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# WORKING MEMORY DYSFUNCTION IN SCHIZOPHRENIA: AN EVENT-RELATED POTENTIAL STUDY

by

JOHN ALAN BATES III

A dissertation submitted to the Graduate Faculty in Psychology
in partial fulfillment of the requirements for the degree of Doctor of Philosophy,
The City University of New York

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## ABSTRACT

WORKING MEMORY DYSFUNCTION IN SCHIZOPHRENIA:

AN EVENT-RELATED POTENTIAL STUDY

by

John Alan Bates III

Advisor: Ray Johnson Jr., Ph.D.

There is considerable evidence to support an integral relationship between pre-frontal cortex (PFC) function and working memory (WM). Recently PFC and WM have been implicated as structures and functions respectively, that may underlie some of the cognitive deficits and symptomatology observed in schizophrenia. The present study employed a test of auditory-verbal WM (i.e., Letter Number Span) and tests of visual-verbal WM (i.e., Continuous performance tasks). The continuous performance tasks (CPTs) taxed the WM system, manipulating load in two dimensions; 1) rule complexity and 2) delay. The CPTs were administered while concurrently obtaining event-related potentials (ERPs). ERPs were employed to index the registration of sensory stimuli (N1), and the time course of subsequent cognitive analysis (P3), allowing for identification of the information processing stage, or stages, where WM dysfunction became manifest. Sixteen clinically and diagnostically stable outpatients and sixteen well matched healthy controls participated. Multimodal WM dysfunction in schizophrenic subjects was evident in the present study. Behavioral measures proved *sensitive* to WM dysfunction in schizophrenics revealing reduced accuracy and slowed reaction time (RT). Auditory-verbal WM showed clear deficits in the patient group. In the visual-verbal modality,

patients consistently displayed reduced accuracy and increased RT across the CPT tasks. However, patient performance did not worsen when task complexity and delay intervals were increased, suggesting a generalized cognitive deficit, not a dysfunction specific to WM processes. ERP measures were *specific* in elucidating the stages of WM where dysfunction manifested. N1 amplitude in response to target stimuli was larger in the patient group, suggesting altered sensory processing of stimuli during CPT tasks. The increased N1 amplitude findings suggested that dysfunction in the WM system was present as early as the stage of sensory registration, and is consistent with hypotheses of an early processing imprecision in schizophrenia. N1 latency and P3 latency did not reveal significant differences between groups, therefore, processing speed appeared normal up to P3. The finding of normal P3 latency in schizophrenic subjects with concurrently delayed RTs, indicated slowed response selection and execution in the patient group. Response inhibition deficits suggested by more FAs, along with a possible frontal shift in P3 distribution suggestive of greater recruitment of frontal cortex, provided evidence that frontal structures contributed to the deficits observed in the schizophrenic group.

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Philosophically I want to express a deep gratitude to my children who have taught me the greatest lesson I have ever learned, perspective. I dedicate this thesis to Marybeth and the children.

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## INTRODUCTION

### SCHIZOPHRENIA

#### History of Schizophrenia

Schizophrenia is a disabling mental disorder characterized by cognitive, emotional, social, and occupational dysfunction that arises during late adolescence or early adulthood, and generally persists for the duration of the individual's life. The notion that schizophrenia is a "brain disease" appears in the literature as early as 1852 when the Belgian psychiatrist Benedict Augustine Morel described a condition in which a young individual experienced severe emotional and intellectual disturbance. Morel labeled this disorder "demence precose" (Swartz & Africa, 1988).

Over a century ago the Scottish psychiatrist Thomas Clouston proposed the idea of a developmental, or adolescent, insanity. He characterized the condition as having a male predominance, a poor outcome, and noted the frequency of a familial history of minor physical abnormalities. He considered it a disorder of cortical development with the onset of psychotic symptoms due to maturation during adolescence "of certain parts of the brain which had lain dormant before." Clouston's idea was subsequently eclipsed by the broader "dementia praecox" espoused by Emil Kraepelin (O'Connell, Woodruff, Wright, Jones, & Murray, 1997).

The German psychiatrist Emil Kraepelin (1896) described a subset of mentally ill

patients who displayed both emotional and cognitive impairment that began in adolescence and progressively worsened. He termed the disorder "dementia praecox." His original diagnosis had a narrow definition and was based on factors such as early age of onset, an insidious dementing course, and poor outcome. This view was narrow in its definition and led to a homogenous group of patients with a surprising 3:1 male to female ratio. The diagnosis was founded on factors that appear to represent long-term trait-like qualities.

After Kraepelin's initial description, the Swiss psychiatrist Eugen Bleuler (1908) replaced the term "dementia praecox" with the term "schizophrenia," which means "splitting of the mind." Like his predecessors, he believed schizophrenia was a brain disorder. However, Bleuler did not believe the disorder inherently followed a chronic and deteriorating course, or that it necessarily had an onset in early adulthood. With the initiation of this new criterion the male to female ratio disparity was reduced, age of onset rose, and course and outcome became more varied (Murray, O'Callaghan, Castle, & Lewis, 1992; Garver, 1997). This theoretical framework initiated a divergence from the original Kraepelinian concept of the disorder, and subsequent research pursued this track (Carson & Sanislow, 1993; LaFosse, 1991). This broadening of the categorization intrinsically caused the selection of a more heterogeneous group. The new diagnosis focused on present symptomatology, placing the emphasis on state like qualities (Mauri et al., 1992). The wave of research that followed in the ensuing years remained more or less on the path that Bleuler initiated. Subsequent to Blueler, the foundations for the current conceptualization of schizophrenia emerged. The Schneiderian school of thought,

which emphasized first rank and positive symptoms, continued up until late 70's early 80's. At that time findings of functional hypo-activity in frontal brain regions and ventricular enlargement brought more compelling evidence that schizophrenia was a brain disease (Weinberger, Berman, & Zec, 1986), (Johnstone et al., 1989). Additionally, the work of Crow (1980) began a focus on negative symptoms and type I/II distinctions (Crow, 1985).

**Current Conceptualization of Schizophrenia (Symptomatology)**

Currently, the DSM IV classification schemes are among the most widely used for diagnosing schizophrenia in the United States (The Task Force on DSM-IV, 1994). Five- sub-types of schizophrenia are defined: catatonic, disorganized, paranoid, undifferentiated, and residual.

The DSM IV criteria for the diagnosis of schizophrenia are based largely around the ideas of Schneider and his first rank symptoms (positive symptoms such as hallucinations and delusions). First rank symptoms, however, appear in many other disorders (e.g. affective disorder with psychotic features), they *do not* occur in one third of schizophrenic patients, and they have no predictive validity (Carson et al., 1993; Murray et al., 1992). This has led to a great deal of heterogeneity in the classification of individuals as schizophrenic (Garver, 1997; Ban, Guy, & Wilson, 1984); (Kirkpatrick, Buchanan, Breier, & Carpenter, Jr., 1994; Crow, 1995).

More recently, subtypes of schizophrenia have been broken down by symptom clusters. Overt Symptomatology is often described in terms of three broad categories: positive, negative, and disorganized. The use of the positive and negative symptom

clusters scheme was first introduced by Crow (1980). The positive symptoms of schizophrenia are those that are characterized by a presence of abnormal behavior or experiences. Positive symptoms include distortions or exaggerations of perception (hallucinations), and inferential thinking (delusions). Negative symptoms are those that involve a lack of normal behavior or experience. Negative symptoms include restricted range of affect (affective flattening), lack of motivation or will for goal directed behavior (avolition), inability to experience pleasure (anhedonia), and poverty of thought and speech (alogia). Since the initial conceptualization of the positive and negative symptoms categorization, a third broad category, termed disorganization, has emerged (Bilder, 1985). It was demonstrated that these three domains were statistically unrelated. Disorganized symptoms include language and speech (disorganized speech), behavioral monitoring (disorganized or catatonic behavior, inappropriate affect) and thought disorder.

Crow (1980) demonstrated that positive and negative symptoms are statistically unrelated. Therefore, patients can present with both types of symptoms. Historically negative symptoms have been more difficult to treat. Newer generation anti-psychotic medications have offered some promise in ameliorating these symptoms, however, they continue to be more persistent than positive symptoms (Kane, 1996).

**Current Conceptualization of Schizophrenia (Structure/Function Relationships)**

Since the 1950's when it was discovered that phenothiazines produced substantial improvements in psychotic symptoms, the idea that schizophrenia is due to a neuropathological process became more widely accepted (Zuffante, 1995). While

numerous investigations into the mechanisms of schizophrenia followed, early studies failed to identify gross brain abnormalities or hallmark histopathological markers of schizophrenia (Zuffante, 1995).

In the ensuing years many brain areas have been identified as being involved in schizophrenia, ranging from frontal cortex (Weinberger & Berman, 1996a), (Goldberg & Weinberger, 1988), to the limbic system (Arnt, 1998), (Tamminga et al., 1992). However, to date, no single structure, pathway, or combination of the two, has been identified as the sole source of the disturbances in schizophrenia. Much research, though, has focused on frontal and temporal lobe abnormalities.

PET studies of brain function in schizophrenia have demonstrated hypoactivation of frontal regions in comparison to healthy controls (Weinberger, Berman, et al. 1988). Evidence provided by Andreasen (1992) indicated that non-medicated schizophrenia patients showed hypofrontal blood flow while performing the Tower of London task, a test dependent upon intact frontal structures (Goldman-Rakic, 1994). Furthermore, Buchsbaum (1992), using PET to measure cortical activation, demonstrated that medication naive schizophrenic patients exhibited less activity in frontal cortex when performing frontally mediated tasks (Buchsbaum et al., 1992).

MRI research indicates multiple abnormalities of brain structure in schizophrenia, and much attention has focused on findings in temporal and mesiotemporal-limbic structures (Bogerts & Lieberman, 1993). Studies observing such structures have demonstrated gross volume reductions of the whole temporal lobe, the superior temporal gyrus, and/or mesiotemporal structures including the hippocampal formation and/or

amygdala (Bilder et al., 1993).

A series of studies attempting to correlate structural and functional relationships in schizophrenia indicated that deficits on measures of temporal lobe *function* were associated with *structural* deficits within the temporal lobes. Volume reductions within the left superior temporal gyrus, but not whole temporal lobe or hippocampal formation, were associated with: thought disorder (Shenton et al., 1992); left lateralized abnormalities of cognitive ERP's (McCarley et al., 1993); and neuropsychological deficits (Nestor et al., 1993).

Further research suggests that anatomic abnormalities in schizophrenia are asymmetric, with the left hemisphere most often being implicated (Bilder et al., 1993). Studies have found a lack of normal asymmetries among first episode schizophrenic patients affecting cortical (Bilder et al., 1993), mesiotemporal (Bogerts et al., 1990), and cerebellar regions (Snyder, Bilder, Wu, Bogerts, & Lieberman, 1995). Taken together, these findings highlight the possibility that pathologic processes affecting multiple brain structures may be important to understanding the pathophysiology of schizophrenia.

**Cognitive Models of Schizophrenia**

Hemsley (1994) proposed that the basic cognitive disturbance in schizophrenia is a disruption in the normal integration of past stored experience with current sensory input, and the ability of neural circuits to predict forthcoming regularities of sensory stimuli. Repeated exposure to stimuli causes stored memories to form of the spatial and temporal regularities inherent in those stimuli. These stored memories are activated when stimuli are presented and help to automate stimulus processing, thereby reducing

information processing demands. The process by which an individual uses stored memories to automate processing of sensory information is termed "response bias." Hemsley suggested that schizophrenics fail to utilize the temporal and sequential cues in their environment, and as a result do not establish appropriate response biases. Without the formation of appropriate response biases schizophrenic patients can not adequately reduce information processing demands. This places schizophrenics in a state of "information overload." The reduced influence of regularities of past experience on current perception affects cognition in several ways. First, sensory input can be ambiguous and unstructured, resulting in the intrusion of unexpected/unintended material from long term memory. Additionally, it can result in heightened awareness of irrelevant stimuli. This altered sensory perception can in turn lead to cardinal symptoms of schizophrenia such as delusional beliefs (Hemsley, 1994).

Frith (1992) developed a model to describe the information processing deficits and brain regions involved in producing many of the positive and negative symptoms of schizophrenia. This model centers around deficits of "willed action" and "willed intention." Willed actions are behaviors guided by internal motivations and cues, as opposed to being triggered by environmental stimuli, they are volitional acts. Willed intentions are the conscious representations of volition, which signal that our acts are under our control. In this model, deficits of willed action should result in several consequences. First, initiation of activity should be greatly reduced resulting in symptoms such as social withdrawal, poverty of action, and poverty of thought content. Secondly, a failure to terminate otherwise appropriate responding should result in a

tendency to repeat previous actions or produce stereotyped automatic responses. Third, a lack of normal voluntary inhibition of responses to irrelevant stimuli should lead to the production of inappropriate behavior to stimuli in the environment (Frith, 1995). Failures in willed intention can also explain key schizophrenic symptoms. Frith's model suggests that willed intentions should not only lead to a motor response, but also send a corollary discharge to neural mechanisms that label our actions as internally generated (Christensen & Bilder, 2000). When this system is damaged, volitional acts seem as if they are under external control leading to symptoms of hallucinations and delusions.

*Negative symptoms* (withdrawal, affective flattening, alogia, anhedonia, and avolition), according to Hemsley's model, are seen as compensatory measures in response to the "information overload" experienced by patients (Hemsley, 1994). And according to Frith, impaired willed action could result in the inability to initiate action, leading schizophrenics to demonstrate a lack of activity including poverty of speech, flattening of affect, and social withdrawal (Frith, 1995).

*Positive symptoms* (hallucinations and delusions), according to Hemsley's model, become manifest as a result of perceptual distortions and exaggerations (Hemsley, 1994). Frith explains these symptoms in his prediction of damage to willed intention. He states that schizophrenic patients fail to appropriately discern stimuli generated in the external world from those generated internally. Normal individuals are able to monitor their own thoughts and actions. People with schizophrenia are thought to have a defect in their internal monitor. As a result they mistakenly experience their own thoughts and actions as arising from external agents. This misallocation of causality, and the perception of

some internal actions as being initiated by external agents, can result in delusional symptoms such as thought insertion (Frith, 1995). This model is consistent with Shallice's (1988) supervisory attentional system which was put forth to describe automatic versus consciously selected action, which the author suggests is mediated by the frontal lobes. Lastly, Frith's prediction that people with a damaged willed action will demonstrate a tendency to repeat previous actions (i.e., perseveration), or produce stereotype responses, is supported by schizophrenic patients' tendency to perseverate on themes, words, and actions.

## WORKING MEMORY

### Working memory - initial conceptualization

Working memory (WM) refers to the ability of the brain to store and manipulate information over brief time periods, ranging from seconds to minutes. In order for an individual to appropriately respond to internal and external stimuli, information about the stimuli and the source of the stimuli must be kept in mind, relevant features must be extracted, and then that information must be maintained in short-term memory until the response is made. This constellation of processes is often termed working memory(Baddeley, 1998a).

WM was originally conceptualized by Baddeley (1974) as consisting of three subcomponent systems: the central executive, the visual-spatial sketchpad, and the phonological loop (Baddeley, 1992). The *central executive* system was assumed to be an attentional-controlling system, which selected the materials made available for conscious processing. This central executive system coordinated the efforts of its two slave

systems, the *visual-spatial sketchpad* and the *phonological loop*. The visual-spatial sketchpad is responsible for the maintenance and manipulation of visual images. It is postulated that this loop comprises two processes: a short term buffer, and a 'sketchpad.' The short-term buffer is responsible for registration of visual (non-verbal) material (e.g., form). The 'sketchpad' is responsible for the rehearsal and maintenance of images until they are utilized in subsequent processing (Ruchkin, Johnson, Grafman, Canoune, & Ritter, 1992). The phonological loop stores and rehearses speech-based information. It is postulated that this loop comprises two functionally linked processes: a short term buffer, and an output buffer. The short term buffer registers initial sounds, and the output buffer passes the encoded information on to the phonological store (Ruchkin et al., 1992). Verbal information is stored in the phonological store and kept online through rehearsal of material within the phonological loop.

Baddeley's (1974) initial characterization of a three part WM system (central executive, phonological loop, and visuospatial sketchpad) has been confirmed, and greatly expanded upon. Separate systems for visual-spatial, visual-object, and verbal information have been refined. Each of these systems have been subdivided on the basis of storage and rehearsal processing demands. The effects of increasing memory load, and task complexity, have been explored in these systems. Additionally, cortical organizational theories have been proposed to explain how the brain processes stimuli from different modalities, and how it operates with varying task demands.

**Animal Studies of WM**

The first evidence about the physiological substrates of WM came in the early

1970's from studies of non-human primates trained on delayed-response tasks (Fuster & Alexander, 1971; Kubota & Niki, 1971). In a delayed response task the animal must retain a specific location over a delay period. This requires activation of the spatial WM system. Delayed response tasks differ from traditional conditioning paradigms in that the desired response is different from trial to trial, so that information relevant to the response on one trial is irrelevant on the next. Electrophysiological studies performed on awake, behaving, non-human primates trained on such tasks revealed that neurons in and around the principal sulcus in the prefrontal cortex (BA 46) became activated during the delay period of a delayed response trial (Fuster et al., 1971; Kubota et al., 1971).

Goldman-Rakic (1994) postulated that the prefrontal cortex is important for producing behavior guided by information maintained and updated in WM. She administered a delayed match to sample task, requiring the animal to hold a representation in mind over a delay in order to respond to a later cue, while concurrently obtaining electrophysiological recordings (Goldman-Rakic, 1994). Her findings showed that during delay periods, when the animals were required to keep memories on line in order to react to later stimuli, neurons in and around the principal sulcus in the prefrontal cortex were activated. The results indicated that Brodmann's Area (BA) 46 was involved in the processing of visual stimulus location (visual-spatial WM), while BA 12 and BA 45 were more concerned with visual stimulus features (visual-object WM) (Goldman-Rakic, 1994)

One study of non-human primates distinguished spatial WM from associative memory processes (Friedman & Goldman Rakic, 1994). Associative memory is the

process by which stimuli and events acquire permanent meaning. Reference memory, semantic memory and procedural memory are all *associative*. Two groups of monkeys were trained either on tasks that specifically engaged WM, or on tasks that relied upon associative memory (Friedman et al., 1994). Local cerebral glucose utilization was measured in each group. The results showed that spatial WM tasks significantly enhanced glucose utilization by 19% in the principal sulcus region of prefrontal cortex, and by 11–20% in regions of the inferior parietal cortex (Friedman et al., 1994). These findings are important in that they show concurrent activation in both the prefrontal and parietal cortex which suggests that these areas represent important nodes in a neural network mediating spatial WM in non-human primates(Friedman et al., 1994).

Animal studies can only approximate visual-spatial WM in humans, and have no capacity to address verbal WM. Human WM experiments are more complex because language is often employed to encode and represent stimuli. Experiments designed to identify subsystems of WM generally employ visually presented stimuli. However, visual stimuli are not unidimensional. There are three types of visual information employed in WM tasks. Visual information can be coded with respect to its spatial, object, and verbal content. Visual *spatial* information is mediated by the occipital-parietal pathway, sometimes referred to as the "where" aspect of a "where/what" system (Mishkin, Ungerleider, & Macko, 1983). Visual *object* information is mediated by the occipital-temporal pathway, sometimes referred to as the "what" aspect of a "where/what" system (Mishkin et al., 1983). Visual *verbal* information requires recoding. Access to the phonological store is relatively direct for auditory verbal

information, since it already exists as a phonological code. However, visual inputs that are linguistic symbols must first be converted by the phonological loop system into phonological code (i.e., grapheme to phoneme) (Becker, MacAndrew, & Fiez, 1999). Therefore, there exist three types of visual information; spatial, object, and verbal (phonological). Human WM experiments are generally framed within these three modalities

**Central-executive system WM - information load and information manipulation**

The central executive system allocates attentional resources to different task components, and coordinates slave-system properties (Rypma, Prabhakaran, Desmond, Glover, & Gabrieli, 1999). The central executive system becomes activated under conditions of high load, or when manipulations of online information are required. Evidence for physiological substrates of central-executive WM in humans began to emerge in the 1980's with the advancement of functional imaging techniques. One of the first such studies sought to identify areas of cortical activation in subjects performing a demanding WM task (Weinberger et al., 1986). This experiment utilized a xenon inhalation technique to measure regional cerebral blood flow (rCBF) in subjects performing the Wisconsin Card Sort (WCS) (Weinberger et al., 1986). The WCS is a complex task which likely recruits the central executive system of WM. Although there are spatial, object and verbal components to the task, these aspects require little active rehearsal since cue cards containing these essential elements are provided for the subject. During performance of the WSC healthy control subjects showed a clear increase in rCBF in dorsolateral prefrontal cortex (DLPFC(Weinberger et al., 1986)), and DLPFC

was the *only* area which showed such an increase (Weinberger et al., 1986). The results indicate that the DLPFC comprises at least one area that is important in central executive WM function. Electrophysiological recordings obtained from healthy controls further implicate the frontal lobes as a neural substrate vital to the integrity of central executive WM functioning (Ruchkin, Johnson, Jr., Canoune, & Ritter, 1990).

The importance of DLPFC in central executive WM functioning has been supported by other researchers. A group of healthy controls performed the WCS while single photon emission computed tomography (SPECT) data were collected (Rezai et al., 1993). The results showed increased rCBF in the left DLPFC (Rezai et al., 1993) supporting the notion of a locus in DLPFC, possibly left biased, for central executive functioning. In an experiment designed to observe brain activity related to short-term storage of information in WM, a Sternberg paradigm was employed to parametrically manipulate load (Ruchkin et al., 1990). The results indicate that the DLPFC comprises at least one area that is important in central executive WM function. Electrophysiological recordings obtained from healthy controls further implicate the frontal lobes as a neural substrate vital to the integrity of central executive WM functioning (Ruchkin et al., 1990).

The central executive system of WM appears to be mediated by bilateral prefrontal cortical structures. Rypma (1999) demonstrated that middle and superior frontal cortex is activated not only by tasks that overtly demand manipulation in WM, but also when the demands of maintenance exceed the capacity of slave systems (Rypma et al., 1999). When short-term storage capacity is exceeded, strategic processes may need to

be employed to maintain items in WM. Results from behavioral studies support the notion of central executive involvement in WM storage tasks with above-capacity memory loads (Rypma et al., 1999). Under such circumstances increased activation in middle and superior PFC was observed (Rypma et al., 1999). Therefore, it is apparent that the central executive WM system can become involved in simple maintenance tasks when load is high enough, and that it is mediated by BA 9/46 (Rypma et al., 1999). Further evidence of DLPFC involvement in central executive WM is provided by Smith and Jonides (1997). In this experiment WM load was parametrically altered using an n–back task with four levels of difficulty (Smith & Jonides, 1997). The results indicated that, as load increased, activation in WM areas increased. The only new region to apparently be recruited was the DLPFC, indicating that as task difficulty increased the central executive system was employed. In this task it was in an effort to maintain updating of temporal codes (Smith et al., 1997). An electrophysiological experiment of healthy controls comparing an X-CPT task to an AX-CPT task, using steady state visual evoked potentials, displayed transient reductions in right prefrontal amplitude and latency in the more difficult AX-CPT (Silberstein et al., 1998). In this methodology a reduction in amplitude is consistent with increased regional activity, and a reduction in latency suggests increased neural information processing speed (Silberstein et al., 1998). The authors suggest a specific role for the right PFC in the AX-CPT task (Silberstein et al., 1998).

Central-executive WM has bi-lateral characteristics, but is also mediated by the type (e.g. visual or verbal) and extent of processing demands. Depending on the

combination of load and modality, central-executive WM may display a hemispheric bias. Rypma (1999) showed that activation of prefrontal regions was limited to the left hemisphere (left inferior frontal gyrus) under conditions of low load (Rypma et al., 1999). As load increased inferior frontal cortex showed a greater extent of activation in the left hemisphere than the right hemisphere, consistent with other WM maintenance studies (Rypma et al., 1999). However, in middle and superior frontal regions activation was bilateral, but greater in the right hemisphere. This greater right frontal activation suggests that the right hemisphere may play the principal role in the executive components of WM (Rypma et al., 1999). Smith and Jonides' (1997) review of their WM experiments, indicated that activation was observed in DLPFC when subjects were required to carry out computations in WM (Smith et al., 1997). Activation was somewhat bilateral in spatial WM tasks but with greater right DLPFC activation. Activation in verbal memory tasks was almost exclusively in left DLPFC. The findings indicate that although activation of DLPFC may be somewhat bilateral, hemispheric preferences for processing of spatial (right) and verbal (left) information still exist (Smith et al., 1997).

**Visual-verbal WM - storage and rehearsal**

A number of studies indicate that visual-verbal WM is mediated by structures in the left hemisphere. Paulesu (1993) sought to delineate subcomponents of the 'articulatory loop' (verbal WM). Subjects were administered tasks thought to uniquely tax either the rehearsal system or the phonological store, while measures of rCBF were obtained (Paulesu, Frith, & Frackowiak, 1993). The distribution of cerebral blood flow in these conditions localized the phonological store to the left supra marginal gyrus, whereas

the rehearsal system was associated with Broca's area (Paulesu et al., 1993). This represents one of the first demonstrations of the anatomy of the components of verbal WM. Baddeley's (1998) review article of converging neuroimaging findings also associates the phonological store with left supra marginal gyrus (Wernicke's area), and the articulatory rehearsal loop with Broca's area (BA44) (Baddeley, 1998b).

