.D (Carleton University, Psychology Dept.)

Co-Investigator: Alain Labelle, M.D.

Description of Study: Attentional deficits have been consistently documented in schizophrenia research. It has been hypothesized that attentional and information-processing dysfunctions underlie formation of psychotic symptoms of this disorder. These deficits have been observed in both chronic and treatment-responsive patients as well as in groups at high-risk (e.g. children of schizophrenics) for schizophrenia. However, there is evidence that attentional dysfunctions may be more common and profound among patients with a family history of schizophrenia than in those without a family history. The objective of this study is to compare attentional processing deficits in schizophrenics with and without a family history of schizophrenia using both behavioral and electrophysiological measures of attention.

Study Procedure: Subjects will attend the laboratory for one orientation session and one test session. During the orientation session, subjects will be introduced and become familiar with the study procedures and will be required to practice on the computer task measuring attention. The task is ten minutes in duration and requires that you try to detect targets on the computer screen using a computer mouse key. While you are carrying out this task, sensors placed on your scalp will monitor brain electrical responses that have been shown to be sensitive to attention. Testing will be carried out in the morning following overnight abstinence of drugs (e.g. aspirin, antihistamines, herbal drugs etc.), alcohol, caffeine-containing substances and cigarettes. Neuroleptics and adjunct medications will be withheld from the patients for the same time period.

Possible Risks: The risks are very minimal. Brain wave activity monitoring procedures are similar to those carried out in hospitals except these study procedures use computers for measurement and for controlling performance tasks. Slight redness may occur where electrodes are placed on the scalp and skin.

Data Confidentiality: Information will be coded and your privacy will be protected. Any publications from this work will be designed as to preserve your anonymity.

Appendices B:**CONSENT FORM**

Consent Statement: I, _____, agree to participate in the above-described project, the nature and possible complications of which have been explained to me.

I also consent that any data collected as a result of my participation in this project may be utilized for education and/or scientific purpose.

I have received promise that my identity will be protected in the use of this material.

I have received guarantee that I may withdraw from participation at any time and that my withdrawal will not affect my clinical treatment.

I further understand that my legal rights, regarding negligence and the liability of the institution of its agents, are not waived.

Although details of this study have been explained to me, if I have any additional questions concerning the study I can contact Dr.Knott (722-6521, Ext. 6843).

Date

Signature of Research Subject

Date

Signature of Witness

Date

Signature of Investigator

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