Smith and Jonides (1997) lend further support for a two component architecture of verbal WM. In these experiments posterior cortex was associated with the storage/retrieval of information, while anterior regions were seen to mediate rehearsal of online material (Smith et al., 1997). The storage/retrieval system in left posterior parietal cortex, seems to be homologous to that area in right hemisphere which serves as a spatial buffer (Smith et al., 1997). The frontal regions activated in this verbal WM experiment included Broca's area, the premotor area, and the supplementary motor area, indicating that these areas are important for verbal rehearsal processes. (Smith et al., 1997). This finding is not surprising given these areas integral relationship with language. As with spatial WM tasks, when verbal WM tasks are made more difficult by increasing the number of items that must be kept in memory for subsequent comparisons, and employing multiple stimulus types, some bilateral activation appears in posterior parietal regions (Smith et al., 1997). Rympa (1999) used a Sternberg task requiring subjects to remember either 1, 3, or 6 letters in an effort to manipulate verbal load while obtaining fMRI. The results indicated a left-biased bilateral-frontal activation as verbal WM load increased, consistent with the notion that rehearsal/maintenance of verbal material is mediated near Broca's area (BA 44) (Rypma et al., 1999). Therefore, Broca's area and

adjacent speech related regions (supplementary motor area) appear to be important for verbal rehearsal processes.

Lateral PFC may be more specific for the processing of verbal, as opposed to spatial, information. An fMRI study assessing differences between verbal and spatial WM showed that lateral PFC, rather than dorsal PFC, was activated during a verbal WM task (Thomas et al., 1999). The authors felt that this pattern of results supported the notion that spatial and nonspatial information may be represented in different locations in prefrontal cortex (Thomas et al., 1999).

**Visual-Spatial WM - storage and rehearsal**

The results of a number of studies indicates that visual spatial WM is mediated predominantly by structures in the right hemisphere. In a spatial working memory experiment conducted by Smith and Jonides (1997), four areas of activation were noted, all in the right hemisphere. Further analysis revealed that two of the activated regions were in the *inferior* posterior parietal cortex, and *superior* posterior parietal cortex (Smith et al., 1997). They interpreted the findings to mean, in light of lesion studies, that this superior posterior parietal area is involved in the storage of visual-spatial information (Smith et al., 1997). The function of the two regions activated in right-frontal cortex in the spatial task were less clear, but they interpreted them as being involved in rehearsal of visual spatial material (Smith et al., 1997). One caveat of the aforementioned research is that each WM system tested used a different type of stimulus (e.g. spatial tasks used asterisks, while verbal tasks used letters). To address the issue that differences in cortical activation between visual-spatial and visual-verbal WM tests could be due to the type of

stimulus used, Smith and Jonides (1997) described another series of experiments in which more than one type of stimulus was employed (two-dimensional tasks) (Smith et al., 1997). The results of these experiments contrasted with earlier findings suggesting that spatial WM is not completely a right hemisphere function. An additional area in the left posterior parietal region was activated during these two dimensional tasks. However, there continued to be more right, rather than left, activation. The researchers attributed the additional left activation to the greater difficulty of the tasks. This finding is important because it indicates that spatial WM may be a bilateral process, especially when tasks demand increase. Awh and Jonides (1995), offered a more explicit segregation of the spatial WM system indicating that the spatial storage buffer is located in right inferior posterior parietal cortex; which is equivalent to the findings of Smith and Jonides (1997) (Smith et al., 1997). However, the spatial rehearsal system was described as a cortical loop including the right superior posterior parietal cortex, *and* the right premotor region.

There is corroborating evidence that the right hemisphere is dominant for processing spatial information. An fMRI study designed to assess developmental differences in spatial WM showed that right DLPFC (BA 10/46) was activated during a spatial WM task (Thomas et al., 1999). This right lateralization of prefrontal activation is consistent with other studies of spatial WM noted previously. However, this study also indicated that spatial tasks activated more *dorsal* PFC as opposed to *lateral* PFC areas (Thomas et al., 1999). This is important because it indicates that there may be a specific dorsal/lateral cortical organization with regards to spatial information processing.

In summary, spatial WM tasks clearly activate right hemisphere regions of parietal and prefrontal cortex. (Jonides et al., 1993; Thomas et al., 1999). Storage processes are mediated by inferior parietal cortex, whereas rehearsal processes are likely mediated by a superior parietal to premotor loop.

**Visual-Object WM**

Visual object WM appears to be mediated more by structures in the left hemisphere. Smith and Jonides' (1997) indicate that visual-object WM is similar to visual-verbal WM. Three of four areas activated in a visual-object WM experiment were in the left hemisphere, while a fourth structure was in a midline area (Smith et al., 1997). The cortical regions activated for object WM are for the most part analogous to those for verbal WM, with the exception of a region in the inferotemporal cortex, an area known to be involved in object recognition (Smith et al., 1997). This inferotemporal activation is unique to the object condition, and may play a role on the storage/retrieval of object information. This experiment did not show any areas of activation specific to visual object rehearsal. Rather, activations noted in the left premotor area (known to be involved in speech) and in left posterior parietal cortex (the verbal buffer) were interpreted to mean that subjects internally generated verbal descriptions of objects and *verbally* rehearsed them (Smith et al., 1997). Therefore, visual-object WM appears to share the same mechanisms that subserve visual-verbal WM rehearsal. As such a unique storage vs rehearsal system has not been clearly made for visual object WM. Although very similar to the visual verbal system, the fact that visual-object WM uniquely activates inferotemporal cortex indicates that it is an independent aspect of WM.

**The role of load in WM**

Two variables employed to elucidate differences in WM subsystems are the amount of material to be remembered, and the duration that it must be retained. WM capacity is about 3 - 4 items when the contributions of mnemonically useful processes such as rehearsal and long-term memorization have been eliminated (Cowan, 1998). This is about the number of items that can be recalled without errors across many trials, and about the maximum number of items that can be grouped together into a single "chunk." This storage capacity of approximately 3 to 4 chunks of data appears to exist for both visual and verbal material(Cowan, 1998).

One possible confound in PET and fMRI activation studies is that manipulation of load intended to tax specific aspects of the WM system may have a general effect on brain activation leading to non-specific cortical activation. In fact Baddeley (1998) suggested that as task difficulty increases, more brain areas are activated (Baddeley, 1998b). However, other researchers have provided evidence to the contrary. Smith and Jonides (1997) described a PET experiment using an test requiring the subject to evaluate a currently presented stimulus in relation to a stimulus presented either one, two or three trials earlier (n-back task). Load is increased by requiring the subject to remember further back. Their data suggested that as load increased the same areas showed increasing activation, not that different areas were recruited (Smith et al., 1997). These results support the hypothesis of more processing in fixed areas. In addition, the data showed that only areas involved with WM increased in activity as load increased. Other areas of the brain did not become more active when WM tasks became harder (Smith et al., 1997).

So there was no general cortical recruitment in response to higher loads.

**Dorsolateral and Ventrolateral PFC Organization**

Dorsal and ventral theories of prefrontal cortical organization have been proposed to explain differences between: 1) spatial and nonspatial information processing (domain specific); 2) maintenance and manipulation of information (process specific); and 3) low or high information requirements (demand dependent).

Domain-specific theories suggest that non-spatial processing is subserved by ventral lateral frontal cortex, while spatial processing is subserved by dorsal lateral frontal regions. It has been proposed that lateral PFC in nonhuman primates is organized in a dorsal/ventral fashion subserving the temporary storage of "where" and "what" information respectively (D'Esposito, Postle, Ballard, & Lease, 1999). D'Esposito (1999) indicates that dorsolateral PFC is critical for maintaining an object's location in space, whereas ventrolateral PFC is critical for maintaining information about an object's color and shape (D'Esposito et al., 1999). However a review of the literature by D'Esposito indicated that there is insufficient support for a dorsal/ventral dissociation of spatial vs object WM (D'Esposito et al., 1999). Another form of domain specific frontal organization, based on results from studies with humans, posits that spatial information is processed in the right hemisphere while non-spatial information is processed in the left hemisphere (Rypma et al., 1999).

Process-specific theories suggest that maintenance of information is subserved by the ventral lateral frontal regions, while manipulation of information is subserved by dorsal lateral frontal regions. Petrides (1989) proposed that lateral PFC is organized in a

dorsal/ventral fashion subserving the manipulation or maintenance of information respectively (D'Esposito, Zarahn, & Aguirre, 1999; D'Esposito et al., 1999). BA 9/46 is thought to be involved in manipulation of information, whereas BA 45/47 is involved in maintenance. Therefore, dorsal and ventral systems are seen to be important in terms of processing demands, rather than the type of information being processed (D'Esposito et al., 1999). In a fMRI study, D'Esposito (1999) measured DLPFC activation during maintenance and manipulation verbal WM delayed response tasks. The findings indicated that both DLPFC and VLPFC became more active during delay periods for both types of task. However, there was significantly greater bilateral activation in DLPFC in the manipulation task. The authors suggested that DLPFC uniquely subserves manipulation (D'Esposito et al., 1999).

Demand-dependent theories suggest there is a functional segregation of frontal cortex that can be either domain specific or process specific depending on load requirements (Rypma et al., 1999). Rypma's (1999) review of several experiments showed that less demanding tasks tend to invoke more ventral frontal regions, and the laterality of activation in these tasks appears to be largely determined by the nature of the material (i.e., verbal material is left lateralized, and spatial information is right-lateralized), consistent with domain specific theories of frontal functions (Rypma et al., 1999). More demanding tasks on the other hand, tend to invoke dorsal and bilateral activation that is material independent in nature (Rypma et al., 1999). When memory load exceeds capacity the executive system may be invoked. Such central executive activation was observed bilaterally, but was dominant the right hemisphere, in DLPFC.

These results are consistent with the process specific theories of frontal function (Rypma et al., 1999).

**Summary**

In general there appears to exist a qualitative double dissociation between spatial and verbal WM (Smith et al., 1997; Baddeley, 1998b). Overall, right-hemisphere posterior parietal and premotor regions are part of the network for spatial WM, whereas left-hemisphere posterior parietal and Broca's regions are part of the network for nonspatial WM. In that Broca's area is adjacent to the left-hemisphere premotor cortex, there is substantial symmetry between the regions subserving spatial and non-spatial WM. The DLPFC appears to mediate the central executive system and to be critically involved when computations must be performed on WM, regardless of the whether spatial or non-spatial stimuli are used (D'Esposito et al., 1999). In contrast, activation within VLPFC during tasks that require only maintenance of different types of information tend to be lateralized with right hemisphere processing spatial information, and left hemisphere processing nonspatial information (D'Esposito et al., 1999).

Attentional systems which modulate WM processes are also grouped into dorsal and ventral systems according to the dual cytoarchitectonic trends theory (Christensen et al., 2000). The ventral-lateral trend, which arises from paleocortical structures, mediates the arousal system responsible for phasic response to stimuli (Christensen et al., 2000). Through the arousal system the brain orients to novel stimuli, facilitating the ability to process stimuli from the environment. The dorsal-medial trend, which arises from archicortical structures, mediates the activation system responsible for maintaining tonic

readiness for action (Christensen et al., 2000). The activation system supports postural readiness and motivationally directed action, supporting the ability to act on the environment. Given the shared cortical structures, it is possible that the tonic attentional system is intertwined with central executive mediated WM, and the phasic attentional system with the maintenance of modality specific information in WM.

## REVIEW OF ELECTROPHYSIOLOGY

### Background on ERPs

Before beginning a discussion of the use of ERPs in WM research, a brief review of ERPs will be provided. Electroencephalography (EEG) is a technique utilizing electrodes placed on the scalp to record brain electrical activity. EEG has proved a useful tool for the investigation of organic mental syndromes and underlying pathophysiology (Fenton, 1984). Continuous EEG recordings can be segmented into smaller units termed 'epochs'. Epochs therefore represent some duration of EEG. Although an epoch can theoretically be any duration in length, generally it will encompass anywhere from several hundred milliseconds to several seconds. Epoching data provides a means to analyze specific segments of an EEG recording. Averaging epochs that are time locked to a specific event produces what is termed an event-related potential (ERP). By selecting only epochs in which a specific event occurs, and then averaging them together, a waveform is produced that represents the average cortical response to the event. The averaging process also helps to reduce the contribution of cortical activity unrelated to the event (noise). Any cortical activity present in the epochs that is not dependent on the event is most likely occurring at random, in temporal terms. By taking multiple epochs

and averaging them together, this random noise tends towards zero, and the remaining waveform is exclusively representative of cortical processing of the event (Picton, 1994). Epoching of digitized EEG recordings allows for virtually unlimited classification of stimuli and responses. ERPs have proven very useful in identifying some of the functional anatomy (Klein, Rockstroh, Cohen, & Berg, 1996), neurotransmitter systems (Oades, Dittmann Balcar, Zerbin, & Grzella, 1997), and stages of information processing, involved in the dysregulation of the WM system (Shelley, Grochowski, Lieberman, & Javitt, 1996; Javitt, Doneshka, Grochowski, & Ritter, 1995).

ERPs provide an index of information processing through a cognitive system. One advantage of this technology is its ability to catalog the linear progression of brain activation at a time resolution in the millisecond range. Additionally, it is the only non-invasive technique that can do so. Cognitive processes taking place in parallel can be observed through multi-electrode systems that allow many brain regions to be sampled simultaneously. Such electrophysiological recordings can provide an indication of the time course of neural activation under varying cognitive tasks.

**Components of the ERP**

The ERP waveform consists of a series of positive and negative voltage deflections, or 'peaks', that mark the passage of information through the nervous system. ERP 'components', unlike peaks, are usually defined as variations in the waveform that are related to specific experimental variables (Johnson, Jr., 1995). Thus, at least some ERP components may therefore encompass more than one peak (Johnson, Jr., 1995). For instance, the processing negativity component can have effects measurable at the N1, P2,

and N2 peaks. The naming convention employed for most components is a combination of the polarity (positive or negative), and the latency (in ms) at which the component displays peak amplitude after stimulus presentation. For example, the component P300 indicates a positive deflection in the waveform occurring approximately 300 ms after stimulus presentation. Components can be broken down into two broad categories; exogenous, and endogenous.

*Exogenous components* (e.g. N1, P2) are those whose amplitudes and latencies are determined by the physical properties (e.g. intensity) of the stimuli (Johnson, Jr., 1995). Exogenous components occur shortly after stimulus presentation and are thought to index automated aspects of stimulus registration. As such they are also often referred to as *sensory components*. *Endogenous components* (e.g. N2, P3), which follow exogenous components, depend upon task demands and represent cognitive processing of the meaning of stimuli, as opposed to simple sensory registration. As such they are often referred to as *cognitive components*. Endogenous components are insensitive to the physical properties of the stimuli. Endogenous component amplitudes and latencies depend almost entirely on the presence and nature of the cognitive tasks associated with the stimuli. The amplitudes of endogenous components tend to reflect the amount of information processed, while latencies reflect the speed with which processing occurs (Johnson, Jr., 1995).

Regan (1989) clearly reiterated Hillyard's (1987) classic illustration of the nature of exogenous and endogenous components. ERPs were obtained in four different experimental paradigms. In the first paradigm a subject listened to a sequence of tones

and kept a running mental count of the number of improbable tones of higher pitch. The ERPs elicited by both probable and improbable tones contained N1 and P2 components, whereas only the improbable tone contained the additional P3 component (Regan, 1989). This indicates that P3 is a response to a cognitively relevant event (identification of target) rather than a simple obligatory response to a stimulus, as N1 and P2 appear to be. In the second paradigm, stimulus intensity was decreased from a sensation level of 70dB to 40dB. In this paradigm N1 and P2 were diminished in amplitude, while P3 was unchanged (Regan, 1989). This illustrates that P3 is not dependent on the physical characteristics (e.g. intensity) of the stimulus, whereas N1 and P2 are. The third paradigm required the subject to count the number of times a tone was omitted from a repetitive train of stimuli. A P3 component appeared after this omission, although there were no earlier N1 or P2 components (Regan, 1989). This demonstrates that N1 and P2 are completely dependent on the presence of a physical stimulus. However, P3 is generated when an internal representation of an expected stimulus is maintained. Clearly the cognitive representation of the stimulus is what is most important for the generation of the endogenous P3 component. In the fourth paradigm, the subject ignored auditory stimuli and read a book, there was no late positive component associated with ignored, improbable stimuli. This indicates that when there is no active cognitive processing of the deviant stimuli, P3 does not occur. This illustration shows that P3 is dependent on the cognitive characteristics of the task, whereas N1 and P2 are much more dependent on the physical characteristics of the stimuli (Regan, 1989). Therefore, N1 and P2 will be considered exogenous, and P3 will be considered endogenous.

*N1/P2 component*

N1 is observed as a negative deflection in the waveform occurring approximately 100 ms after stimulus presentation in the auditory modality, and shortly thereafter in the visual modality. N1 is maximal at frontal leads in the auditory modality, and occipital leads in visual tasks. In healthy controls visual N1 displays a laterality effect with larger amplitude observed at O2 then at O1 (Strandburg et al., 1999). N1 is thought to index stimulus detection and to some extent attention (Verbaten et al., 1994). N1, being exogenous, is sensitive to the physical characteristics of stimuli. N1 is evoked by abrupt changes in the energy level impinging on the sensory receptors (Naatanen, 1992). Stimuli with very slow onsets do not elicit this response (Naatanen, 1992). N1 can also be elicited by the offset of a stimulus, but only if the stimulus has been continuously presented for at least 500 ms. If stimulus intensity is decreased, the N1 response displays amplitude attenuation and increases in latency. N1 amplitude is seen to increase along with increasing stimulus intensity, although there is a saturation level at which N1 no longer increases. N1 is also sensitive to stimulus rate, displaying increasing amplitude with increasing inter-stimulus interval up to 10 sec. The P2 component varies quite similarly in most conditions to the N1 component, however, they can be dissociated from one another based on scalp topography (Naatanen, 1992).

*P3 component*

P3 is observed as a positive deflection in the waveform occurring approximately 300 ms after stimulus presentation in the auditory modality, and shortly thereafter in the visual. P3 is maximal at central parietal leads in both modalities. P3 is thought to reflect

temporally and spatially overlapping contributions from multiple intracortical generators (Johnson, 1993), (Johnson, Kounios, & Nolde, 1996). Some generators for posterior P3 activity have been identified in association regions of the superior temporal gyrus and the temporoparietal junction (Knight, Scabini, Woods, & Clayworth, 1989). A role of the hippocampus in modulation of P3 also has been suggested, although these findings are not based on scalp recorded P3 (Halgren & Smith, 1987).

The initial observation of the P3 component was reported in 1965 by Sutton, Braren, Zubin and John (Sutton, Braren, Zubin, & John, 1965). These researchers conceptualized the P3 as reflecting the resolution of uncertainty. Increased P3 latency has been interpreted as a slowing of attentional processing, stimulus evaluation, or of memory updating, whereas reduction in P3 amplitude has been interpreted as an index of decreased attentional resources available for performing task related processing (Reinvang, 1998).

P3 is an endogenous component and therefore dependent on the cognitive aspects of the task from which it is elicited. P3 occurs at highest amplitude to low probability stimuli that are both attended and convey information. P3 amplitude is affected by several factors. P3 amplitude is known to have an inverse relationship with stimulus probability (Johnson, 1986; Johnson, Jr., 1995). In addition, P3 amplitude is known to be proportional to "stimulus meaning"; stimulus meaning is the processing of stimulus information not related to probability. The portion of P3 amplitude sensitive to changes in meaning is a function of three independently manipulable variables; 1) Task Complexity, 2) Stimulus Complexity, and 3) Stimulus value. Increases in task

complexity lead to increases in P3 amplitude (Johnson, 1986; Johnson, 1993). P3 amplitude reduction can be interpreted in terms of Johnson's (1986) model to reflect equivocation and inappropriate allocation of attention (Strandburg et al., 1994).

## ERPS IN THE STUDY OF WM

### Specialized systems for verbal and visual information

ERPs are frequently utilized in the study of information processing. Hillyard (1993) argues that electrical and magnetic recordings can help to delineate the neural system and information processing operations that underlie auditory and visual perception, selective attention, mental chronometry, and memory (Hillyard, 1993). Evidence for ERP's specific effectiveness in tracking changes in WM is supplied by Gevins (1996). ERPs were recorded from 8 subjects during WM (high memory load) and control tasks (simple matching) (Gevins et al., 1996). The tasks required matching each stimulus with a preceding stimulus on either verbal or spatial attributes. All stimuli elicited a central positive potential approximately 200 ms after stimulus presentation that was larger in the spatial tasks than in the verbal tasks, and larger in the WM tasks than in the control tasks (Gevins et al., 1996). Frequent, non-matching stimuli elicited a frontal, positive peak at approximately 300 ms that was larger in the spatial WM task relative to the other tasks. Irrespective of whether subjects attended to verbal or spatial stimulus attributes, non-matching stimuli in the WM tasks also elicited an enhanced positive potential over the left frontal cortex approximately 450 ms after stimulus presentation, followed by a sustained potential over the superior parietal cortex (Gevins et al., 1996).

These results indicate that WM is a function of a distributed system with specialized systems for processing verbal and spatial information types (Gevins et al., 1996).

Many ERP studies of WM employ variations of delayed match to sample paradigms. In these tasks, subjects are presented with an initial stimulus (S1) that must be committed to memory for a delayed comparison with a subsequent stimulus (S2). Following which subjects must decide whether the two stimuli matched or not (mismatch). Sternberg (1969) demonstrated that in such tasks increases in stimulus set size resulted in decreases in response accuracy and concomitant increases in RT.

ERP experiments provide converging evidence with findings in fMRI and PET studies that there are separate specialized brain systems for the processing of visual-spatial and visual-verbal information. One early ERP study found that negative slow waves were largest over the left hemisphere during phonological memory operations, and largest over right hemisphere during visual memory operations (Rugg, 1984). A follow up to the prior study demonstrated and confirmed that slow waves over right hemisphere indexed visual-spatial material in WM and left hemisphere activity indexed visual-verbal WM material being held on line (Barrett & Rugg, 1990). Another experiment comparing visual-spatial and visual-verbal (phonological) memory showed that in a phonological task there was a parietal positive slow wave that was larger over left hemisphere shortly after stimulus presentation, probably during encoding (Ruchkin et al., 1990). It was followed by a left anterior negativity. Both the posterior and anterior slow waves increased with the amount of phonological information being held in working memory (Ruchkin et al., 1990). In contrast to the result of the phonological task, in the visual-

spatial task there was a parietal positive slow wave which was larger over the right rather than the left parietal scalp. This wave displayed increasing amplitude with the amount of visual-spatial material that needed to be kept in memory (Ruchkin et al., 1990). The phonological results of the Ruchkin (1990) experiment were replicated in a study of patients with multiple sclerosis (Ruchkin et al., 1994). Ruchkin (1994) showed that left frontal negativity was sensitive to phonological working memory deficits such that lower aptitudes were associated with higher error rates (Ruchkin et al., 1994).

One study designed to delineate the electrophysiological profile of the maintenance of visual information in WM utilized a Sternberg paradigm which manipulated memory load by requiring subjects to memorize either three or five items (Ruchkin, Canoune, Johnson, Jr., & Ritter, 1995). After presentation of the stimuli, during the retention interval, there was high amplitude-slow wave negative activity largest over right parietal and central scalp, indicating that this wave indexes maintenance of visual information (Ruchkin et al., 1995). Ruchkin et al (1994) found that variation of phonological memory load was associated with a lower amplitude negativity over left frontal sites (Ruchkin et al., 1994). It was correlated with performance accuracy, and neuropsychological measures of articulation rate. Thus this left sided slow negativity is thought to represent rehearsal of phonological information in the working memory system. Further evidence supporting specialized verbal and spatial systems comes from an experiment which manipulated memory load through variation of the number of letters (visual-verbal) or figure locations (visual-spatial) to be remembered (Ruchkin et al., 1992). Slow negative activity localized over occipital and left posterior temporal scalp

appeared to index phonological processing. Slow negative activity over right posterior scalp sites appeared to index visual-spatial information processing (Ruchkin et al., 1992). This posterior negative slow wave began right after P3 and was larger for visual material. Early on, probably during an encoding phase, it was lateralized to the right hemisphere, but later during the retention interval it shifted to the midline (Ruchkin et al., 1992). The fact that the amplitude of this wave increased with increasing memory load indicates it indexes WM operations. Ruchkin (1995) stated that studies showing negative slow waves associated with working memory retention operations were open to the criticism that the slow negativities actually may have been related to preparation to make the response required in each study (Ruchkin et al., 1995). Preparatory responses have been implicated by the results of numerous experiments showing the presence of negative slow waves (the contingent negative variation CNV) similar to those observed in the working memory experiments. Typically, CNV activity occurs in the interval between warning and imperative stimuli. However, Ruchkin (1995) provided evidence that the CNV does not account for the activity observed in WM paradigms. An experiment was conducted observing conditions of low and high memory load. In both conditions subjects needed to respond. Analysis of these two conditions indicated that the negativity observed was present in high memory load conditions, but not in a simple preparedness to respond condition (Ruchkin et al., 1995).

More evidence for separate systems of verbal and spatial information processing come from study of the P3 component. The earliest evidence of differential processing as a function of material type and information load occurs at the P3 component. The latency

of P3 at Pz is shorter in a visual spatial task, indicating that visual spatial stimuli are processed more quickly (Ruchkin et al., 1992). Faster encoding of visual-spatial information indicates this system may have direct access to the visual spatial sketch pad. P3 amplitude is seen to increase with increasing phonological load, but not visual-spatial load, implicating differential processing based on material type.

**Registration, retention, and the recruitment of central executive processes**

ERPs are valuable because they can fractionate working memory into components of encoding and retention, something technologies with lower temporal resolution can not achieve (Gevins et al., 1996). ERP studies have provided convincing information that phonological information is rehearsed and maintained in left hemisphere, and visual spatial information is rehearsed and maintained in right hemisphere. In addition, the ERP can also index the initial sensory registration of information. An early negativity located over occipital scalp sites and approximately 200 ms after stimulus presentation is seen to index the extraction of information from the stimulus and its initial encoding into the visual-spatial working memory system where it is maintained (Ruchkin et al., 1995). The initial sharp negative deflection was observed as increased amplitude of the exogenous N1 component. The authors suggest that N1 is an index of sensory processing associated with the increase in size and complexity of the stimulus (Ruchkin et al., 1995).

Ruchkin (1990), conducted an experiment to identify slow waves associated with the storage and, more specifically, with the sustained processing which should accompany the retention of information in working memory (Ruchkin et al., 1990). Information load was manipulated by varying the number of unique consonants to be

remembered. A string of six consonants was presented and there could be either 1, 3, or 6 unique characters in the set.

A posterior positive wave was associated with retention of information in working memory, but not with acquisition since it was absent during a search task but varied with load in a memory test (Ruchkin et al., 1990). This posterior positive wave was maximal from approximately 750 ms to 1500 ms, after which it began to diminish but was clearly visible out to 2500ms. The fact that this component varied with load, yet was unaffected by performance accuracy, indicates that its amplitude reflects effort rather than efficiency of performance.

A frontal negativity observed only in high memory load tasks is also believed to index retention of information in working memory (Ruchkin et al., 1990). The frontal negativity was most evident from approximately 1750ms out to 2500 ms after stimulus presentation. The amplitude of this negativity decreased with increasing load in the memory test, but it showed relatively little change as a function of load during the search task. This frontal wave did not vary with accuracy, so its amplitude evidently reflects performance effort and not efficiency, similar to the posterior positive wave. WM capacity is hypothesized to be roughly 3 to 4 "chunks" (Cowan, 1998). When WM capacity is exceeded central executive processes are thought to be recruited to help handle information retention (Rypma et al., 1999; Cowan, 1998; Ruchkin et al., 1990). Since the frontal negative wave discussed here was observed only in the most difficult 6 item memory trials, and was largest over left frontal sites (F3), it may specifically index central executive mediated functions of WM retention. Another experiment showed that

in both visual-spatial and visual-verbal tasks, a left frontal negativity was observed (Ruchkin et al., 1992). It was thought that this frontal negativity may have reflected working memory operations which are not specific to visual-spatial or phonological process, implying that it represents a central executive system (Ruchkin et al., 1992).

P3 is thought to index cognitive function that is not associated with storage or retention (Ruchkin et al., 1990). There is evidence to indicate that P3 indexes working memory load by changes in latency (Ruchkin et al., 1990). In the Ruchkin et al. (1990) study, P3 latency was seen to increase with increasing load. The P3 latency increases were at least partly due to delays in processing stages occurring prior to the stage reflected by P3 (Ruchkin et al., 1990). P3 amplitude, however, was relatively unaffected by changes in information load in search and memory tasks (Ruchkin et al., 1990). P3 amplitude only varied in the 6 item condition where memory loads were highest (Ruchkin et al., 1990). The authors suggested that P3 indexes information acquisition operations not specific to memory retention. Since the P3 does not appear to play a direct role in storage or retention operations, the increased latency of P3 onset may be a manifestation of information processing operations associated with the decision about what information is to be retained until the probe is presented (Ruchkin et al., 1990).

## PFC DYSFUNCTION IN SCHIZOPHRENIA

Schizophrenia is the mental illness that has most often been related to the prefrontal cortex (Weinberger & Berman, 1996a; Weinberger et al., 1986; Goldman-Rakic, 1987); neuropsychological, electrophysiological, and brain imaging studies have all demonstrated PFC dysfunction in schizophrenic populations. Thus, recent cognitive

models of schizophrenia have begun to focus on PFC and WM (Goldman-Rakic, 1994; Goldman-Rakic & Selemon, 1997). This region and its integrity has received much attention as one possible source of dysfunction/dysregulation contributing to the manifestation of schizophrenia. Schizophrenic patients display significant impairment of working memory in the visual, spatial, and auditory modalities (Cohen & Servan-Schreiber, 1992; Cohen & Servan-Schreiber, 1993). Goldman–Rakic (1994) posited that deficits in the working memory system could explain cardinal features of the schizophrenic disorder. Symptoms such as thought disorders, attentional problems, and lack of initiative, plans, and goals, could arise from working memory deficits resulting from PFC dysregulation (Goldman-Rakic, 1994).

The first evidence for an interconnection between PFC and WM dysfunction in schizophrenia arose from comparisons of schizophrenic patients with frontal lobe lesion patients. Damage to the prefrontal cortex leads to blunted affect and deficits in initiation and planning similar to those seen in schizophrenia (Park & Holzman, 1992; Shallice, Burgess, et al. 1991; Stuss, Benson, et al. 1986). Both schizophrenia and frontal patients maintain basic sensory-motor skills, and their performance on simple associative tasks generally falls within the normal range (Goldman-Rakic, 1994). However, WM tasks (those requiring a representation of context) show impairments. Patients with frontal lobes lesions and schizophrenia patients are similarly impaired on the CPT, WCS, Stroop, Tower of London, and delayed response tasks (Goldman-Rakic et al., 1997), all of which require WM. These neuropsychological deficits have been shown to be independent of chronicity, of ongoing psychotic symptoms, and of treatment (Weinberger et al., 1996a).

The PFC is crucial for inhibition of inappropriate responses and behavior. Failure in inhibition can result in attention being allocated to irrelevant stimuli or aspects of a task resulting in diminished performance to relevant stimuli or tasks. For instance, although PFC is *unnecessary* for formation of associative memories, it is *necessary* to inhibit and extinguish behavior based on associative memories. Failure to extinguish behavior results in the classic symptom of perseveration (Goldman-Rakic, 1994). Patients with prefrontal damage perform poorly on neuropsychological tests that require response inhibition such as the WCS (Weinberger et al., 1996a). The PFC is also important for the inhibition of cortical activity elsewhere in the brain. The PFC cortex has powerful regulatory effects on posterior cortical (Goldman-Rakic et al., 1997), and subcortical regions (Weinberger et al., 1996a). Lack of inhibitory output from the PFC is thought to result in abnormally increased activity elsewhere in the brain (Weinberger et al., 1996a). Electrophysiological data supports this notion. Chao (1998) showed that when PFC was blocked auditory ERP amplitude responses become enhanced in primary auditory cortex (Chao & Knight, 1998), indicating that release from PFC inhibition lead to an overreaction in other cortical areas (Chao & Knight 1998). Failure in inhibition then results in higher levels of processing for less relevant stimuli, leading to saturation of cognitive resources and diminished performance on relevant task demands.

Ingvar and Franzen (1974) provided the first physiological evidence of frontal lobe dysfunction in schizophrenia when they showed that chronic schizophrenic patients had less frontal relative to posterior rCBF while resting, when compared with controls who tended to show the opposite pattern (Weinberger et al., 1996a). This finding,

referred to as 'hypofrontality', correlated with the severity of symptoms, especially negative symptoms (Weinberger et al., 1996a). Hypoactivation located more specifically in DLPFC has been found for both high- and low-functioning schizophrenic patients (Cohen et al., 1987). However, hypofrontal findings in schizophrenia are variable and their validity has been questioned, with some studies indicating *hypo*frontality, and other studies indicating *hyper*frontality (Weinberger et al., 1996a). Weinberger (1996) made a strong argument that the variability in the findings is due to the experimental conditions under which the data were obtained. The early studies were done with all subjects resting, which is problematic because they introduce an uncontrolled state. Patients and subjects at rest could easily engage in differing internally generated behaviors. A comprehensive review of the literature reported that only 60% of resting studies found hypofrontality (Weinberger et al., 1996a). Many recent studies have had subjects engage in some cognitive task during data acquisition. These are referred to as cognitive activation studies. The WCS and CPT, which tax central executive WM, are tasks that have often been employed. When only cognitive activation studies (e.g. WM studies) are examined, 90% show hypofrontality in PFC (Weinberger et al., 1996a).

## WM DEFICITS IN SCHIZOPHRENIA

Schizophrenia patients display significant impairments in central executive, visual-spatial, and visual-verbal WM; across the visual, oculomotor, haptic (proprioceptive), and auditory modalities (Cohen & Servan-Schreiber 1993; Shelley, Ward, et al. 1991; Javitt, Doneshka, et al. 1993; Park & Holzman 1992). Tasks that are sensitive to DLPFC damage are often employed to demonstrate these deficits (Gold,

Carpenter, et al., 1997; Park & Holzman, 1992; Spitzer, 1993; Goldberg, Gold, et al., 1990).

**Cognitive activation studies**

PET studies of WM have shown hypoactivation of frontal regions of schizophrenic patients in comparison to healthy controls (Weinberger, Berman, et al., 1988). For instance, poor performance on the WCST is associated with lower regional cerebral blood flow in the prefrontal cortex of schizophrenic patients (Weinberger, Berman, et al., 1992; Waltrip, Buchanan, et al., 1997; Yoshii, Watabe, et al., 1997). One study of twins who were discordant for schizophrenia revealed that, during activation, all the affected twins were hypofrontal in comparison to both their non-affected twin controls and the healthy controls (Weinberger, Berman, Suddath, & Torrey, 1992). A report by Andreasen (1992) indicated that non-medicated schizophrenia patients have impaired performance on the Tower of London task, which requires central executive WM, and showed hypofrontal blood flow while performing the test (Goldman-Rakic, 1994). Buchsbaum (1992), using PET to measure cortical activation, demonstrated that medication naive schizophrenic patients exhibited less activity in frontal cortex when performing the CPT, the observed deficit was interpreted to reflect a failure to activate frontal cortex normally (Buchsbaum et al., 1992). These findings have been replicated. A PET study using an n-back version of the CPT was conducted to look at the effect of increasing memory load on PFC activation (Carter et al., 1998). The n-back task requires the subject to evaluate the current stimulus (a letter of the alphabet) with the stimulus immediately preceding it (1-back) or a stimulus appearing two trials earlier (2-back), etc.

Such tasks likely tax central executive mediated visual-verbal WM. N-back tasks reliably activate DLPFC as a function of working memory (Carter et al., 1998). Activation is sustained during mnemonic activity and varies monotonically with memory load (Carter et al., 1998). This study used a 0-back condition (simple detection of a letter "X") and a 2-back condition to manipulate memory load. Hypoactivation in right frontal regions was observed when WM load increased (Carter et al., 1998). Similar hypofunction was observed in right posterior parietal cortex, an area previously shown to coactivate with DLPFC (Carter et al., 1998). This right sided activation is not consistent with that generally seen in verbally mediated tasks. However, central executive WM is less clearly lateralized than visual-verbal WM. A bias in the central executive WM system has been proposed for the right hemisphere (Rypma et al., 1999), the left hemisphere (Rezai et al., 1993) and either the left or right hemisphere depending on the material to be processed (Verbal=Left, Visual=Right)(Smith et al., 1997). Therefore, perhaps central executive WM plays the predominant role in these CPT type tasks, superceding the visual-verbal components.

Schizophrenics also show consistent deficits on the CPT, particularly when a large demand (longer delay period) is placed on WM (Cohen & Servan-Schreiber 1992). The X-CPT task requires subjects to monitor a continuous series of letters on a computer screen and respond to a target letter (X) and is dependent on PFC integrity. Pass (1980) administered the X-CPT test to schizophrenic subjects and psychiatric controls to assess sustained attention. Difficulty was varied by introducing distracting stimuli from another modality (e.g. noises) during the experiment, thereby increasing load and resulting in

recruitment of the central executive WM system. Schizophrenic subjects displayed smaller P3 amplitude to target stimuli in both the distracted and undistracted conditions, when compared to psychiatric controls (Pass, Klorman, Salzman, Klein, & Kaskey, 1980), indicating impaired attention and compromised PFC function(Pass et al., 1980).

One electrophysiological study using the AX-CPT in schizophrenics revealed disrupted visual-verbal WM that resulted in an inability to inhibit responses appropriately, a function intimately linked to frontal lobe integrity (Shelley, Grochowski, et al., 1996). The AX-CPT task requires subjects to monitor a continuous series of letters on a computer screen and respond to a target letter (X) following a valid cue (A), but not respond to a non-target letter following a valid cue. This task directly taxes working memory because a representation of the cue must be kept in mind and compared to a designated target in order to correctly respond. This study set up a response bias to the target (X) by raising the probability of targets to 80%. The task then became one of inhibition. Schizophrenic patients produced significantly more false alarms (responding to an "X" that was not preceded by an "A") than controls, presumably because they were unable to inhibit a response to invalid targets following valid cues. The data showed paradoxical amplitude effects with schizophrenic patients displaying significantly *larger* P3 amplitude to invalid targets in comparison to controls (Shelley et al., 1996). These data indicate PFC dysfunction resulting in a lack of inhibition on responding and on parietal cortex activity. This demonstrates cortical *dysregulation* in schizophrenic patients, rather than a more general *hypofunction*. Strandburg (1999) also showed paradoxical amplitude effects in schizophrenic patients (Strandburg et al., 1999). This

study employed a visual CPT task that varied context maintenance demands by requiring subjects to respond to a designated target in one task, and the hold in mind one stimulus for comparison to a subsequent stimulus in the other task. Schizophrenic patients showed a larger processing negativity amplitude at temporal leads to non-targets, but smaller amplitude to targets, when compared to controls (Strandburg et al., 1999). This indicates a possible lack of inhibition of PFC on temporal cortex when irrelevant stimuli need to be ignored. In a subsequent experiment, employing virtually identical task conditions, schizophrenic subjects displayed delayed P3 latency as task difficulty increased. P3 latency marks the completion of the processes that comprise stimulus evaluation (encoding, recognition, and classification) (Strandburg et al., 1994). The results indicate a positive correlation between information processing speed and task difficulty (Strandburg et al., 1994). The author interprets the findings to represent deficiencies in the executive control of the neural mechanisms involved (Strandburg et al., 1994).

Cortical dysfunction in schizophrenia is not limited to PFC. Electrophysiological investigation indicates auditory WM deficits for schizophrenic patients. One study employed an auditory continuous performance task to evaluate functioning of auditory sensory memory (Javitt et al., 1995). Auditory sensory memory (ASM), or "echoic" memory, stores information about the *acoustic* attributes of stimuli. This is separate form the phonological loop which maintains *phonological* attributes of stimuli. Information in ASM, is maintained without rehearsal or subvocalization and is thought to be mediated by primary auditory cortex (Javitt et al., 1995). Mismatch negativity (MMN) amplitude, thought to index ASM function, is attenuated in schizophrenic patients (Javitt et al.,

1995). A deficit in this aspect of information processing indicates that dysfunction in schizophrenia is not limited to PFC and extends to the level of sensory cortex (Javitt et al., 1995).

**Behavioral studies**

Park and Holzman (1992) conducted a spatial WM experiment in both visual and haptic (proprioceptive) modalities to see whether schizophrenic patients display multi-sensory deficits. They sought to confirm that spatial WM deficits in schizophrenia arise from a disruption of the internal representation of spatial location, rather than a more basic sensory deficit (Park et al., 1992). Twelve schizophrenics were compared to 12 psychiatric, and 12 healthy controls. For visual-spatial WM they employed an oculomotor delayed response task. Patients were briefly shown a dot in a specific location which they had to keep in WM during a delay. Then, when prompted, they had to guide their eyes to where they thought the dot had been. In the haptic version of this test, subjects kept their eyes closed and had to move their hand to a specific location on a board in front of them. The subject's hand was then guided back to a central fixation point, and after a delay the subject was required to move the hand back to the location in space where it had been. Subjects were also given an auditory-verbal WM task (digit span). Bipolar patients served as psychiatric controls, and healthy volunteers served as normal controls. Schizophrenic patients showed substantial impairment, that worsened with longer delays, on both spatial WM tasks indicating modality independent deficits (Park et al., 1992). The healthy controls, and the psychiatric controls, showed no impairments (Park et al., 1992). Surprisingly, results for the verbal working memory task

did not show any impairment for any group. However, the digit span is a simple task that does not require the manipulation of information in the working memory system. The authors interpreted their findings to mean that there is DLPFC dysfunction in schizophrenia. The authors commented that the PFC has great interconnectivity with other cortical and subcortical structures, and that dysfunction throughout these systems should not be overlooked (Park et al., 1992).

Schizophrenic patients have been shown to make significantly more errors on the continuous performance test (CPT), which requires sustained attention, short-term memory, and inhibition of inappropriate responses; processes dependent on pre-frontal integrity (Gold & Harvey, 1993; Seidman, Yurgelun-Todd, et al., 1994). These behavioral findings implicate a role of the central-executive system in the WM deficits observed in schizophrenia.

**WM deficits in schizophrenia are not an artifact of medication**

Many studies conducted with schizophrenic subjects necessarily include patients receiving medication. Therefore, there is a possibility that working memory deficits observed in schizophrenia patients are an artifact of medication. There is evidence to suggest that this is not the case. For instance, in one spatial WM study schizophrenic patients were compared to a psychiatric control (bipolar disorder) who were receiving similar medications (Park et al., 1992). Whereas schizophrenic subjects showed clear impairments, the medicated psychiatric controls actually performed slightly better than the healthy control group, indicating medication alone can not explain spatial WM impairments (Park et al., 1992). Medication naive patients have been shown to

demonstrate hypofrontality when doing tasks that tax working memory and prefrontal function (Weinberger et al., 1996a). Buchsbaum (1992), using PET to measure cortical blood flow, demonstrated that medication naive schizophrenic patients exhibited less activity in frontal cortex when performing the CPT (Buchsbaum et al., 1992). Therefore, working memory deficits observed in schizophrenia are not an artifact of medication (Sharma & Mockler, 1998).

## PFC CONNECTIVITY

The strong evidence for prefrontal lobe dysfunction in schizophrenia does not mean that pathology exists exclusively in that region. Inter-connectivity between PFC and hippocampal/limbic, parietal, and temporal structures better models the full range of schizophrenic defects. Therefore, many researchers suggest it is a disturbance in the functional connectivity of the brains of schizophrenic patients that is at the root of the disorder (Christensen et al., 2000), (Bilder & Degreef, 1991), (Liddle, 1995). Weinberger hypothesized that schizophrenia involves a subtle static brain lesion that interrupts connections between limbic structures and DLPFC, this lesion would effectively deafferent prefrontal cortex of its mesocortical dopaminergic innervation which would result in dopamine hypoactivity (Weinberger, 1987). This suggests that deficits seen in schizophrenia result from abnormal innervation of, and feedback from PFC, rather than to damage to the region itself. Goldman-Rakic (1994) reported there are several multi-synaptic routes of connectivity between PFC and the hippocampus, and that these connections subserve a cooperative relationship with regard to working memory (Goldman-Rakic, 1994). She argued that cortical feedback pathways between prefrontal

cortex and parietal/temporal association areas, subserving WM, are affected in schizophrenia. These areas play a role with regard to bringing representational data into line with reality, disruption results in the positive symptoms of the disorder including thought disorder, hallucinations and delusions (Goldman-Rakic, 1994). Impairment in some of the feed-forward projections to and from Prefrontal cortex may also be important in certain negative symptoms such as lack of initiative, poverty of speech, and lack of goal directed behavior (Goldman-Rakic, 1994).

Evidence for abnormal functional connectivity in schizophrenia has also come from electrophysiology (Morrison-Stewart, Williamson, Corning, Kutcher, & Merskey, 1991). This study examined the relationship between EEG activity detected at different scalp sites and demonstrated that in normal individuals there is an increase in the alpha wave coherence between left frontal and parietal regions and a *decrease* in coherence between left frontal and temporal regions during a continuous calculation task (Morrison-Stewart et al., 1991). Schizophrenic patients performing the same task showed an *increase* in coherence between left frontal and temporal areas (Morrison-Stewart et al., 1991). These findings of altered coherence indicate that schizophrenic patients have abnormal functional connectivity between left frontal and temporal regions (Morrison-Stewart et al., 1991).

## RELATIONSHIP OF PFC TO SCHIZOPHRENIC SYMPTOMOTOLOGY

PFC is critical for gating or filtering out irrelevant information (Chao & Knight, 1998). Damage in this area results in an inability to focus attention on task *relevant*

information, and to screen out task *irrelevant* information (Damasio, 1995). Early researchers proposed that schizophrenics suffered from a defect in their filtering mechanism. This reflected the influence of Broadbent's early model of attention, which consisted of a selective filter protecting a single channel central-processor of limited capacity (Michie, 1995). Characteristic symptoms of schizophrenia, such as formal thought disorder and hallucinations, were attributed to such a defective filter mechanism (Michie, 1995). However, more recent theories of symptomatology focus on the interconnectivity of PFC (Goldman-Rakic et al., 1997).

Dysfunction in the connectivity between PFC and temporal/parietal regions is thought to be responsible for some symptoms observed in schizophrenia. Goldman-Rakic hypothesized that a likely focus of a lesion in schizophrenia may be the cortical processing networks by which the PFC interacts with parietal and limbic centers to access, and hold on line, representational knowledge of the outside world (Goldman-Rakic, 1994), (Goldman-Rakic et al., 1997). In other words, a dysfunctional connection between WM and associative memory. Such WM dysfunction resulting from disruptions of PFC projections to both parietal and temporal association areas may lead to altered consciousness of sensory experiences, and the manifestation of positive symptoms such as formal thought disorder and hallucinations (Goldman-Rakic, 1994). Spitzer (1997) also supports the notion that schizophrenic symptoms, such as thought disorder, can be accounted for by dysfunctional information processing between WM and associative memory. He hypothesized that the neurobiological equivalent of the WM deficit was a

dysfunctional left lateralized frontal lobe, caused by either a structural deficit or a hypo-dopaminergic state (or both) (Spitzer, 1997).

The perseveration observed in schizophrenia may also be due to irregular connectivity between WM and associative memory. Goldman-Rakic reports that switching categories on the WCS poses a problem for schizophrenic patients because the patient has a deficit in WM and associative learning connectivity (Goldman-Rakic et al., 1997). Patients learn a discrimination task well, but in the WCS that learning must be extinguished when the rule is changed. WM is needed to assess the learned behavior in terms of current feedback to determine that the behavior is no longer appropriate (Goldman-Rakic et al., 1997). This system fails in schizophrenia and results in perseverative behavior (Goldman-Rakic et al., 1997).

Frith (1996) hypothesized that dysfunctional PFC connectivity may underlie schizophrenic symptoms involving the incorrect allocation of causality, such as thought insertion and delusions of control (Frith & Dolan, 1996a). The ability to distinguish ones own behavior as self generated is termed 'agency'. A sense of agency arises when one is aware of choosing between several possible courses of action. If one course of action dominates there is little sense of choice, or agency, and action can be said to be stimulus or context driven. Agency allows one to appropriately interpret what happens in the inside versus outside world, and to correctly allocate causality. There are physiological mechanisms that help identify internally verses externally generated stimuli. For instance, when people speak, there is reduced activity in temporal cortex (Frith & Dolan, 1996b), this feedback mechanism most likely prevents an individual from experiencing

their own speech as arising from an external source. Because of its connections with other cortical structures, the DLPFC is thought to play a central role in agency. Frith (1996) conducted an experiment to see whether internally and externally generated responses produced different patterns of cortical activation. Subjects had to *choose* for themselves which of two fingers to move. This was contrasted with a condition in which they were *instructed* to move a particular finger. During self-generated movement bilateral DLPFC activation occurred. When subjects were told which response to make similar activation did not occur (Frith et al., 1996b). Word generation tasks produce increased activation in DLPFC, and decreased activation in left temporal areas (Frith et al., 1996b). Frith (1996) reports that in both healthy controls and patients, word generation tasks produced DLPFC activation similar to that seen in movement generation paradigm. This indicates that DLPFC is a common substrate in self-generated behavior (Frith et al., 1996b). However, there was a striking failure on the part of patients to show the normal pattern of reduced activity in superior temporal cortex on the left (Frith et al., 1996b). This indicates a lack of PFC inhibition on temporal cortex in schizophrenia patients. Brain imaging studies further support the notion of dysfunctional connectivity between PFC and temporal cortices. Frith reports on brain imaging studies which have shown activity in Broca's area and left temporal cortex during hallucinations (Frith et al., 1996b).

These observations suggest that schizophrenic patients are experiencing intrinsically generated activity as if it were extrinsically generated. In the major psychoses, many of the key symptoms involve a loss of the feeling of agency or the false

perception of agency in the outside world. For example, patients with schizophrenia sometimes report that alien forces are controlling their actions (delusions of control), or that alien thoughts are being inserted in their minds (thought insertion). Frith postulated something is going wrong with the interaction between PFC and posterior brain areas concerned with the content of the experience. Therefore, psychotic symptoms are thought to arise when PFC and posterior areas fail to communicate and a subsequent misallocation of intrinsic and extrinsic sources occurs (Frith et al., 1996b).

## UTILITY OF ERPs IN SCHIZOPHRENIA RESEARCH

ERP research in schizophrenia has provided evidence of impaired information processing, and abnormal patterns of brain activation in patient groups. Reduced P3 amplitudes are thought to reflect impaired information processing of stimulus encoding and have been consistently observed in simple tone discrimination tasks (Verleger & Cohen, 1978) and choice reaction time tasks (Shagass, Roemer, Straumanis, & Amadeo, 1979; Pfefferbaum, Wenegrat, Ford, Roth, & Kopell, 1984; Levit, Sutton, & Zubin, 1973; Maurer, Dierks, Strik, & Frolich, 1990). Prolonged P3 latency during standard auditory discrimination tasks (Souza et al., 1995; Sara, Gordon, et al., 1994) and dichotic auditory selective attention tasks (Baribeau Braun, Picton, et al., 1983) have also been noted. Even when compared to depressed psychiatric controls on a two tone matching task, schizophrenics displayed P3 amplitude attenuation and prolonged latency (Blackwood et al., 1987). Blackwood's (1987) findings were obtained at baseline (prior to neuroleptic intervention) and remained unchanged after 4 weeks of neuroleptic treatment (Blackwood

et al., 1987). In addition, P3 in the two-tone matching task was not influenced by the presence of acute psychotic symptoms (Blackwood et al., 1987).

Analysis of P3 amplitude distributions indicates that differences in scalp topographies may exist for schizophrenic subjects. In an auditory "oddball" paradigm, some researchers revealed selective decreases in P3 amplitude at left temporal leads in schizophrenic subjects (Faux et al., 1993; McCarley et al., 1993). One study required subjects to respond to a rare auditory tone, while at the same time being exposed to novel auditory stimuli (Merrin & Floyd, 1994). P3 to the novel auditory stimuli was located more centrally then that to rare attended target, and latency was faster in controls. Schizophrenics failed to show this faster more centralized P3 response (Merrin et al., 1994). In addition a correlation between P3 amplitude and negative symptoms in the schizophrenics were noted. These findings were interpreted to be consistent with, but not conclusive evidence of, prefrontal impairment (Merrin et al., 1994). P3 in a hebephrenic subtype has been shown to be attenuated in frontal leads, whereas a paranoid group showed lateralized P3 with lower amplitude in right parieto-temporal leads (Maurer & Dierks, 1988). Additionally, different scalp distributions between groups of schizophrenics, depressives, and healthy controls have been observed, inversely correlating amplitude changes with negative symptoms (Maurer et al., 1990). Other researchers, however, have found a generalized decrease in P3 amplitude with no focal selectivity (Pfefferbaum, Ford, White, & Roth, 1989). Schizophrenics were tested with paradigms designed to elicit P3 response automatically or effortfuly (i.e., with a choice reaction time task) (Pfefferbaum et al., 1989). Patients showed reduced P3 amplitudes for

both effortful and automatic paradigms, but there was no evidence that P3 was smaller over left temporal electrode sites in schizophrenics. The authors concluded that P3 amplitude reduction in schizophrenia is a robust phenomenon that is present regardless of medication status or task demands (Pfefferbaum et al., 1989). The frequency of reported P3 attenuation and possible topographical differences indicate that the neural generators for P3 in schizophrenia are either under active, or that different combinations of generators are activating.

ERPs have been utilized to determine subject groupings into schizophrenic subtypes, mood disorders, and healthy controls. One study sought to differentiate patient groups of healthy controls, psychiatric controls, and schizophrenics based on electrophysiological measurements (Sandman, Gerner, O'Halloran, & Isenhart, 1987). This experiment showed that discriminant analyses of auditory ERP's paired with psychometric data, allowed for the differentiation between several patient groups including healthy controls, alcoholics, depressives, and schizophrenics (Sandman et al., 1987). A similar analysis utilizing P3 latency, P3 amplitude, N2 amplitude, N1 amplitude, and eye tracking data was shown to correctly classify 83% of schizophrenic patients and controls into their correct groups (Blackwood, St Clair, Muir, & Duffy, 1991) Beyond the discrimination of broad patient groups amongst the mentally ill, ERPs have the potential to differentiate between subtypes of schizophrenic patients presenting with differing symptomatologies, as well as the ability to reveal physiological patterns implicating anatomical underpinnings of divergent pathophysiological dysfunction. Positive and negative symptom subtypes of patients with schizophrenia have been shown

to display dissimilar neurophysiological profiles, most likely relating to frontal-striatal deficits in negative symptom patients (Gerez & Tello, 1995), (Merrin et al., 1994), and dominant temporal lobe deficits in positive symptom patients (Gerez et al., 1995). Such results are consistent with hypotheses of hypofrontality and temporal lobe dysfunction respectively, in schizophrenia (Gerez & Tello, 1995).

Electrophysiological studies have also attempted to identify components which can index trait like qualities. Several psychophysiological abnormalities associated with schizophrenia have been proposed as genetic trait markers of vulnerability to the disorder. Smooth pursuit eye tracking dysfunction and abnormal long latency ERPs are the most promising candidates. Approximately half of non-schizophrenic relatives showed eye tracking dysfunction and/or abnormal event-related potentials (P3 latency) in a two-tone auditory discrimination task (Blackwood et al., 1991). The P3 latency results were bimodal with one population having latencies similar to the schizophrenic group, and the other with latencies similar to controls. Therefore, P3 latency may be a biological marker for a schizophrenic genotype (Blackwood et al., 1991). Squires-Wheeler (1993) reported P3 amplitude decrements in both the auditory (via an auditory oddball paradigm), and visual modalities (via a visual CPT), were indicative of poor psychological functioning at the time of recording, and 10 years later (Squires Wheeler, E., Friedman, D., Skodol, A. E., & Erlenmeyer Kimling, L., 1993). This suggests that P3 indexes a stable trait.

ERPs in combination with motor responses can also be used to delineate the stage, or stages, at which stimulus processing becomes compromised. For instance, Alzheimer's disease is considered a "cortical" dementia, such dementias have shown

specific patterns of electrophysiological responding (Johnson, Jr., Litvan, & Grafman, 1991). In particular "cortical" dementias generally produce normal early exogenous components (N1, P2), but have abnormal later endogenous components (P3). The class of dementia labeled "sub-cortical" (Huntington's disease, Parkinson's disease) generally exhibit abnormal early components (N1, P2) as well as abnormal late components (P3) (Johnson, Jr. et al., 1991). Increases in RT as load is manipulated provides evidence for the slowing of information processing.

This "stage of information processing" approach can be employed to evaluate schizophrenic patients. Since it is known that increases in task difficulty result in amplitude and latency changes in the ERP (Johnson, 1986), ERPs in schizophrenics should shed light on whether there are early sensory deficits in the automated registration of stimuli (N1, P2) (Ruchkin et al., 1995), later processing deficits (P3) (Johnson, 1986), or both. Deficits in the exogenous components (N1, P2) would indicate an early disruption in the analysis of stimulus information and support the hypothesis that schizophrenics suffer from a rudimentary processing imprecision located at the level of sensory cortex (Shelley, Silipo, & Javitt, 1999), (Javitt, Grochowski, Shelley, & Ritter, 1998), (Javitt, Strous, Grochowski, Ritter, & Cowan, 1997). Deficits in the late P3 component would indicate abnormal endogenous processing of the stimuli, suggesting dysfunction at the later stages of cognitive processing, and would imply that schizophrenia is associated with diffuse higher level cognitive cortex dysfunction (Javitt et al., 1995; Javitt, 1999).

Since WM is a dynamic process that manipulates information very quickly, ERPs provide an excellent means by which to study it. ERPs are able to track information flow at early sensory registration of information indexed by N1 between 100 ms and 200 ms, and encoding operations indexed at approximately 300 ms by P3 (Ruchkin et al., 1995). Storage of phonological information in WM has been indexed by a posterior positive wave observed in the 750 ms to 1500 ms range, and rehearsal in WM has been indexed by a left frontal negativity observed from 1750 ms out to 2500 ms. (Ruchkin, Johnson, et al., 1990). Electrophysiological techniques applied to the measurement of WM have led to a better understanding of neural substrates of this process in healthy individuals implicating frontal lobes in central executive functions and frontal-parietal systems in the maintenance of phonological information in WM (Ruchkin et al., 1995),(Ruchkin et al., 1990),(Garcia Larrea & Cezanne Bert, 1998). In addition, since ERPs provide *continuous* measures of brain functioning they have proven more sensitive than traditional *discrete* behavioral measures (e.g. reaction time, accuracy), which were to date the most commonly used indices of WM function (Shelley et al., 1996).

## RATIONALE FOR THE CURRENT STUDY

There is considerable evidence to support an integral relationship between PFC function (especially BA 46) and central executive WM (Goldman-Rakic, 1994; Smith et al., 1997) (Rypma et al., 1999). Recently PFC and WM have been implicated as structures and functions respectively, that may underlie some of the cognitive deficits and symptomatology observed in schizophrenia. Evidence from neuropsychology (Gold, Carpenter, Randolph, Goldberg, & Weinberger, 1997), brain imaging (Buchsbaum et al.,

1992) and electrophysiology (Shelley et al., 1996) all converge to implicate impaired WM function in schizophrenics. As such, the neural substrates which subsume WM and the temporal course of information flow through this system are currently topics of interest in schizophrenia research.

Most studies investigating WM function in schizophrenics have utilized PET, SPECT, or fMRI. While these techniques provide reasonable spatial resolution of cortical activation during WM tasks, they lack the temporal resolution to capture discreet stages of information processing (e.g. sensory registration and cognitive processing). To date, few studies have employed them to investigate WM function in schizophrenics. Most studies that have utilized ERPs in this effort have focused on early stages of information processing indexing sensory registration and mismatch detection via N1 and MMN (Javitt et al., 1995; Javitt et al., 1997; Strous, Cowan, Ritter, & Javitt, 1995) have left topographical distributions of recorded activity relatively unexplored (Umbricht et al., 1998; Shelley et al., 1996; Shelley et al., 1999).

ERPs will be employed to index the registration of sensory stimuli (N1), and the time course of subsequent cognitive analysis (P3). This will allow for identification of the information processing stage, or stages, where dysfunction becomes manifest. Topographical analysis will assess whether schizophrenic patients show reduced amplitude over frontal leads in comparison to controls, when performing WM tasks. The study will employ continuous performance tasks (CPT) to tax the WM system, manipulating load in two ways; 1) rule complexity and 2) delay. Such load manipulations should enhance any existing differences between groups.

# METHODS

## Subjects

Sixteen clinically and diagnostically stable outpatients (no hospitalizations in the three months prior to testing) willing to participate in ERP assessments were recruited. This sample was drawn from a cohort of over 220 patients evaluated during their first episode of psychotic illness as part of a study conducted at Hillside Hospital. Participant selection comprised individuals who had been in the Hillside study for at least 2 years, but not more than 6 years. There were 12 schizophrenic and 4 Schizoaffective subjects. At the time of testing 10 patients were receiving atypical neuroleptic medication, 4 were receiving typical neuroleptics, 1 was receiving medication for mood disorder, and 1 patient was medication free at the time of testing but had been on a typical neuroleptic up until approximately 1 year prior to the testing.

Sixteen healthy controls, matched on age, sex, race, handedness, and parental socioeconomic status estimated by paternal years of education (Carter et al., 1998), to the patient sample, were also tested. There was a significant difference between the educational level of the healthy controls and patients (HC = 15.2, PT = 13.2; p = .003), however, this was expected because patients often present with symptoms during the college years and are unable to complete their schooling. It has been suggested by some investigators that parental education is a more appropriate variable on which to match controls with patients (Gur, Gur, & Saykin, 1990). Subjects were not matched on I.Q. because as Chapman and Chapman (1973) indicated, equating schizophrenic individuals with normal subjects on the basis of current IQ measurements is problematic due to the

effect of schizophrenic disorder on IQ test performance. Nonetheless, a post hoc analysis of I.Q. was conducted for thoroughness. Data was available on 13 patients and 11 controls. A T-test indicated no significant differences in WAIS-R Full Scale I.Q. (Patients: $\bar{x}$ = 97.1 ± 16.2; Controls: $\bar{x}$ = 103.5 ± 13.5; p = .311). The groups then are considered well matched (see Table 1).

**Table 1: Subject Demographics**

| | Healthy Controls | Schizophrenics | Significance |
|---|---|---|---|
| **Age** | $\bar{x}$ = 27.1 ± 6.1 | $\bar{x}$ = 30.7 ± 7.4 | p = .142 (n.s.) |
| **Paternal Education** | $\bar{x}$ = 13.2 ± 2.8 | $\bar{x}$ = 13.8 ± 3.28 | p = .606 (n.s.) |
| **Sex** | 68.8 % male | 62.5 % male | $Chi^2$ = .701 (n.s.) |
| **Handedness** | 81.25 % right | 87.5 % right | $Chi^2$ = .626 (n.s.) |
| **Race** | 62.50 % White<br>12.50 % Black<br>12.50 % Hispanic<br>6.25 % Asian<br>6.25 % Other | 37.50 % White<br>31.25 % Black<br>12.50 % Hispanic<br>6.25 % Asian<br>12.50 % Other | $Chi^2$ = .623 (n.s.) |

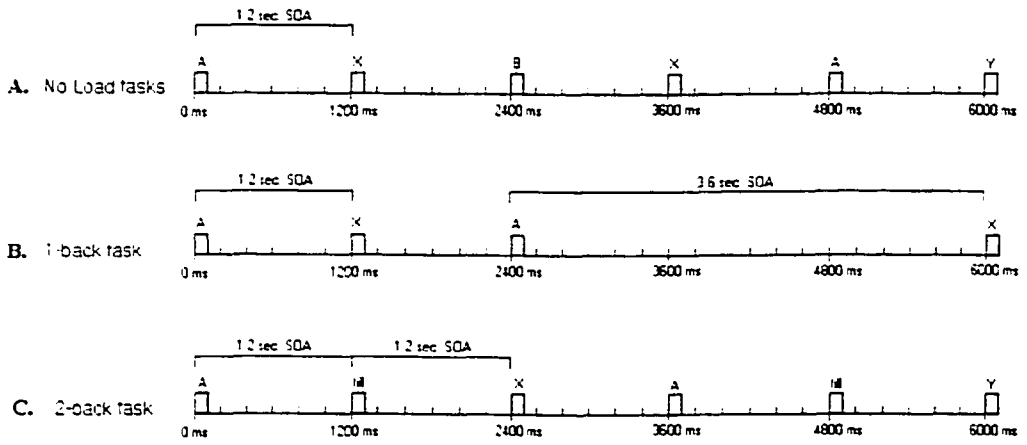
Informed consent was obtained in accordance with the guidelines of the Queens College and North Shore-Long Island Jewish Health System's Institutional Review Boards. No patients were included in the study who were considered incapable of providing informed consent. Subjects were told at the time of informed consent that they had the right to withdraw at any time. Thorough explanation of procedures and procurement of informed consent anteceded commencement of experimental procedures.

Monetary compensation provided to patients and healthy controls was $30.00 for the testing session. Sessions lasted approximately two hours.

**Procedure**

EEG data was collected continuously during all cognitive tasks except for the Letter Number Span. All stimuli and responses were stamped to the digital file. Offline analyses were performed to extract ERP waveforms, accuracy, and RT results. Once connected to he EEG equipment subjects were seated in a comfortable chair 1 meter in front of a computer monitor. Stimuli were presented via the computer monitor, and responses were made on a stimulus response pad with 2 valid response keys. Participants were given standardized instruction for each of four versions a visual CPT task (No Load 50%, No Load 20%, 1-back, and 2-back). Two tests were termed "No-Back" because there was no memory component to them. The other two tasks were termed "1-back" and "2-back" implying the memory load for the task. In the No-Load conditions subjects responded to stimuli based on a predefined target stimulus ("X" or "non-X"). In the No-Load 50% the "X" appeared 50% of the time, and in the No-load 20% the "X" appeared only 20% of the time. These No-load trials were intended to establish a baseline performance in a simple non-WM CPT task and to evaluate the effects of probability manipulation on the ERP response. These tasks were designed to be a *visual* equivalent to the "oddball" paradigm that is often employed in *auditory* ERP research. The manipulation of probability has proven to be a particularly effective method in

**Figure 1.** Schematic representation of stimulus sequences.




modulating P3 amplitude responses (Johnson, 1993; Johnson, 1986). Such parametric manipulation affords an opportunity to observe the generation of P3 across multiple tasks in both groups, ensuring that the wave observed in both groups represents the same component. In the 1-back condition subjects had to identify a stimulus based on the preceding stimulus. In the 2-back condition stimuli had to be categorized based on the stimulus appearing two trials earlier. These *n*-back conditions manipulated WM load in two dimensions. The 1-back task presented stimuli at both a long and a short ISI, providing a *delay* manipulation. The 2-back task served as a *complexity* manipulation. The presentation of stimuli are graphically depicted in figure 1.

*No Load CPT (No-Load 50% and No-load 20%)*

In separate series, the subjects received visual stimuli presented randomly with probabilities of either 20/80 (20% targets and 80% non-targets), or 50/50 (50% targets

and 50% non-targets). The letter "X" was the target, all other letters (e.g. "A", "B", "C", etc.) were non targets. Subjects were instructed to press one of two buttons classifying each letter as a target or non-target as quickly as possible after each stimulus. The visual stimuli consisted of easily discernable letters ("A" through "Z") presented on the center of a CRT for 100 ms A small central fixation spot was presented continuously on the center of the screen except during stimulus presentation. The stimulus onset asynchrony (SOA) was 1200 ms. There was a 1-second time limit for making a response. There were 300 stimuli in each condition (20/80 and 50/50).

*Delay Load CPT (1-back short ISI, and 1-back long ISI)*

In an AX version of the CPT subjects were presented with a string of varying letters on a computer monitor. Targets comprised each "X" that was preceded by an "A". The letter "A" constituted the valid cue; the letter "X" constituted the target. Letters other than "A" or "X" constituted either invalid cues (designated as "B") or incorrect targets (designated as "Y"). Trials were presented in random order in the following proportions: 60% "A" followed by "Y", 20% "B" followed by "X" and 20% "A" followed by "X". Subjects were instructed to press a response button classifying each stimulus as a target or non-target as quickly as possible. There was a 1-second time limit for making a response. Stimulus duration was 100 ms. Stimulus onset asynchrony (SOA) for cues to targets was either 1200 ms or 3600 ms, with a probability of 50% each. These two levels of SOA served as the delay load manipulation on WM. Two blocks of 300 stimuli each were presented.

*Complexity Load CPT (2-back)*

In a "two back," AX, version of the CPT subjects were presented with a string of varying letters on a computer monitor. Targets comprised each "X" that was preceded, two letters previously, by an "A". The letter "A" constituted the valid cue; an intervening random letter constituted the "filler"; and the letter "X" constituted the target. Letters other than "A" or "X" constituted either invalid cues (designated as "B") or incorrect targets (designated as "Y"). Trials were presented in random order in the following proportions: 60% "A" followed by "filler" followed by "Y", 20% "B" followed by "filler" followed by "X" and 20% "A" followed by "filler" followed by "X". The experimenter instructed subjects to press a response button classifying each stimuli as a target or non-target as quickly as possible. There was a 1-second time limit for making a response. Duration of stimulus presentation was 100 ms. Stimulus onset asynchrony (SOA) from one stimuli to the next was constant at 1200 ms. Two blocks of 300 stimuli each were presented.

*Letter Number Span*

This test of working memory function requires the subject to put a mixed list of numbers and letters in numeric and alphabetical order (Gold et al., 1997). Arranged in order of increasing difficulty, this task consists of 24 items. It is discontinued after four consecutive failures.

**Recording**

ERP studies were accomplished using Neuroscan STIM system for stimulus presentation and SCAN system for signal acquisition and data analysis. The study

utilized a 32 channel recording montage that included 19 standard recording positions of the International 10/20 System (Fz, Cz, Pz, Fp1, Fp2, F3, F4, F7, F8, C3, C4, T3, T4, T5, T6, P3, P4, O1, O2), 10 electrodes interpolated at the center of each group of four electrodes (AF3, AF4, AF7, AF8, FC1, FC2, FC5, FC6, CP1, CP2, of the Revised 10/20 system) and electrodes on the left and right mastoid. Eye movement (EOG) monitoring was accomplished through use of an electrode placed 1 cm above the outer canthus of the left eye. Scalp recordings were obtained using an Electro-Cap International recording cap with embedded tin electrodes. Tin cup electrodes were employed for reference and eye movement (EOG) monitors. Electrode impedances were maintained below 5 KΩ. Subjects were grounded with a forehead electrode placed above nasion. Recordings were referenced to the nose. EEG was amplified 20K with a bandpass of 0.1 - 32 Hz by a SynAmp amplifier. The electrophysiological signals were digitized at a rate of 400 Hz per channel and recorded continuously along with stimulus markers denoting stimulus onset and type, as well as behavioral responses. Artifact rejection was performed by off-line visual inspection of continuous EEG waveforms and/or automated rejection of trials with EOG amplitude exceeding preset threshold. Residual artifacts were removed using a sweep by sweep correlational correction procedure. EEG epochs were constructed and averaged for each experiment using a 150 ms pre-stimulus baseline. Only trials with correct responses were included in the averages.

**Data Analysis**

Visual component amplitudes and latencies were determined by automated peak detection within the following latency ranges: N100 was measured at O1 between 75 and

225 ms and P3 was measured at Pz between 275 and 650 ms. The windows were constructed to be large enough to capture peak amplitudes in the event that latencies between groups differed. The windows were based on those used by other researchers who have used visual CPT tasks in schizophrenic patients (Shelley et al., 1996; Strandburg et al., 1999). The timing of the peaks were used for latency and for determining amplitudes at the remaining electrode sites. The same data analyses techniques were used in all conditions.

Repeated measures ANOVA's of group (control vs patient) by condition (No Load 50 %, No Load 20 %, 2-back, 1-back short ISI, and 1-back long ISI) by electrode (Fz, Cz, Pz, Fp1, Fp2, F3, F4, F7, F8, C3, C4, T3, T4, T5, T6, P3, P4, O1, O2, AF3, AF4, AF7, AF8, FC1, FC2, FC5, FC6, CP1, CP2) were performed to test for main effects between groups and conditions on scalp recorded amplitudes of N1 and P3, and to evaluate interaction effects. The Greenhouse-Geisser epsilon adjustment was used for all calculations.

In the event of an interaction effect of group by electrode, N1 and P3 amplitude data was normalized. This normalization technique eliminates amplitude differences between subjects using a percent of Pz amplitude transformation adapted from McCarthy and Wood (1985) (McCarthy & Wood, 1985). Amplitude scores were normalized by converting peak amplitudes to a percentage of the amplitude at the Pz electrode. 3-Way repeated measures ANOVA's of group by condition by electrode (29) were again applied, and the Greenhouse-Geisser epsilon adjustment used for all calculations.

Analysis of brain activity during WM tasks requiring the maintenance of cue stimuli necessitated observation of ERP activity over long recording epochs (750 ms following cue stimulus presentation). This analysis was accomplished by constructing across-subjects average (grand mean) waveforms for each group. Across-subjects average waveforms were then compared between the control and schizophrenic groups using running t-tests, which evaluate group mean values independently at each of the 300 sampling points. Running t-tests are less likely to be affected by single, outlier points than are peak measurements, and indicate whether between group differences are confined to a latency range of interest (Javitt et al., 1995). However, because running t-tests entail multiple comparisons, t-scores were considered significant only if they reached the 95% confidence interval on 15 consecutive points of the recording epoch. At any given elctrode there are 300 possible comparisons. Requiring 15 successive significant values reduces the actual number of comparisons to 20. A Bonferroni correction for 20 comparisons with $\alpha = .05$, requires a $t = 3.0233$, and was the criterion applied.

## HYPOTHESES

### Hypothesis I

Schizophrenic subjects display spatial WM deficits in multiple sensory modalities (Park et al., 1992). However, Park and Holzman (1992) found that verbal WM, as measured by the digit span subtest of the WAIS-R, is unimpaired. The digit span is a simple memory test that does not require the active manipulation of material in memory, bringing into question whether it produces a high enough load on WM to reveal deficits.

Observing verbal WM in schizophrenics performing a more complex WM task requiring the manipulation of information would better assess any existing deficits. The letter-number span task taxes central executive mediated auditory-verbal working memory by requiring subjects to maintain and manipulate a list of scrambled numbers and letters (Gold et al., 1997). Subjects must maintain the novel material, actively unscramble the letters and numbers, and then order them alphabetically or numerically. This task also requires retrieval of the rules for ordering lexical information from semantic memory. The letter number span task appears to be a valid test of auditory-verbal WM since it requires activation of the PFC/posterior system involving associative memory (Goldman-Rakic et al., 1997). Gold (1997) has concurrently validated the letter-number span with other neurocognitive measures of working memory indicating that the test is sensitive to WM deficits in schizophrenic patients (Gold et al., 1997). It is hypothesized that if an auditory-verbal WM deficit exists in the current sample of schizophrenic subjects then it should be manifest as a reduced letter-number span compared to healthy controls. To test this hypothesis an independent groups (control vs schizophrenic) t-test of correct responses on the letter number span was employed

**Hypothesis II**

Schizophrenic patients display relatively normal performance on simple cognitive tasks (i.e. low load tasks) (Strandburg et al., 1999), (Goldman-Racik, 1994). However, as complexity increases, schizophrenic patients are more likely to display deficits (Strandburg et al., 1999). Easier versions of the CPT (those that require only simple target detection) are thought to be related to severity of psychotic symptoms such that

only very psychotic patients show deficits (Strandburg et al., 1999). More difficult versions of the CPT (where stimuli must be evaluated in relation to preceding stimuli) are more related to cognitive deficits in schizophrenia (Strandburg et al., 1999). Since the current schizophrenic sample consists of stable outpatients that are relatively asymptomatic, it is not expected that there will be performance differences between patients and controls in the easier CPT tasks. However, as WM task demands increase, it is hypothesized that group differences will emerge with patients performing disproportionately less accurately than controls. A 2-way repeated measures ANOVA of group (control, schizophrenic) by condition (No Load 20%, No Load 50%, 2-back vs. 1-back short ISI, 1-back long ISI) on percent correctly detected targets was performed.

**Hypothesis III**

Schizophrenic patients have been shown to have slowed information processing (Nuechterlein, Dawson, & Green, 1994). The speed with which a subject can encode a stimulus, compare it to a rule held in WM, and provide a motor response (RT) is a method often employed to index processing speed. It is hypothesized that schizophrenic subjects will demonstrate slower information processing as measured by RT when responding to items on the CPTs. Since schizophrenic patients often do worse when task demands increase, this slowing should be greatest when stimulus comparison and evaluation demands are highest. Therefore, a group by task interaction of RT is also expected. A 2-way repeated measures ANOVA of group (control, schizophrenic) by condition (No Load 20%, No-Load 50%, 2 Back, 1 Back short ISI, 1 Back Long ISI) on RT to match-target "Xs" was performed.

**Hypothesis IV**

One consequence of PFC dysfunction is thought to be an inability to inhibit inappropriate responses (Weinberger et al., 1996a). Schizophrenics express such dysfunction by perseverating. In the CPT, the rule for when to respond must be held in WM, and as each stimulus is presented a decision must be made about how to respond. The 1-back and 2-back WM paradigms contain catch trials where the usual target stimulus is occasionally presented under circumstances in which it should *not* be responded to. These catch trials measure perseverative behavior by indexing when subjects mistakenly respond to the usual target stimuli when in fact they should not have. This occurs when subjects fail to appropriately apply response rules maintained in WM. Therefore, an inability to inhibit responses to catch trials represents a failure in WM. It is hypothesized that schizophrenic subjects will fail to inhibit inappropriate responses more often than controls, resulting in a larger number of false alarms (FA) to catch trials. A 2-way repeated measures ANOVA of group (control, schizophrenic) by condition (No Load 20%, No-Load 50%, 2 Back, 1 Back short ISI, 1 Back Long ISI) on FA rate was performed.

**Hypothesis V**

WM paradigms generally require the subject to register a stimulus, compare it to a rule, and to respond. Schizophrenics show deficits in WM, but where in the sequence of events dysfunction first occurs is not clear. It is possible that the WM deficits observed in schizophrenia stem from the earliest stages of information processing, stimulus registration. Dysfunction at this level of processing would impact WM performance by

causing information entering the system to be less precise for evaluation to rules at later stages. Some researchers have demonstrated that PFC dysfunction leads to a disinhibition of PFC on other cortical areas, resulting in a cascading effect of hyper-activation in areas responsible for early sensory processing of stimuli (Chao et al., 1998). It is hypothesized that N1 amplitude, an index of sensory registration, will be abnormally large in schizophrenic subjects as compared to controls implicating hyper-activation of visual sensory cortex. This effect should be observed over occipital leads where scalp recorded visual ERPs are at greatest amplitude. Such hyper-activation would be indicative of inappropriate allocation of resources. Paradoxical effects have been observed in the past with visual P3 amplitude being larger in schizophrenics under certain cognitive demands (indexing cortical cognitive processing of information) (Shelley et al., 1996), but no mention has been made of such effects in visual N1. A 3-way repeated measures ANOVA of group (control, schizophrenic) by condition (No Load 20%, No-Load 50%, 2 Back, 1 Back short ISI, 1 Back Long ISI) by electrode (29) on N1 amplitude to correctly detected match-target "Xs" was performed. Although N1 amplitude is maximal at occipital leads, multiple brain areas contribute to component. It is possible that the neural generators underlying scalp recorded N1 differ between groups. A group by electrode interaction would be indicative of such differences. In the case of such an interaction further topographical analyses to quantify differences in scalp distributions between groups will be employed using amplitude normalization techniques which eliminate amplitude differences between subjects.

**Hypothesis VI**

Visual P3 amplitude generated to CPT type tasks is thought to index contextual updating and encoding (Donchin et al., 1984), among other processes that are closely related to the brain's WM system (Shelley et al., 1996), (Strandburg et al., 1994). Although P3 amplitude attenuation to rare tones in an oddball task is a robust finding in the auditory modality, visual P3 amplitude reduction findings are not consistent, indicating that within the visual modality this aspect of WM may be relatively spared in schizophrenics. One reason that the visual modality (Duncan, 1988) is less likely to be impaired (Strandburg et al., 1999) is that it is thought to be inversely related to severity of symptoms (Duncan, 1988). Strandburg (1994) indicated that inpatient versus outpatient status is an adequate basis by which to judge severity of clinical status. Given that the current sample of schizophrenics are stable outpatients and have not had any hospitalizations for at least 3 months prior to testing, it is hypothesized that P3 amplitude will not differ between patients and controls.

However, since schizophrenic patients display difficulty in the inhibition of inappropriate responses it is possible they will display deficits on catch trials of the CPT. Abnormal responding to such catch trials is likely to be observed as increased P3 amplitude in comparison to controls, paradoxical effects as these have been reported by Shelley et. al. (1996) who stated that such aberrant P3 generation might be due to premature escape of parietal association cortex from an inhibitory trace maintained prefrontally (Shelley et al., 1996). Therefore it is also hypothesized that schizophrenics will show larger P3 amplitudes than controls to catch trials. A 3-way repeated measures

ANOVA of group (control, schizophrenic) by condition (No Load 20%, No-Load 50%, 2 Back, 1-back short ISI, 1-back long ISI) by electrode (29) on P3 amplitude to correctly detected *target* Xs, and *non*-target Xs, was performed. It is possible that the neural generators underlying scalp recorded P3 differ between groups. A group by electrode interaction would be indicative of such differences. In the case of such an interaction further topographical analyses will be employed using the previously discussed amplitude normalization techniques to quantify differences in scalp distributions between groups.

**Hypothesis VII**

Central executive mediated verbal WM is thought to have key areas of cortical processing located in PFC, and is thought to be at least somewhat left lateralized (Ruchkin et al., 1990; Ruchkin et al., 1992; Rypma et al., 1999). Schizophrenic subjects have demonstrated deficits in this system (Goldman-Racik, 1994), (Buchsbaum et al., 1992). Therefore, following a valid cue "A", we would expect to see greater left frontal activity in controls than in patients in the period following the cue as the subjects hold in WM the rule by which to evaluate subsequent stimuli. It is hypothesized that WM deficits will be manifest as hypoactivation over left frontal leads in schizophrenic subjects during the delay period between cue, and subsequent stimuli. Analysis of cue stimuli was performed by constructing across-subjects average (grand mean) waveforms for each group. Across-subjects average waveforms were compared between the control and schizophrenic groups using running t-tests, which compare group mean values independently at each of the 300 sampling points.

# RESULTS

## Behavioral Measures

### *Debriefing Questionnaire*

A debriefing questionnaire was administered immediately after the testing session to determine participants' subjective experience of task difficulty. The original pilot data indicated that the No Load tasks were easiest, it was also noticed that the 1-back long ISI condition was more difficult than the 1-back short ISI condition. Pilot data on the supposedly most difficult 2-back condition was inconclusive at the time, but assumed to be an issue of power. The tasks were designed with the intent that the No Load tasks would be easiest, the 1-back task somewhat harder, and the 2-back most difficult. However, results of the debriefing questionnaire indicated that this was not how subjects interpreted task difficulty (See Table 2). All controls, and 87.5 % of patients, rated the No Load tasks easiest, as expected. No subjects indicated that they experienced the 50/50 No Load task differently from the 20/80 No Load task. Surprisingly, the 2-back task was rated as intermediate in difficulty between the No Load and the 1-back tasks. All controls judged the 2-back task to be intermediate in difficulty, whereas half of patients judged it so. One possible explanation of this result is that the longer interval between cue and stimulus in the 2-back task was advantageous to subjects because it gave subjects more time to rehearse or review the rules, and thereby be more assured of the correct response to the stimulus when it appeared. In fact this strategy/interpretation was reported by one control on the debriefing questionnaire. Overall, patients were less consistent in their interpretation of task difficulty when compared to controls, however, both groups seem to

have experienced the tasks similarly as a Chi-Square test was non-significant (sig. =.245).

**Table 2: Subjective experience of task difficulty**

| | | Ranking of task difficulty | | |
|---|---|---|---|---|
| **Task** | **Subject Type** | Easiest | Harder | Hardest |
| **No Load** | Healthy control | **100%** | | |
| | Patient | **87.5%** | 12.5% | |
| **2-back** | Healthy control | | **100%*** | |
| | Patient | 12.5% | **50%** | 37.5% |
| **1-back** | Healthy control | | 10% | **90%** |
| | Patient | 12.5% | 31.25% | **56.25%** |

** One control indicated the 2-back and 1-back were equivalent, but harder than No-Load.*

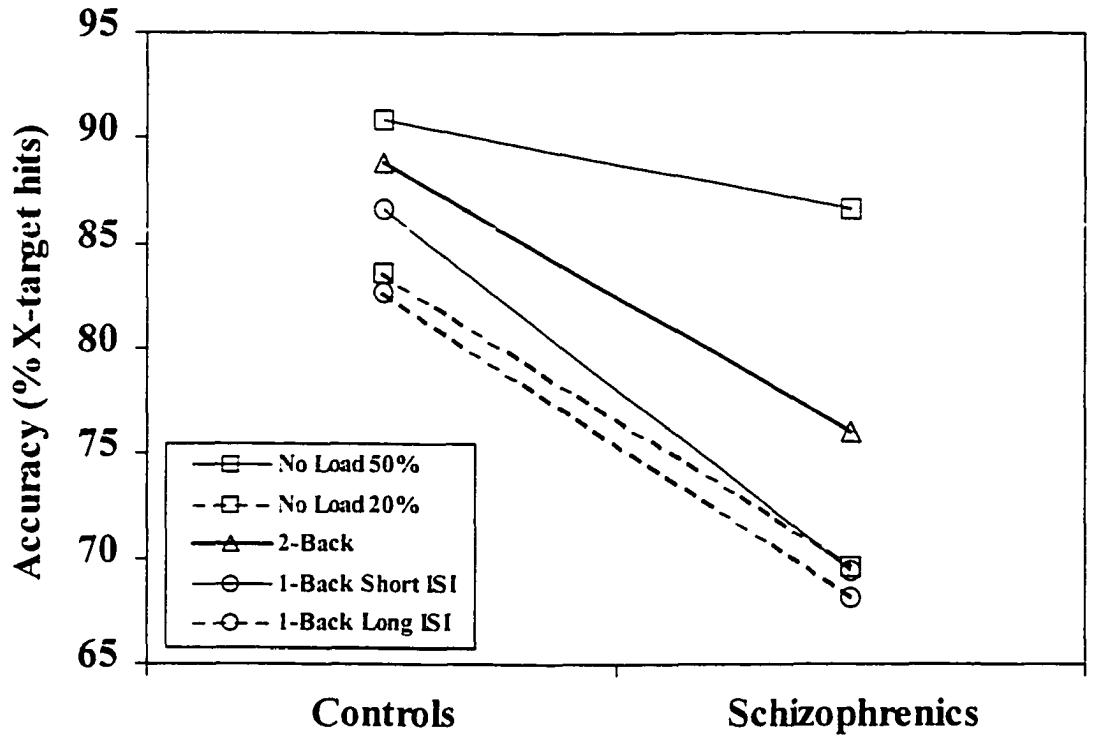
*Letter Number Span*

The Letter Number Span task was employed as a complex test of auditory-verbal WM. Performance was measured as the number of correctly completed items with possible scores from 0 to 24. No subject displayed either a ceiling or floor effect. An independent samples T-test revealed that schizophrenic subjects were not able to manipulate auditory-verbal information in WM as efficiently as controls resulting in fewer correct responses (Patients: $\bar{x} = 13.3 \div 2.6$; Controls: $\bar{x} = 17.4 \div 2.4$; $df = 1,30$, $T = 4.73$, $p < .001$), indicating that schizophrenic subjects display deficits in auditory-verbal WM.

*CPT Accuracy*

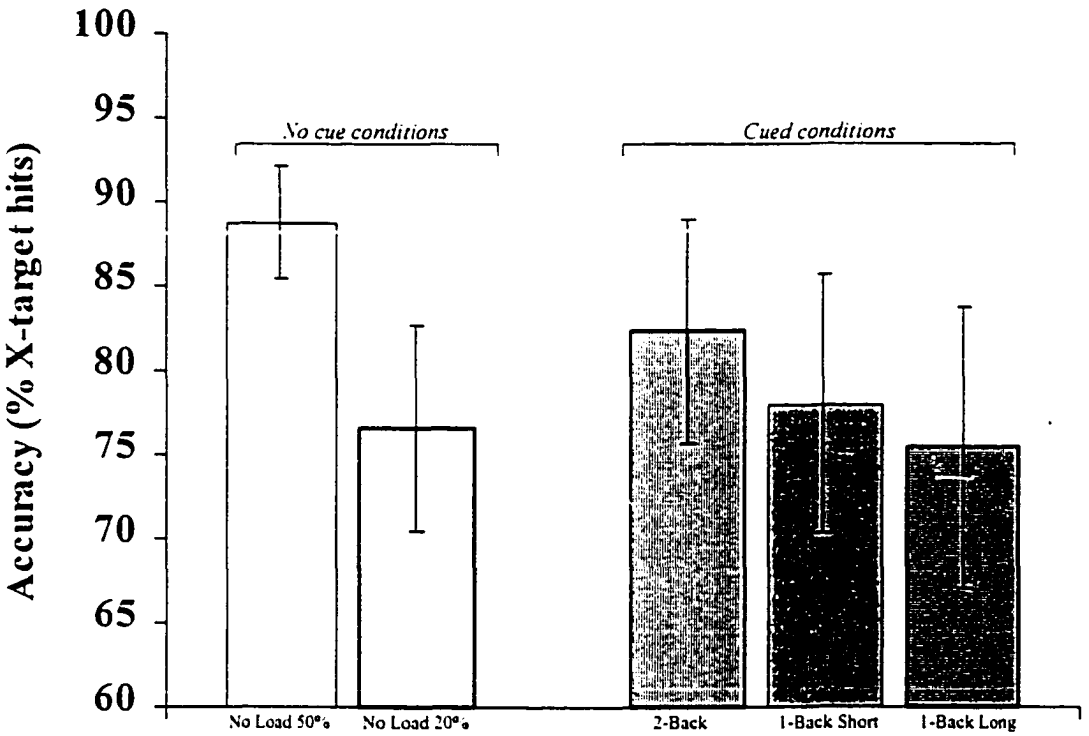
Patients were consistently 14% to 20% less accurate than controls in the more

**Figure 2.** CPT accuracy comparisons between groups




difficult WM tasks (i.e., 1-back and 2-back), suggesting deficits in visual-verbal WM (see Figure 2). Both simple and complex WM tasks were administered to schizophrenics and controls to elucidate the level of load at which schizophrenics would display WM dysfunction. Analyses were done on raw accuracy scores, and accuracy scores adjusted for false alarms. There were no appreciable differences in the two analyses, and the raw scores will be reported here to be consistent with methods used by others (Shelley et al., 1996). Accuracy was measured as the percent of correctly identified target Xs, representing the ability to retain in WM the appropriate rule and to respond correctly. A group (control vs patient) by condition (No Load 50 %, No Load 20 %, 2-back, 1-back

**Figure 3.** CPT accuracy comparisons across tasks (all subjects)



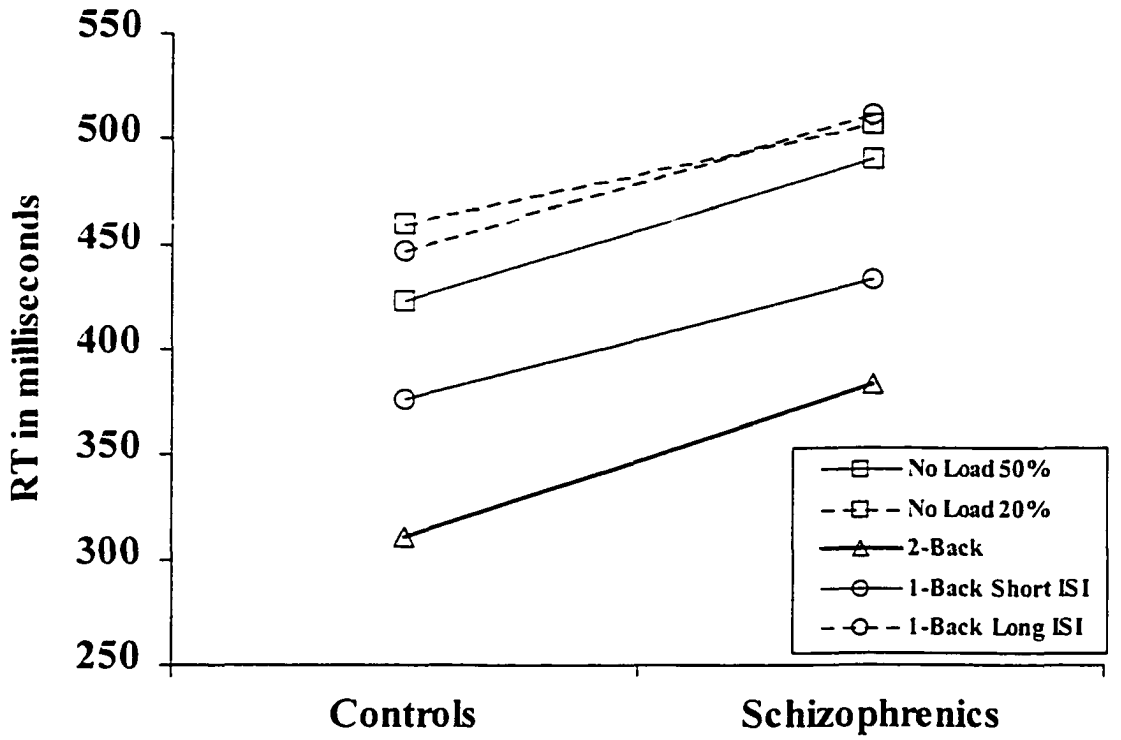

short ISI, and 1-back long ISI) repeated-measures ANOVA on accuracy revealed a main effect of group, with healthy controls identifying significantly more appropriate targets than patients ($df$ = 1,30, $F$ = 5.634, $p$ = .024) (see Figure 2). The manipulation of WM demands was observed across tasks such that higher loads reduced accuracy, resulting in a main effect of condition ($df$ = 1,30, $F$ = 6.465, $p$ = .001). However, there was no group by condition interaction, indicating that while schizophrenics displayed WM deficits in comparison to controls, increasing WM load did not cause them to perform differentially worse than controls ($df$ = 1,30, $F$ = 1.301, $p$ = .280).

Although there was no significant group by condition interaction (see Figure 2),

post hoc t-tests were performed to gain a qualitative picture of the tasks on which groups differed most. Analysis revealed WM deficits, indexed by accuracy, for schizophrenic patients on the No Load 20% where they produced 20% fewer correct answers ($df = 30$, $T = 2.318$, $p = .03$), and the 1-back short ISI where they again produced 20% fewer correct answers ($df = 30$, $T = 2.298$, $p = .034$). Patients showed trend level WM deficits on the 1-back long ISI producing 18% fewer correct answers ($df = 30$, $T = 1.753$, $p = .09$), and 2-back producing 14% fewer correct answers ($df = 30$, $T = 1.982$, $p = .057$). No statistically significant difference in performance was noted on the No Load 50% task with patients producing only 5% fewer correct responses. These results indicate that, when tasks are kept simple, clear deficits are not evident in schizophrenia. The CPT accuracy results indicate that schizophrenic subjects show a generalized deficit in WM that does *not* worsen with increasing task demands (see Figure 2).

Post hoc tests of condition differences across all subjects indicated that the task with the lowest WM demands (No Load 50%) had the greatest number of correct responses (see Figure 3). That is, the No Load 50% condition produced 14% more correct responses than the No Load 20% condition ($df = 31$, $T = -4.925$, $p < .001$), 8% more correct responses than the 2-back condition ($df = 31$, $T = 2.957$, $p = .006$), 12% more correct responses than the 1-back short ISI condition ($df = 31$, $T = 3.085$, $p = .004$), and 15% more correct responses than the 1-back long ISI condition ($df = 31$, $T = 3.912$, $p < .001$) conditions. In the more difficult WM task (1-back long ISI) subjects produced 8% fewer correct responses than on the easier (2-back) WM task ($df = 31$, $T = 2.873$, $p =$

**Figure 4.** CPT RT comparisons between groups

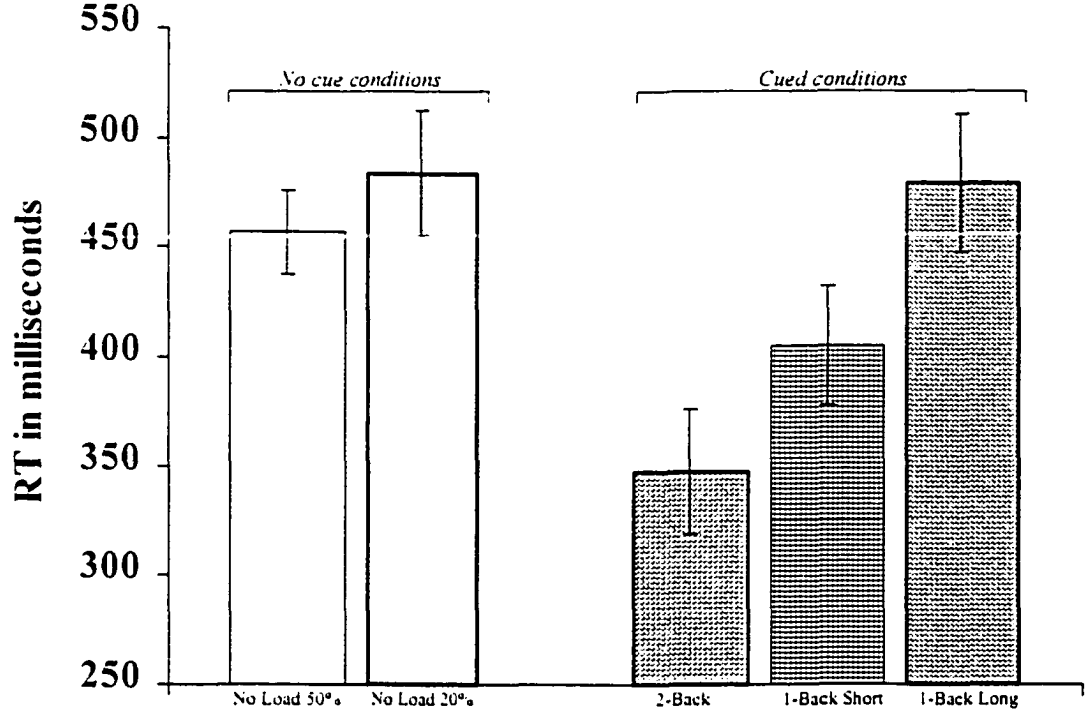



.007). The present data indicates that both groups show reduced CPT accuracy when WM demands are increased.

*CPT Reaction Time*

Across tasks, schizophrenic patients consistently displayed RTs 47 to 71 ms slower than those of controls, suggesting slowed WM processing (see Figure 4). A group by condition repeated-measures ANOVA on RT revealed a main effect of group, indicating that controls responded significantly faster than patients ($df$ = 1,30, $F$ = 7.6, $p$ = .01) (see Figure 4). The effects of manipulating WM demands by increasing rule complexity and delay periods was evident across conditions because higher demands

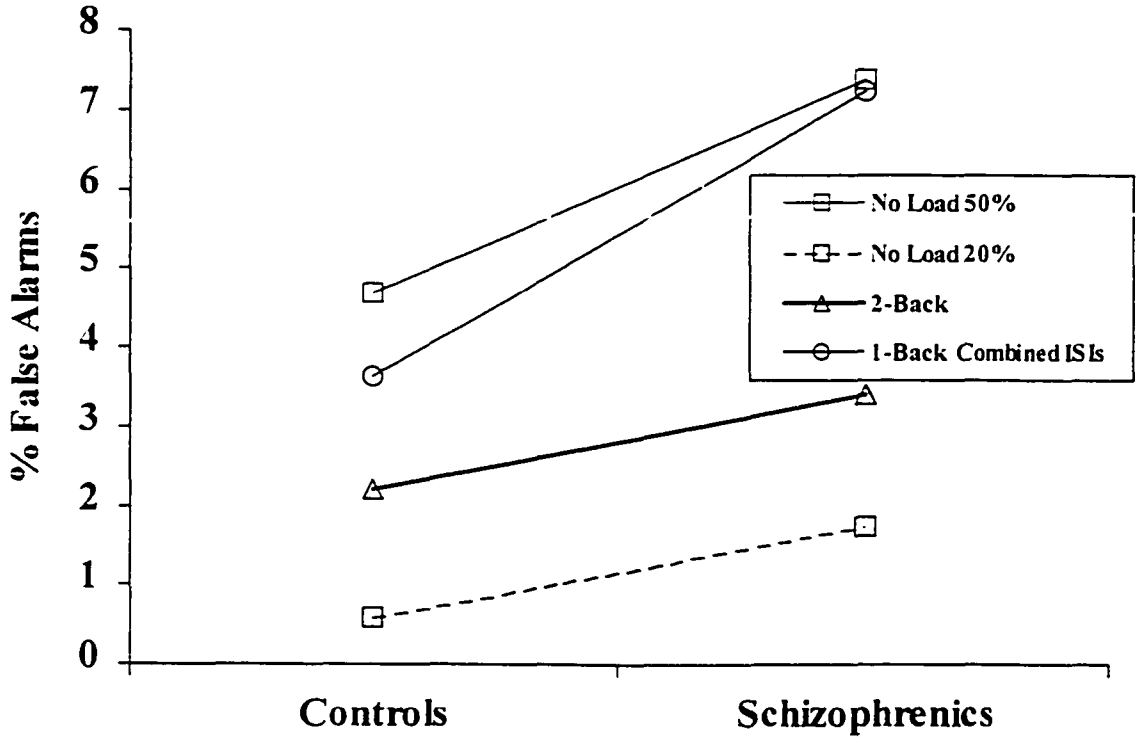
**Figure 5.** CPT RT comparisons across tasks (all subjects)




produced longer RTs, resulting in a main effect of condition ($df = 1,30$, $F = 47.9$, $p < .001$) (see Figure 5). However, there was no group by condition interaction, indicating that patient performance did not decline at a greater rate than that of controls in response to increasing WM load ($p = .868$). The results suggest slowed information processing of material in WM for schizophrenic patients. Controls were 67 ms faster than patients on the No Load 50% task, 71 ms faster on the 2 back task, 58 ms faster on the 1-back short ISI task, 64 ms faster on the 1-back long ISI task, and 47 ms faster on the No Load 20% task (see Figure 4). These results indicate a pattern of consistent generalized slowing, rather than slowing specific to WM load.

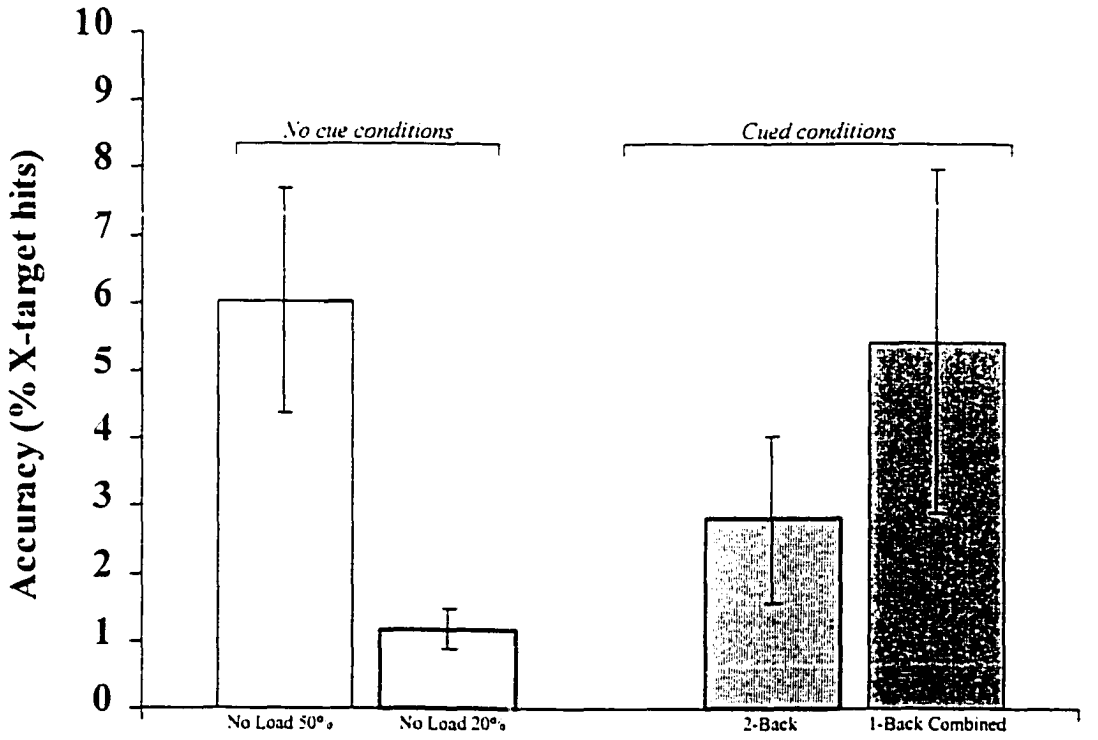
Post hoc tests of condition differences in RT indicated that all subjects were able

**Figure 6.** CPT False Alarm (FA) Rate comparisons between groups




to process information most quickly in easier tasks, and that the presence of a cue also improved RT. In tasks with a cue-stimulus, higher WM load resulted in longer RTs (see Figure 5); the easier 2-back condition (348 ms) was significantly faster than the harder 1 back short ISI (405 ms; $df = 31$, $T = -4.716$, $p < .001$), and 1 back long ISI (479 ms; $df = 31$, $T = -10.101$, $p < .001$) conditions. Additionally, under delay load manipulation the easier 1 back short ISI RT (405 ms) was significantly faster than the RT in the harder 1 back long ISI (479 ms; $df = 31$, $T = 7.078$, $p < .001$) condition. In tasks without a cue-stimulus (see Figure 5), increasing task difficulty was also associated with longer RT; the No Load 50% RT (457 ms) was faster than that for the No Load 20% (484 ms; $df = 31$, $T$

**Figure 7.** CPT False Alarm Rate comparisons across tasks (all subjects)

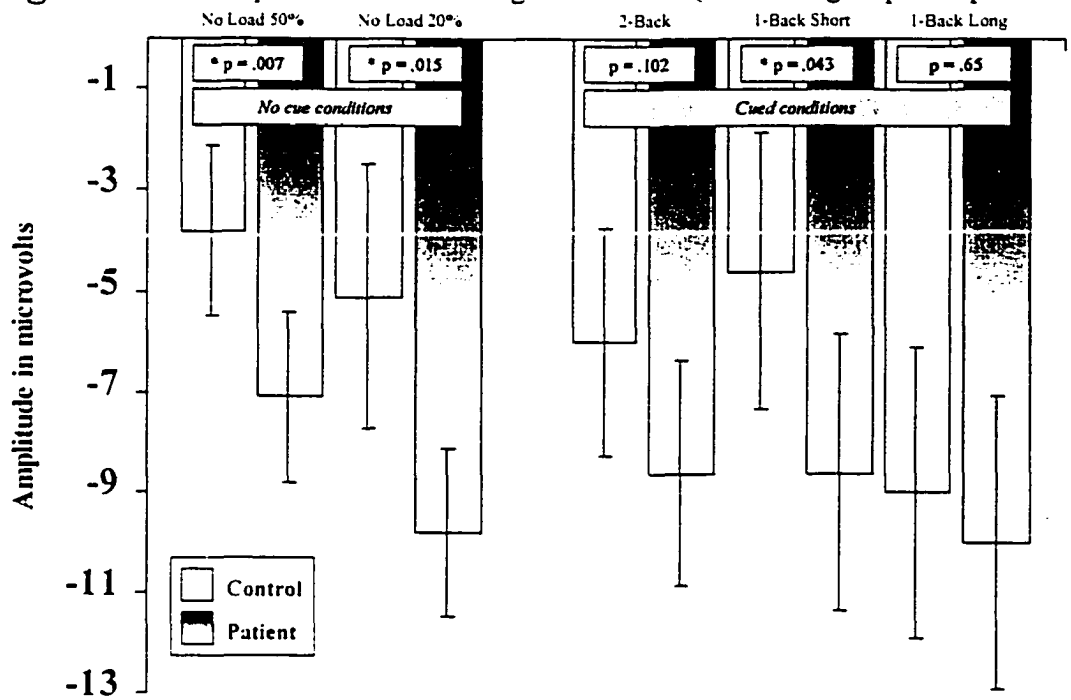



= 2.77, $p < .009$). Together, the results indicate that RT increased directly with task difficulty.

*CPT False Alarms*

Schizophrenic patients showed trend levels of increased false alarm rates in comparison to controls, suggesting the possibility of impaired inhibition (see Figure 6). The inability to inhibit inappropriate responses was measured as the percentage of "Non-X" targets that were inappropriately identified as "X" targets in the No Load tasks, and as the invalid "X" targets that subjects incorrectly responded to in the remaining CPT tasks. The long- and short-ISI conditions of the 1-back test were collapsed across tasks because

**Figure 8.** N1 amplitude at O1 to target X stimuli (between group comparisons)




there were to few responses in the separate conditions to perform a statistical analysis. A group (control vs patient) by condition (No Load 50 %, No Load 20 %, 2-back, and 1-back combined ISI) repeated measures ANOVA of percent FAs revealed a main effect of condition, ($df$ = 1,30, $F$ =12.3, $p < .001$) (see Figure 7), but only a trend level group effect ($df$ = 1,30, $F$ = 3.497, $p$ = .071). However, visual inspection of the data indicates that patients consistently produced more FAs than controls (see Figure 6). There was no interaction ($df$ = 1,30, $F$ = 0.851, $p$ = .429).

Post hoc tests of condition differences indicated that subjects produced more false alarms in the No Load 50% (6.0%) than in the No Load 20% (1.2%) ($df$ = 31, $T$ = - 6.536,

**Figure 9.** O1 amplitude across tasks.

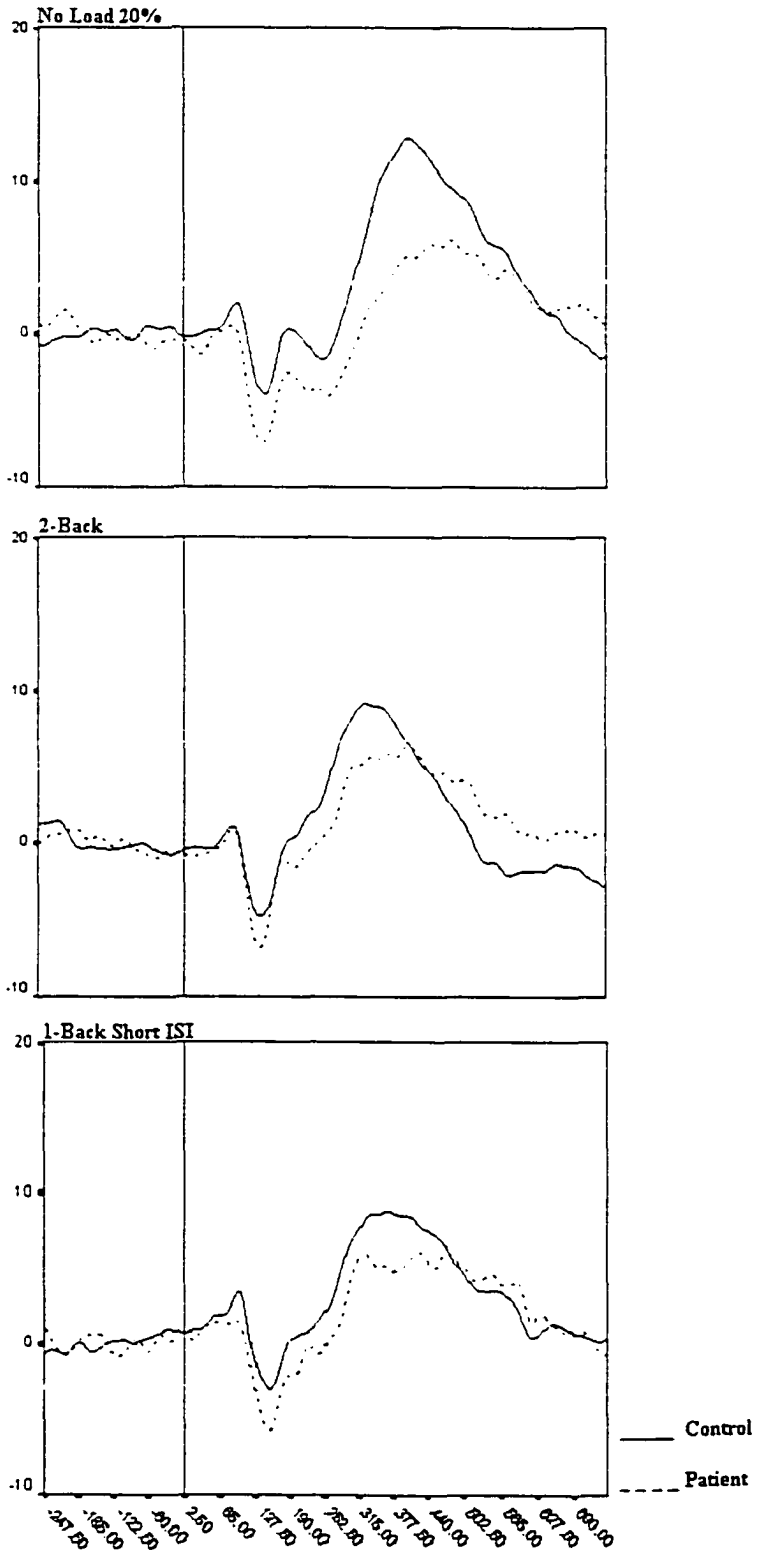
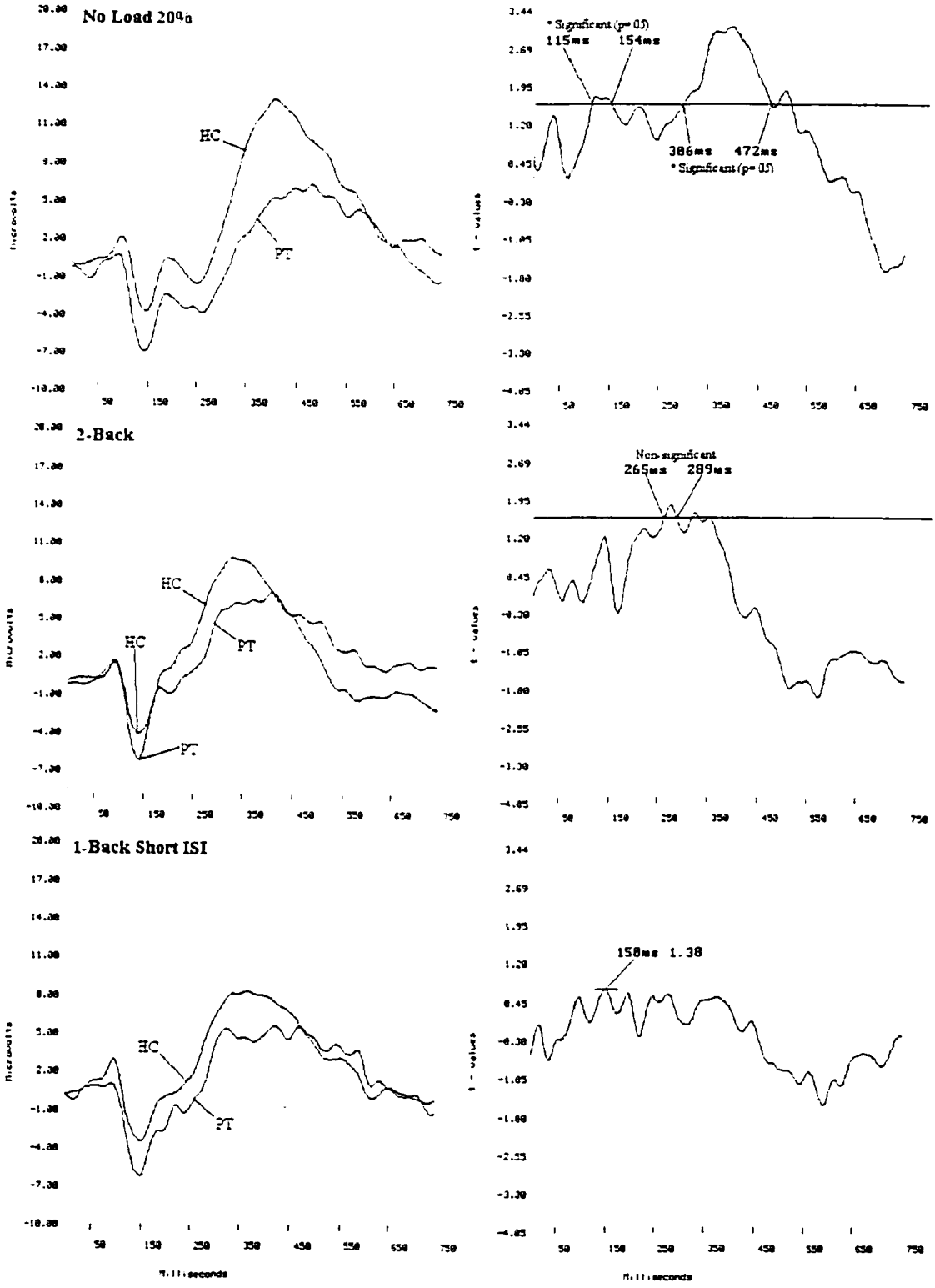


**Figure 10.** Running T-tests at the O1 lead, across tasks (group comparisons)



$p < .001$) and 2 back (2.8%) ($df = 31$, $T = 5.152$, $p < .001$) conditions. The No Load 20% condition had fewer FA's (1.2%) than the 2 back (2.8%) ($df = 31$, $T = -2.848$, $p = .008$) and 1 back (5.4%) ($df = 31$, $T = -3.56$, $p = .001$) conditions. The 1 back (5.4%) produced more FA's than the 2 back (2.8%) ($df = 31$, $T = -2.6$, $p = .014$) condition. The data suggest that higher WM demands resulted in more FAs in both groups.

**Electrophysiological measures**

*N1 Amplitude*

Schizophrenic patients consistently produced N1 amplitudes to target X stimuli that were, on average, 3.1$\mu$V larger than those of controls. N1 amplitude, which was used to index sensory processing of information, increased with task difficulty. A group (control vs patient) by condition (No Load 50 %, No Load 20 %, 2-back, 1-back short ISI, and 1-back long ISI) by electrode (29) repeated measures ANOVA on N1 amplitude to valid "X" targets indicated that patients had larger N1 amplitudes than controls ($df = 1,30$, $F = 5.6$, $p = .025$) (see Figures 8 and 9). Task demand also significantly affected amplitude, with harder tasks resulting in larger N1 amplitudes ($df = 1,30$, $F = 17.1$, $p < .001$). All subjects showed larger N1 amplitudes under the task conditions they considered most difficult. The larger N1 amplitudes in the patients suggest dysfunction in the early sensory processing of stimuli (see Figure 8). However, there was no interaction of group by condition suggesting that patients and controls reacted similarly to changes in WM load in terms of allocating resources to cope with varying task demands ($df = 1,30$, $F = 0.715$, $p = .55$).

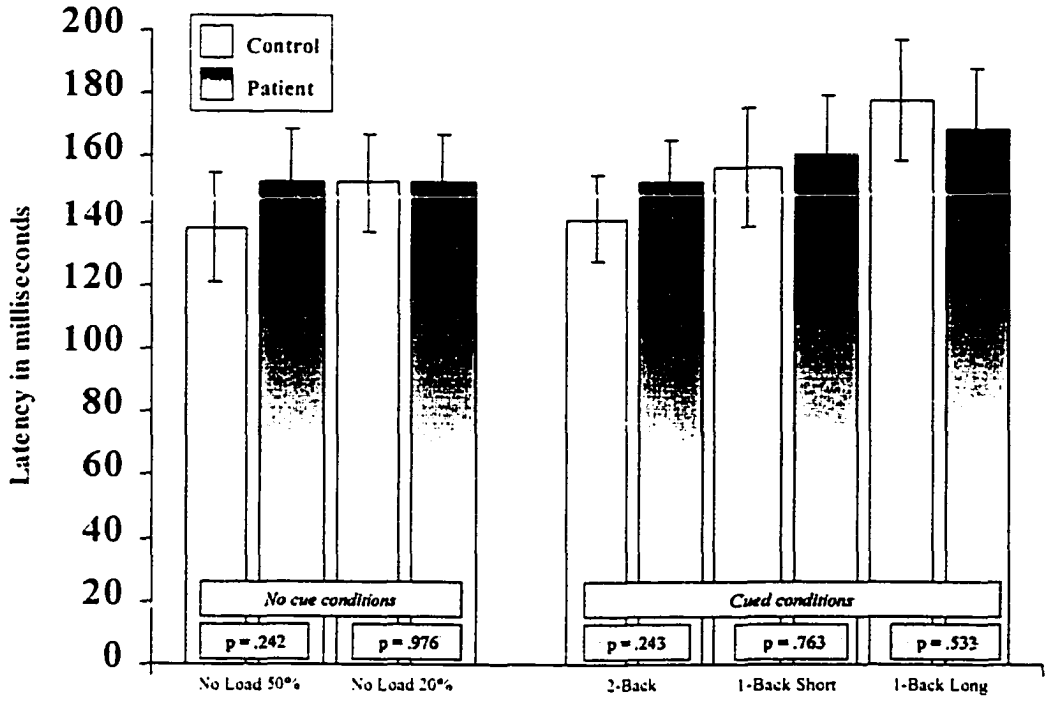
Observation of the waveforms indicated the possibility that a broad negativity was

present in the patient group spanning the interval from the P1 component to the P3 component raising the possibility that the larger N1 amplitudes observed in the patients might be due to such a broad negativity. To test whether such a continuous negativity was present in the patient group, running t-tests were performed over the 750 ms interval after target stimulus presentation. Since N1 amplitude varied as a function of ISI, tasks with a 1.2 sec. ISI and a target probability of 20% were assessed (i.e. No Load 20%, 2-Back, and 1-Back Short ISI). The results are not consistent with the presence of a continuous negativity spanning the P1 to P3 interval. Rather, the only latency ranges where patients and controls differed significantly were at the N1 and P3 components (see Figure 10). There was no evidence for differences between groups at P1, N2, or P2. Maximal amplitudes were consistently observed at the O1 lead producing a main effect of electrode ($df = 1.30$, $F = 45.7$, $p < .001$).

There were no group by electrode ($df = 1.30$, $F = 2.469$, $p = .058$) or group by condition by electrode ($df = 1.30$, $F = 1.073$, $p = .383$) interactions, indicating that topographical profiles were the same for both groups. This suggests that the neural generators contributing to N1 generation across conditions were similar in patients and controls.

Since N1 amplitudes were maximal at O1 and O2 across conditions, O1 was chosen as a representative electrode to assess post hoc differences to gain a qualitative view of patient performance. These tests (see Figure 8) indicated that patients displayed abnormal early sensory processing in the No Load 50% ($df = 30$, $T = 2.874$, $p = .007$), No Load 20% ($df = 30$, $T = 2.585$, $p = .015$), and 1-back short ISI ($df = 30$, $T = 2.111$, $p =$

**Figure 11.** N1 latency to target X stimuli (between group comparisons)




.043) tasks. The 2-back condition showed a trend level in the same direction ($df = 30$, $T = 1.687$, $p = .102$). Hence, the data suggest that patients display altered sensory processing when performing CPT tasks.

Post Hoc tests on the effects of condition on N1 amplitude indicated that easier tasks required fewer resources than the more difficult WM tasks. The No Load 50% task (amplitude = -5.4$\mu$V) was less effortful than the No Load 20% (-7.5$\mu$V; $df = 31$, $T = -2.943$, $p = .006$), 2-back (-7.2$\mu$V; $df = 31$, $T = -2.636$, $p = .002$), and 1-back long ISI (-9.5 $\mu$V; $df = 31$, $T = 3.987$, $p < .001$) tasks. The 2-back task (-7.2$\mu$V) was significantly less effortful than the 1-back long ISI (-9.5$\mu$V; $df = 31$, $T = 2.169$, $p =$

.038), but not the 1-back short ISI (-6.5$\mu$V; $df$ = 31, $T$ = -0.778, $p$ = .442). The 1-back short ISI amplitude (-6.5$\mu$V) was significantly less than that for the 1-back long ISI condition (-9.5 $\mu$V; $df$ = 31, $T$ = -2.589, $p$ = .015).

**N1 Reduced Array (8 electrodes) Analyses** (i.e., O1, O2, P3, Pz, P4, C3, Cz, C4)

*N1 Amplitude - Probability Manipulation (No Load 50% vs No Load 20%)*

During the no load tasks, schizophrenic patients consistently produced N1 amplitudes to target X stimuli that were, on average, 4.0$\mu$V larger than those of controls at the O1 site. N1 amplitude, used to index early sensory registration of information, showed a trend level of increasing when target probability was lowered, and was consistently larger in patients compared to controls. A group (control vs patient) by condition (No Load 50 %, No Load 20 %) by electrode (8) repeated measures ANOVA on N1 amplitude to valid "X" targets indicated that patients had larger N1 amplitudes than controls ($df$ = 1,30, $F$ = 8.4, $p$ = .007). The larger N1 amplitudes in the patients suggest dysfunction in the early sensory registration of stimuli. Although target probability did not significantly affect amplitude, there was a trend level effect suggesting that the lower probability condition may have produced larger N1 amplitudes ($df$ = 1,30, $F$ = 3.04, $p$ = .092). There was no interaction of group by condition suggesting that patients and controls reacted similarly to changes in probability ($df$ = 1,30, $F$ = 0.742, $p$ = .396). Maximal amplitudes were consistently observed at the O1 and O2 leads producing a main effect of electrode ($df$ = 1,30, $F$ = 66.06, $p$ < .001).

*N1 Amplitude - Complexity Manipulation (No Load 20%, vs 2-Back vs 1-Back Short ISI)*

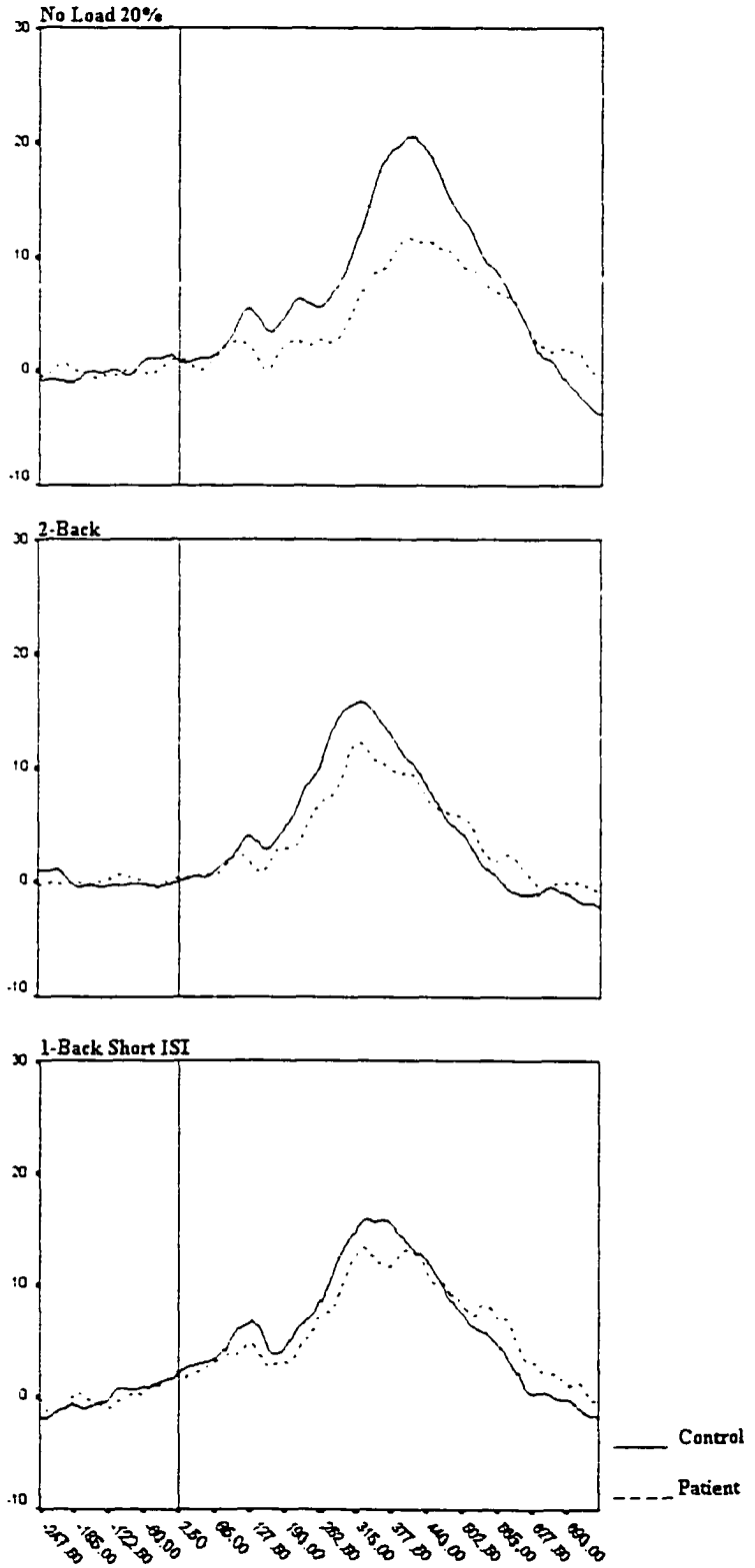
During tasks where rule complexity was manipulated, schizophrenic patients

consistently produced N1 amplitudes to target X stimuli that were, on average, 3.8$\mu$V larger than those of controls at the O1 site. N1 amplitude, used to index sensory registration of information, did not change as a function of rule. A group (control vs patient) by condition (No Load 20 %, 2-Back, 1-Back Short ISI) by electrode (8) repeated measures ANOVA on N1 amplitude to valid "X" targets indicated that patients had larger N1 amplitudes than controls ($df$ = 1,30, $F$ = 7.6, $p$ = .01). The larger N1 amplitudes in the patients suggest dysfunction in the early sensory registration of stimuli. Rule manipulations did not significantly affected amplitude ($df$ = 1,30, $F$ = .664, $p$ = .513). There was no interaction of group by condition suggesting that patients and controls reacted similarly to changes in rule complexity ($df$ = 1,30, $F$ = 0.742, $p$ = .396). Maximal amplitudes were consistently observed at the O1 and O2 leads producing a main effect of electrode ($df$ = 1,30, $F$ = 62.5, $p$ < .001).

*N1 Amplitude - Delay Manipulation (1-Back Short ISI vs 1-Back Long ISI)*

Schizophrenic patients did not produce larger N1 amplitudes in comparison to controls in the 1-Back tasks. However, N1 amplitude increased as a function of the amount of time a rule needed to be maintained in WM. A group (control vs patient) by condition (1-Back Short ISI, 1-Back Long ISI) by electrode (8) repeated measures ANOVA on N1 amplitude to valid "X" targets indicated no differences between groups on N1 amplitude ($df$ = 1,30, $F$ = 1.49, $p$ = .232). However, increasing the amount of time material had to be maintained in WM resulted in increased N1 amplitudes across groups ($df$ = 1,30, $F$ = .25.67, $p$ < .001). Again, maximal amplitudes were consistently observed at the O1 lead producing a main effect of electrode ($df$ = 1,30, $F$ = 40.15, $p$ < .001).

**Figure 12.** Pz amplitude across tasks.



*N1 Latency*

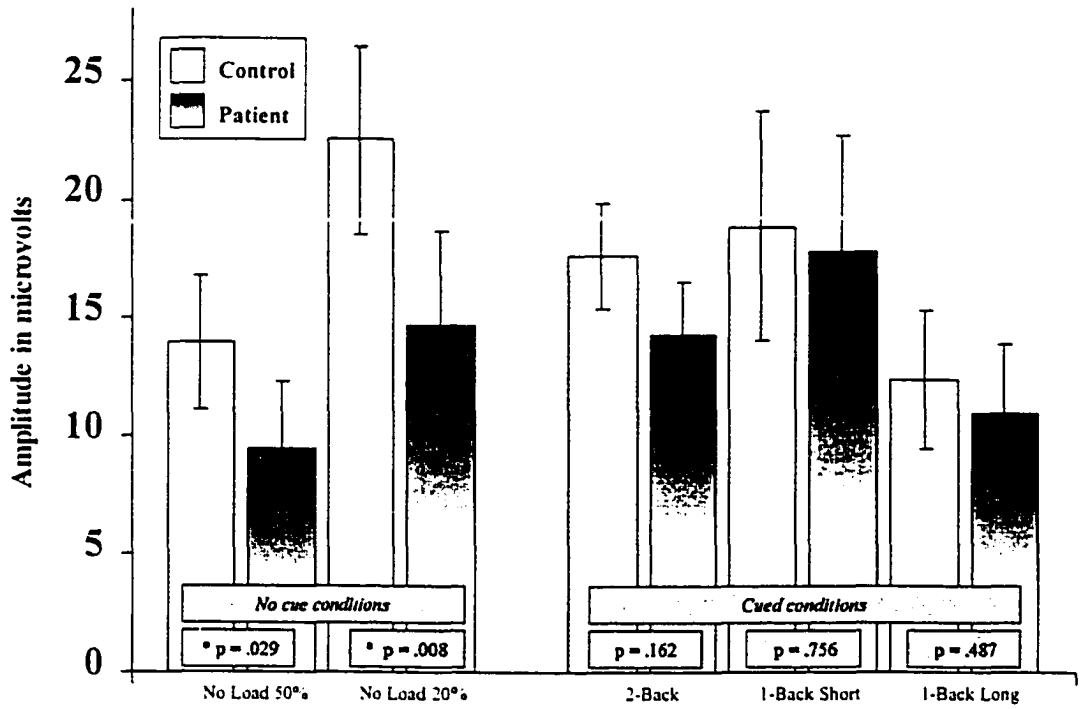
Speed of stimulus registration was measured using N1 latency. The results showed that there were no differences in speed of stimulus registration between patients and controls (see Figure 11) ($df = 1,30$, $F = 0.198$, $p = .66$), suggesting that the slowed information processing observed in schizophrenia must take place at a later stage of processing.

A group (control vs patient) by condition (No Load 50 %, No Load 20 %, 2-back, 1-back short ISI, and 1-back long ISI) repeated-measures ANOVA of N1 latency in response to valid "X" targets revealed a main effect of condition ($df = 1,30$, $F = 9.7$, $p < .001$), indicating that N1 latency differed across tasks. Post hoc tests revealed that N1 latency was earlier in the non-WM tasks (No Load 50% = 144 ms) than in the 1-back WM tasks (1-back short ISI = 159 ms, $df = 31$, $T = -2.465$, $p = .019$; 1-back long ISI = 174 ms, $df = 31$, $T = -5.169$, $p < .001$). Finally, across all subjects N1 latency was earlier in the easier WM condition (1-back short ISI = 159 ms) than the more difficult WM condition (1-back long ISI = 174 ms, $df = 31$, $T = 2.345$, $p = .026$). The lack of a group by condition interaction suggests that the changes in processing speed due to task demands were similar between patients and controls.

*P3 Amplitude, target Xs*

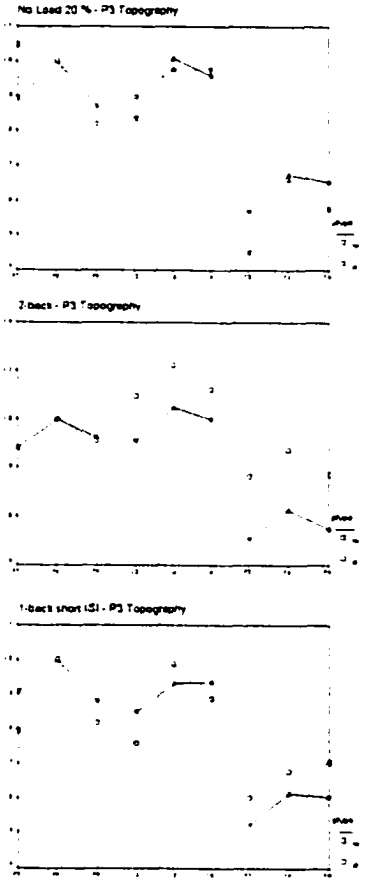
P3 amplitude data displayed the expected effects of increased amplitude in response to higher load and lower probability. The P3 amplitude data also suggests a diminished response in patients across tasks, but a lack of any group by condition interaction. A group (control vs patient) by condition (No Load 50 %, No Load 20 %, 2-

**Figure 13.** P3 amplitude at Pz to target X stimuli (between group comparisons)




back, 1-back short ISI, and 1-back long ISI) by electrode (29) repeated-measures ANOVA on P3 amplitudes elicited by valid X targets showed a trend level group effect of reduced P3 amplitude in patients ($df$ = 1,30, $F$ = 3.762, $p$ = .062). Visual inspection of the data suggests that patients produced smaller P3 amplitudes across all tasks (see Figures 12 and 13). P3 amplitude increased with task demands producing a main effect of condition ($df$ = 1,30, $F$ = 12.606, $p$ < .001). There was a trend level group by electrode interaction, indicating the possibility of differing patterns of neural generator activity between groups ($df$ = 1,30, $F$ = 2.122, $p$ = .096). Although the group by electrode interaction was not significant, ANOVA's were performed for each experimental

**Figure 14.** Normalized P3 amplitude distributions at midline electrodes



condition to explore possible differences in P3 amplitude distribution between groups. To assess differences between groups in scalp topography P3 amplitude data was normalized using a percent of Pz amplitude transformation. After normalization there were no statistically significant topographical profile differences between groups. However, visual inspection of the data suggests that there may be a frontal shift of the P3 component in the patient group (see Figure 14).

Post hoc tests of condition on P3 amplitude revealed that reducing stimulus probability in the non-WM tasks had the expected effect of increasing P3 amplitude such

that No Load 50% P3 amplitude (11.7$\mu$V) to target "X's" was significantly smaller than No Load 20% P3 amplitude (18.6$\mu$V; $df = 31$, $T = 7.74$, $p < .001$). Decay of representational context in WM was evident when material had to be kept online for longer periods of time (1.2 sec vs 3.6 sec) such that the easier 1-back short ISI P3 amplitude (18.4$\mu$V) was significantly larger than in the more difficult 1-back long ISI task (11.7$\mu$V; $df = 31$, $T = -3.839$, $p = .001$).

**P3 Reduced Array Analyses** (i.e., O1, O2, P3, Pz, P4, C3, Cz, C4)

*P3 Amplitude, target Xs - Probability Manipulation (No Load 50% vs No Load 20%)*

The P3 amplitude data revealed a diminished response in patients in the No Load (visual oddball) tasks, but a lack of any group by condition interaction. Schizophrenic patients consistently produced P3 amplitudes to target X stimuli that were, on average, 6.1$\mu$V smaller than those of controls at the Pz site during the No Load tasks. P3 amplitude data displayed the expected effect of increased amplitude in response to lower probability of target stimuli. P3 amplitude, which was used to index later stages of WM processing, increased when target probability was lowered, and was consistently smaller in patients compared to controls. A group (control vs patient) by condition (No Load 50 %, No Load 20 %) by electrode (8) repeated measures ANOVA on P3 amplitude to valid "X" targets indicated that patients had smaller P3 amplitudes than controls ($df = 1,30$, $F = 8.03$, $p = .008$). The smaller P3 amplitudes in the patients suggests dysfunction during later stages of information processing during low load tasks. Target probability significantly affected amplitude, with the lower probability condition producing larger P3 amplitudes ($df = 1,30$, $F = 70.07$, $p < .001$). There was no interaction of group by

condition suggesting that patients and controls reacted similarly to changes in probability ($df$ = 1,30, $F$ = 2.11, $p$ = .156). Maximal amplitudes were consistently observed at the Pz lead producing a main effect of electrode ($df$ = 1,30, $F$ = 58.59, $p$ < .001).

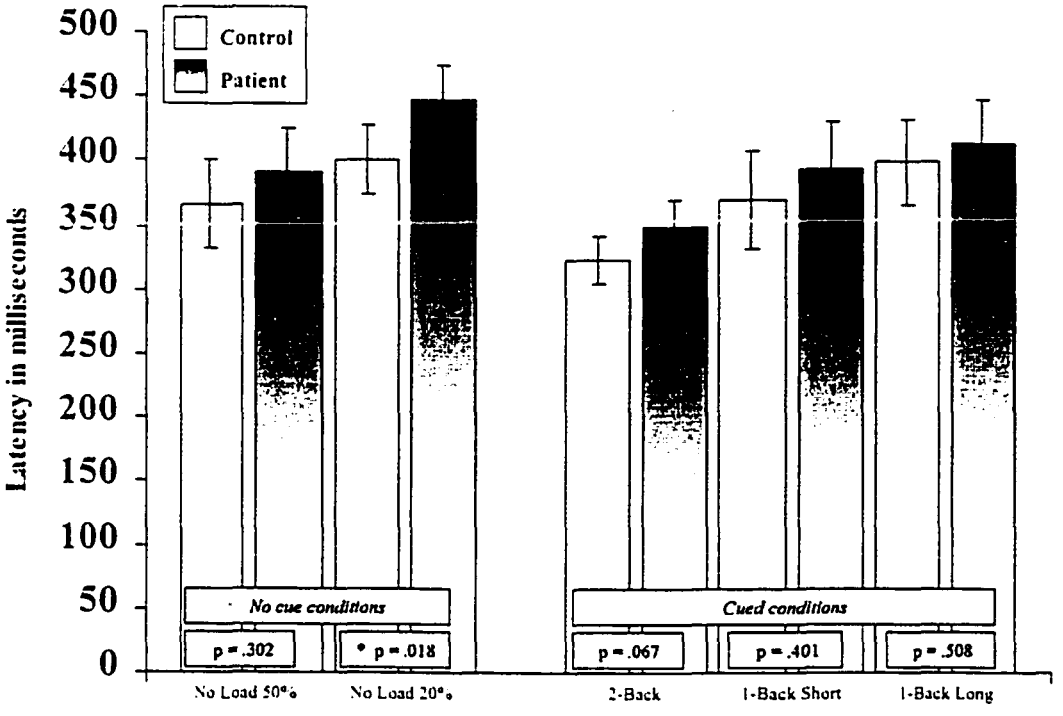
*P3 Amplitude, target Xs - Rule Complexity Manipulation (No Load 20%, vs 2-Back vs 1-Back Short ISI)*

During tasks where rule complexity was manipulated, schizophrenic patients produced P3 amplitudes similar to those of controls to target X stimuli. P3 amplitude, used to index later cognitive processing of stimuli, did not change as a function of rule complexity. A group (control vs patient) by condition (No Load 20 %, 2-Back, 1-Back Short ISI) by electrode (8) repeated measures ANOVA on P3 amplitude to valid "X" targets indicated no significant differences between groups ($df$ = 1,30, $F$ = 3.11, $p$ = .088). Rule manipulations did not significantly affect amplitude ($df$ = 1,30, $F$ = 1.03, $p$ = .36). Maximal amplitudes were consistently observed at the Pz lead producing a main effect of electrode ($df$ = 1,30, $F$ = 39.32, $p$ < .001).

*P3 Amplitude, target Xs - Delay Manipulation (1-Back Short ISI vs 1-Back Long ISI)*

Schizophrenic patients did not produce smaller P3 amplitudes in comparison to controls in the 1-Back tasks. However, across groups P3 amplitude decreased when the amount of time a rule needed to be maintained in WM increased. A group (control vs patient) by condition (1-Back Short ISI, 1-Back Long ISI) by electrode (8) repeated measures ANOVA on P3 amplitude to valid "X" targets indicated no differences between groups on P3 amplitude ($df$ = 1,30, $F$ = .334, $p$ = .567). However, decay of representational context in WM was evident when material had to be kept online for

**Figure 15.** P3 latency to target X stimuli (between group comparisons)

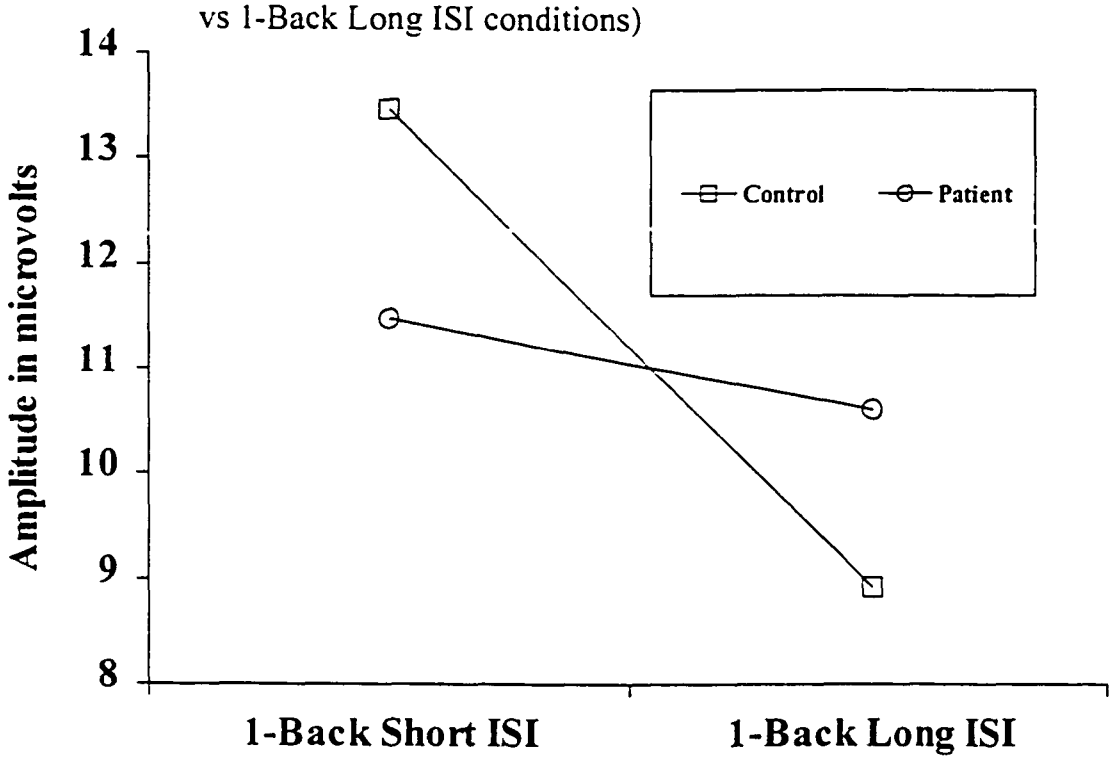



longer periods of time (1.2 sec vs 3.6 sec) such that the easier 1-back short ISI P3 amplitude (18.4$\mu$V) was significantly larger than in the more difficult 1-back long ISI task (11.7$\mu$V) ($df$ = 1,30, $F$ = 12.21, $p$ < .001).

*P3 Latency, target Xs*

In the present study P3 latency differences in the WM tasks were non-significant, suggesting that stimulus evaluation time did not differ between groups (see Figure 15). A group (control vs patient) by condition (No Load 50 %, No Load 20 %, 2-back, 1-back short ISI, and 1-back long ISI) repeated-measures ANOVA on P3 latency at Pz to valid "X" targets was not different between groups, indicating transmission rate up to this stage

**Figure 16.** P3 amplitude at Pz to non-target X stimuli (1-Back Short ISI vs 1-Back Long ISI conditions)




of information processing is not slowed in schizophrenics ($df$ = 1,30, $F$ = 1.65, $p$ = .209). Post-hoc tests revealed that P3 latency was shorter for controls only in the No Load 20% task ($df$ = 30, $T$ = - 2.576, $p$ = .018) (see Figure 15). However, visual inspection of the data indicates some evidence that P3 latency may be earlier in controls (see Figure 15). Stimulus evaluation time was faster for all subjects in tasks that were perceived as easier, resulting in a main effect of condition ($df$ = 1,30, $F$ = 12.4, $p$ < .001). Post hoc tests of condition revealed that P3 latency in the easier 2-back task (337 ms) was faster than both the harder 1 back short (382 ms; $df$ = 1,31, $T$ = - 2.987, $p$ = .005) and long ISI (407ms; $df$ = 1,31, $T$ = - 5.657, $p$ <.001) conditions. In the delay condition comparison, the easier 1-

**Figure 17.** Amplitude distribution at frontal leads and Pz, to cue stimuli in a WM task

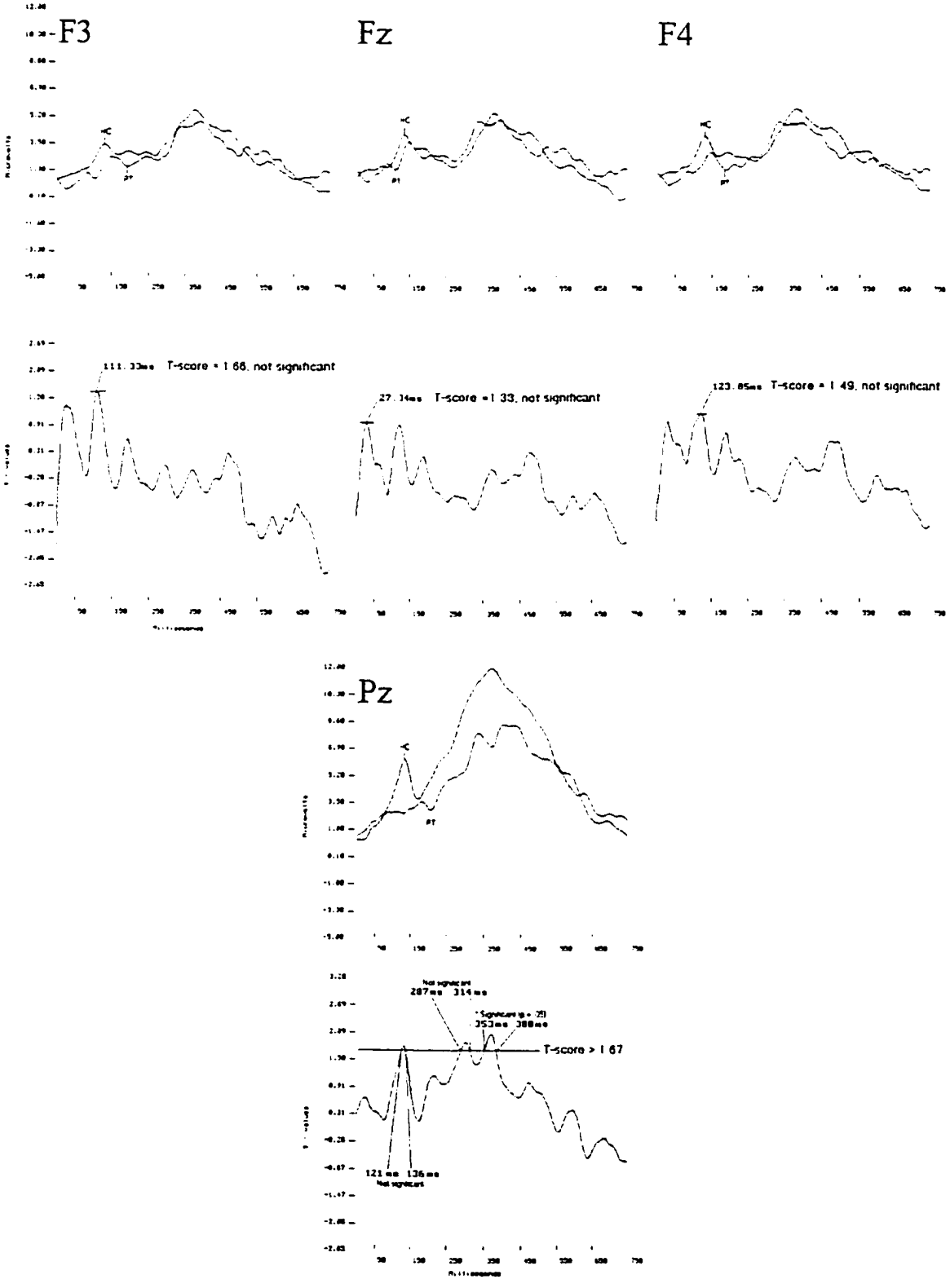
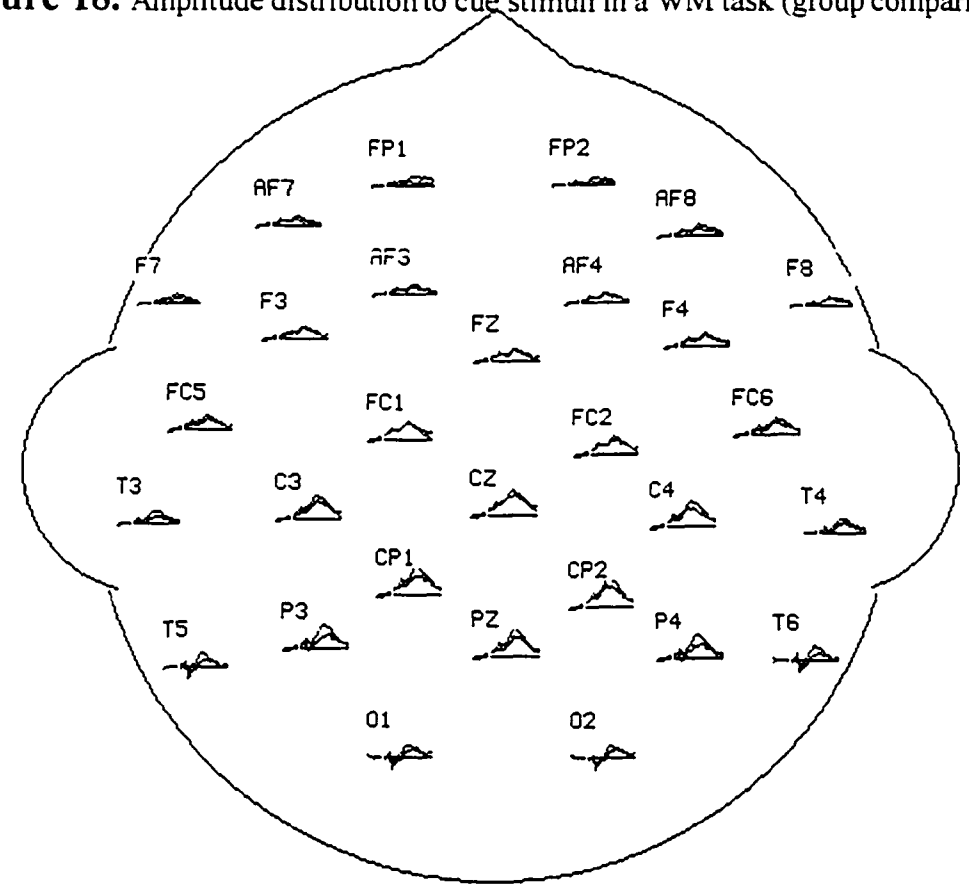


**Figure 18.** Amplitude distribution to cue stimuli in a WM task (group comparison)




back Short ISI (382 ms) condition was faster than the harder 1-back long ISI condition, (407ms; ($df$ = 1,31, $T$ = 1.596, $p$ = .121) but not statistically significant.

*P3 Amplitude, non-target Xs*

Visual inspection of the data shows that, in the delay load comparison, controls produced a slightly larger P3 at the short ISI (1.2 sec). However, as decay of the WM memory trace occurred, increasing the difficulty of this inhibitory task, patients actually produced a larger P3 response at the long ISI (3.6 sec) (see Figure 16). Although the P3 amplitude comparison between groups on the 1-back short and 1-back long conditions was not statistically significant, a similar paradoxical effect in which patients produced

larger P3s has been noted previously by Shelley (1996) (Shelley et al., 1996).

A group (control vs patient) by condition (No Load 50 %, No Load 20 %, 2-back, 1-back short ISI, and 1-back long ISI) repeated measures ANOVA on P3 amplitude to non-target Xs indicated that patients and controls responded similarly ($df$ = 1,30, $F$ = 1.598, $p$ = .216). P3 amplitude varied as a function of task demands resulting in a main effect of condition ($df$ = 1,30, $F$ = 2.773, $p$ = .047).

*Amplitudes, 1-back Cue ("A") Stimuli*

The present study sought to elucidate differences in DLPFC functioning by measuring amplitudes at frontal leads in both patients and controls while performing WM tasks. Cue "A" stimuli in the 1-back WM paradigm were used as the element which subjects needed to maintain in WM. In addition to the differences in occipital sites for the N1 component, and central-parietal sites for P3, amplitudes at frontal leads were examined. Analysis of cue stimuli was performed by constructing grand average waveforms for each group. Waveforms were compared between the control and schizophrenic groups using running t-tests (described earlier). Differences in frontal leads were not present during any point of the recording epoch. The data suggests that differences in DLPFC mediated WM is not present during the first 750 ms interval after stimulus presentation (see Figures 17 and 18).

## DISCUSSION

Multimodal WM dysfunction in schizophrenic subjects was evidenced in several ways in the current study. Behavioral measures proved *sensitive* to WM dysfunction in schizophrenics revealing reduced accuracy and slowed RT. Auditory-verbal WM,

indexed by the Letter Number Span task, showed clear deficits in the patient group. In the visual-verbal modality, patients consistently displayed reduced accuracy and increased RT across the CPT tasks. However, patient performance did not worsen when task complexity and delay intervals were increased, suggesting a generalized cognitive deficit, not a dysfunction specific to WM processes. ERP measures were *specific* in elucidating the stages of WM where dysfunction manifested. N1 amplitude in response to target stimuli was larger in the patient group, suggesting altered sensory processing of stimuli during CPT tasks. These increased N1 amplitude findings indicate that dysfunction in the WM system is present as early as the stage of sensory registration. N1 latency and P3 latency did not reveal significant differences between groups, therefore, processing speed appears normal up to P3. The finding of normal P3 latency in schizophrenic subjects with their concurrently delayed RTs, indicates slowed response selection and execution in the patient group. Furthermore, response inhibition deficits suggested by more FAs, along with a possible frontal shift in P3 distribution suggestive of greater recruitment of frontal cortex, provided evidence that frontal structures contributed to the deficits observed in the schizophrenic group.

**Sensitivity to Dysfunction - Overt Behavioral Responses**

Overt behavioral responses of accuracy and RT obtained on subjects proved to be sensitive measures of WM function within and between groups. In the present study, the use of a demanding WM task (i.e., Letter Number Span) demonstrated that schizophrenic subjects display significant impairments in auditory-verbal WM. In the current study controls produced 4.2 more correct responses than schizophrenic patients, replicating

Gold et als. (1997) results using the same measure where controls produced 4.5 more correct responses than schizophrenic patients. The current Letter Number Span finding supports the hypothesis that schizophrenic patients would exhibit auditory-verbal WM deficits when challenged with demanding WM task. The present results contrast those of Park and Holzman (1992) who reported intact auditory-verbal WM in schizophrenic subjects. However, the task employed in that study (i.e., Digit Span) was likely too simplistic to elicit differences between controls and schizophrenic patients. Auditory-verbal and visual-verbal WM tasks are thought to be relatively equivalent, taxing the same system, with the exception that visual-verbal WM requires lexical decoding of information before it can be passed on to the phonological loop for rehearsal (Becker et al., 1999). In the present study deficits on the Letter Number Span indicate that verbal WM impairments, unrelated to any confounds of lexical decoding, exist in schizophrenic patients.

Visual-verbal WM deficits were evidenced in the CPT tasks for schizophrenic patients. Although all subjects displayed the expected decline in accuracy as task demands increased, patients were consistently 14% to 17% less accurate than controls (see Figure 2). In the difficult 1-back task, controls produced more correct responses in both the long and short ISI conditions, supporting the findings of Shelley (1996) who used a similar task (see Table 3). However, in the present study patient performance did not become differentially worse as task difficulty increased. The fact that patients did not perform differentially worse, is counter to the hypothesis that increasing task demands would result in greater deterioration of performance. This is an important finding

because it suggests a generalized cognitive deficit in schizophrenic subjects. Additionally, the current study appears unique in finding impaired accuracy performance for patients in tasks with minimal WM requirements (No Load 20% and No Load 50%). These No Load tasks served as a *visual* analog to the *auditory* oddball often reported in ERP research.

**Table 3: AX-CPT accuracy comparison between studies**

| | 1-back Short ISI AX-CPT | | | 1-back Long ISI AX-CPT | | |
|---|---|---|---|---|---|---|
| | **hc** | **pt** | **hc-pt** | **hc** | **pt** | **hc-pt** |
| **Present Study** | $\bar{x}$ = 86.6 | $\bar{x}$ = 69.4 | 17.2 | $\bar{x}$ = 82.7 | $\bar{x}$ = 68.1 | 14.6 |
| **Shelley (1996)** | $\bar{x}$ = 95.9 | $\bar{x}$ = 88.7 | 7.2 | $\bar{x}$ = 82.2 | $\bar{x}$ = 65.6 | 16.6 |

The RT data indicated slowed information processing in the schizophrenic patients, and was yet another measure sensitive to differences in WM processes between groups. RT data displayed the expected increases as task difficulty increased, for both groups (see Figure 4). Analyses revealed that the presence of a cue, to alert subjects that the subsequent stimulus needed to be evaluated and classified, had an advantageous effect allowing subjects to respond 60 ms earlier, on average. This replicates the findings of Silberstein (1998) who noted a 70 ms reduction in RT when a priming stimulus was supplied to controls in X-CPT vs AX-CPT type tasks (Silberstein et al., 1998). Given that cues helped both groups respond faster, the results of the cued and uncued tasks should be considered separately. On the cued tasks, both groups responded fastest to the 2-back task, which they subjectively reported as easier than the 1-back task. Also, subjects responded faster to the 1-back short ISI condition than to the 1-back long ISI

which was the more difficult of the 1-back tasks. These results mimic the findings often reported in Sternberg type tasks where increasing demands are seen as increases in RT (Ruchkin et al., 1990). RTs in the uncued tasks followed a similar pattern to the cued tasks, in terms of difficulty, with the No Load 20% task having a longer RT than the No Load 50% task which was the easier in terms of stimulus expectancy.

Nevertheless, RT was slower in patients across all tasks, supporting the hypothesis that schizophrenics would demonstrate slowed information processing when indexed by RT. However, as was seen in the accuracy data, patients responded similarly to controls as task difficulty increased showing increased RTs, indicating that manipulation of WM load did not have the expected effect. Mean differences in performance of patients were from 47 ms to 71 ms slower than controls (see Figure 4). Patients were slowest (71 ms slower) in comparison to controls in the task where there was the greatest chance to use cues in the environment to enhance performance (i.e., 2-back task), indicating that patients did not benefit equally from such cues. The fact that the condition in which patients performed most closely to healthy controls (47 ms slower) was in the one with the fewest external cues to help enhance performance (i.e., the No Load 20% lacked cues and stimulus expectancy), also suggests that schizophrenics fail to utilize cues in their environment as do controls. The present finding of failed utilization of cues appears similar to the effects observed in pre-pulse inhibition paradigms in schizophrenic patients where there is not optimal use of priming stimuli (Bender et al., 1999; Schall, Schon, Zerbin, Eggers, & Oades, 1996).

Although behavioral measures were sensitive to WM deficits in schizophrenic

patients, they did not specify the stage where processing difficulties arose. For example, there is the possibility that patients express impairment in one or more stages of information processing, that then becomes manifest behaviorally as the generalized WM deficit observed as decreased accuracy and increased RT in the present study, and reported elsewhere (Strandburg et al., 1999), (Shelley et al., 1996), (Gold et al., 1997). However, the stage of information processing at which dysfunction manifests can not be elucidated using overt behavioral measures since only the final motor event is indexed.

**Specificity of Dysfunction - Stages of information Processing**

ERP measures were employed to discern the specific stages of information processing where schizophrenic patients displayed abnormal WM function. N1 and P3 amplitudes provided insight into the degree of neuronal recruitment at early and later stages of WM, whereas N1 and P3 latencies indexed the speed of information processing.

*Neuronal Recruitment During WM Processing*

An early stage of WM processing, sensory registration, was assessed using N1 amplitude and latency. Schizophrenics consistently displayed larger N1 amplitudes than controls, indicating that patients had altered sensory processing of stimuli in all tasks (see Figure 8). Hence, patients appear to display greater neuronal recruitment during the early sensory registration of stimuli than do controls. Analyses revealed that the larger N1 amplitude was localized to the latency range when N1 is expected to occur, and was not a result of a larger generalized negativity spanning the interval from P1 to P3. The fact that schizophrenic CPT accuracy and RT performance was generally poorer than that of controls, indicates that the greater degree of neuronal recruitment during the tasks, as

indicated by the larger N1 amplitudes, was not sufficient to bring their behavioral performance to normal levels. The present finding of larger N1 amplitudes in the patient group supports the hypothesis that frontal dysfunction in schizophrenic patients would be manifest as a disinhibition of visual sensory cortex. The larger N1 amplitudes indicate that at early stages of information processing, schizophrenics do not optimally allocate resources. Since visual N1 amplitude indexes early registration of stimuli in sensory cortex, the present dysfunctional N1 amplitude suggests an impairment at the sensory level of cortex in schizophrenia in the visual modality. Shelley et al. (1996) also reported larger visual N1 amplitudes in schizophrenic patients compared to controls, however, this difference (approximately 1.4$\mu$V at occipital leads) was non-significant.

The present finding of early sensory processing dysfunction indexed at the level of visual sensory cortex is similar to the finding of early imprecise processing of information at the level of primary auditory cortex reported elsewhere (Javitt et al., 1997). The current visual results, along with those of a processing imprecision in the auditory modality reported by Javitt et al. (1997), suggest the presence of multi-modal sensory deficits in schizophrenic patients.

Later stages of WM processing were indexed by P3 amplitude. Manipulations of delay and stimulus meaning were employed to test for differences within and between groups. Manipulations of stimulus meaning and probability produced the expected effects on P3 amplitude since greater allocation of resources required to process more complex stimuli resulted in larger P3 amplitudes for both groups. In the cued conditions, subjective reports of task difficulty, accuracy data, and RT data, indicated that the 1-back

task was more difficult than the 2-back task. Comparison of these two tasks revealed that P3 amplitude was greater in the 1-Back task, as expected, for both groups. In the uncued conditions, accuracy and RT data indicated that the low probability No Load 20% task was more difficult than the No Load 50% task, and analysis revealed larger P3 amplitude in the No Load 20% condition, as expected. The current task comparisons demonstrate the expected effects of stimulus meaning and probability on P3 amplitude and fit with the behavioral parameters of P3 amplitude reported elsewhere in the literature (Johnson, 1993).

The delay manipulation in the 1-back AX-CPT demonstrated that, in the short ISI condition (1.2 sec) P3 amplitude was greater than in the long ISI condition (3.6 sec) for both groups. This increased amplitude indicates that all subjects experienced a decrement in information transmission with delay load. Since probability and stimulus meaning were kept constant, changes in variables affecting information transmission likely accounted for the reduced P3 amplitude. Given that behavioral performance between the two conditions was not significantly different, the reduction in P3 amplitude is not likely to be due to information transmission loss (equivocation), but rather to effects of diminishing attention on information transmission, and decreased certainty of ones response (Johnson, 1988; Johnson, Jr., 1993). The reduction of P3 amplitude in both groups from the 1.2 sec delay to the 3.6 sec delay, indicates that even over short time periods (2.4 sec) attentional allocation can change significantly.

Manipulation of load by increasing complexity and delay periods did not produce distinct differences between groups on visual P3 amplitude, supporting the hypothesis

that visual P3 amplitude would not discriminate well between groups. The present P3 findings are similar to those of Shelley et. al. (1996) who reported non-significant differences in visual P3 amplitudes between schizophrenic patients and controls to attended X targets in an AX-CPT task (Shelley et al., 1996). Although there was a trend level difference in P3 amplitude between groups when all conditions were compared, subsequent analyses indicated that the probability manipulation condition was the only one in which patients displayed significantly smaller visual P3 amplitudes. Although P3 amplitude attenuation has been observed in schizophrenic populations in auditory paradigms (Mathalon, Ford, Rosenbloom, & Pfefferbaum, 2000; Umbricht et al., 1998), visual P3 amplitude attenuation in schizophrenic subjects is often non-significant (Strandburg et al., 1999; Duncan, 1988). However, the reports of non-significant P3 amplitude attenuation in schizophrenic patients often relied upon simple discrimination paradigms. In the present study more complex tasks of WM were employed. Even under the higher loads of the present study (i.e. 2-Back and 1-Back), P3 amplitude was not different between groups. Therefore, it does not appear that visual P3 amplitude is as robust a group discriminator as it is in the auditory modality. In the present study, P3 amplitudes of patients were most like those of controls in the 1-back and 2-back tasks, which both contained cue stimuli. Therefore, it may be that cue stimuli alerted patients to transiently raise attentional levels, allowing them to normalize processes indexed by P3. The somewhat normalized P3 amplitude of the patients in the cued tasks where phasic attention came into play, contrasted to their poorer performance in the uncued tasks where sustained attention was employed, suggests that a deficit in tonic arousal may play

a role in the WM deficits observed in schizophrenia.

P3 amplitude studies using auditory oddball paradigms and sample sizes similar to the current study, consistently find reduced P3 amplitudes in schizophrenic subjects. Therefore, the fact that only trend level P3 amplitude differences are present in the current study may indicate that effect size in the visual modality is smaller than in the auditory modality. Future visual P3 research involving schizophrenic subjects may need larger sample sizes, or more demanding tasks, to increase power to an acceptable level.

N1 and P3 amplitude results of this study indicate abnormalities in the recruitment of neural substrates in schizophrenic subjects performing WM tasks. The greatest dysfunction was evident at an early stages of WM processing, sensory registration, indexed by N1. Less distinct deficits in schizophrenics were noted at later stages of WM processing indexed by P3 amplitude attenuation to target stimuli.

*Speed of Information Processing*

In addition to the degree of recruitment of neural substrates, the speed at which information passes through the system indicates the integrity of WM. Speed of information processing at the stage of sensory registration was indexed by N1 latency. N1 latency increased as a function of perceived task difficulty, however, patients did not differ from controls in any of the 5 conditions. The fact that there was no main effect of group on N1 latency indicates that patients behaved similarly to controls from one paradigm to the next, and corroborates N1 latency findings in schizophrenic groups found by others in both the visual (Shelley et al., 1996) and auditory (Javitt et al., 1995) modalities. Although the N1 amplitude data suggest that patients experience tasks as

more effortful. N1 latency data indicated that it did not take patients longer to encode early sensory registration of match-target stimuli, suggesting that speed of processing of early sensory information is not impaired in schizophrenia.

Duration of stimulus evaluation time was assessed by P3 latency which indicated relatively intact performance for schizophrenics in the present study. However, other research has indicated a slowed visual P3 response in schizophrenic patients performing CPT type tasks (Strandburg et al., 1999) though this research employed a CPT without any cue stimuli. Since there was no main effect of group for P3 latency in the current experiment, post-hoc tests were not originally performed. However, given the influence of cue stimuli to help normalize performance, and the fact that the current P3 latency results differed from others, t-tests were performed on P3 latencies for cued and uncued conditions. This analysis confirmed that in the WM tasks containing a cue stimulus (i.e., 1-back and 2-back), there were no differences in P3 latencies between groups. However, the No Load 20% condition, lacking a cue stimuli, showed a significant group difference, with controls having earlier P3 latencies ($df = 30$, $T = -2.576$, $p = .018$). Therefore, when adjusted for the absence of a cue stimuli as in Strandburg et. al. (1999), the current results are congruent with those previously reported (Strandburg et al., 1999). In the present study, mean P3 latency to target Xs in the uncued No Load 20% condition was 425 ms, and similar to the mean 460 ms combined task latency reported by Strandburg et al (1999) obtained using similar tasks. The present finding that P3 latency was impaired in the uncued task, but normal in the cued tasks, supports the notion that transient arousal of attention provided by a priming stimulus helps to normalize schizophrenic performance,

in this case speed of information processing.

Response selection and execution represents the final component of information processing, and was indexed in the current tasks as a button press (i.e., RT). Across groups RT increased along with task difficulty, indicating load manipulations affected processing time. The presence of a cue to alert subjects that the subsequent stimulus needed to be evaluated and classified had an advantageous effect in terms of RT, on average responses were 60 ms earlier on cued tasks for both groups. The results are typical of those often reported in Sternberg type tasks where increasing demands result in increased RTs (Ruchkin et al., 1990). Although there was a significant effect of group on RT with schizophrenics responding significantly slower than controls, there was no difference in P3 latency between groups, indicating that there is slowed response selection and execution in the patient group. Whether the slowing is due to response selection or to execution, can not be discerned from the current data. It is possible that slowed RT is due solely to execution of the motor response. This would not be contradictory to the observation that patients have slowed finger tapping, a task requiring motor execution, but having no WM load or information processing demands (Bates et al., 1995). The current study emphasizes the important differences that exist between speed of processing and the degree of neuronal recruitment during processing.

**Dysfunctional Inhibition Mechanisms**

Traditional measures of WM performance (e.g., accuracy, RT) provide strong evidence for deficits in the ability to *initiate* responses in schizophrenia. The ability to

use WM to *inhibit* inappropriate responses was also examined in the present study. Although the current False Alarm (FA) data is difficult to interpret because few overall FA responses were made in either group, the data suggests that the WM measures may have captured deficits of inhibition. This discussion of FA responding should be viewed carefully, however, as the results were not statistically significant. In the current study the subjects showed trend levels of producing more FA's than controls (see Figure 6), lending some support to the hypothesis that schizophrenic patients would demonstrate an inability to inhibit inappropriate responses. A lack of power most likely explains the sparse FA findings. A paradigm such as Shelley's et als. (1996) would be better equipped to address this particular type of question since it was specifically designed to maximize FAs (Shelley et al., 1996). The reader is referred to figures 6 and 7 which provide a qualitative account of the FA rates between the subject groups. From these figures it appears that patients produce more FA's, however, patients and controls respond very similarly in terms of FA's in response to changing cognitive load (see Figure 6), suggesting again that varying cognitive demands does not have differential effects on the two groups.

Dysfunctional inhibition was also manifest in the N1 component, indicating PFC dysfunction in the regulation of visual sensory cortex. Patients consistently displayed larger N1 amplitudes in comparison to controls, indicating a greater degree of neuronal recruitment in all conditions. Patients appear to be allocating more resources to the early sensory registration of stimuli than controls. Larger than expected visual N1 amplitude can be interpreted as a dysfunction of the PFC's normal inhibitory role on primary

sensory cortex, and is similar to findings in auditory sensory cortex reported elsewhere (Chao et al., 1998). A more recent finding in the visual modality also suggests larger N1 amplitude findings in patients with DLPFC damage (Barcelo, Suwazono, & Knight, 2000).

The present data correspond with the older notion of Broadbent of a processing amplifier which needs appropriately filtered data. Perhaps the overreaction observed in the N1 response is analogous to inadequate filtering, such that the data is in some way distorted. Distortion at early stages of processing would likely have a cascading effect as the data moved through the information processing system, resulting in the WM deficits that are manifest in the current sample, and those that have been reported elsewhere (Strandburg et al., 1999). (Shelley et al., 1996). The present finding of impaired early sensory registration of stimuli supports hypotheses of an early processing imprecision in schizophrenia (Javitt et al., 1997).

Dysfunctional inhibition in patients as indexed by larger P3 amplitude to catch trial stimuli, was a less robust finding in the present study. Other paradigms have been more successful in eliciting P3 differences to catch trial stimuli. Shelley et al. (1996) found a paradoxical increase in schizophrenics P3 amplitudes in response to catch trial stimuli, such that amplitudes were actually larger in patients than controls. The authors suggested that the paradoxically larger P3 amplitude generation in schizophrenics reflected premature escape of parietal association cortex from an inhibitory trace maintained prefrontally (Shelley et al., 1996). However, the current paradigm and

Shelley et als. (1996) differed in important ways. Shelley et als. (1996) paradigm was specifically designed to build up an expectancy bias to respond to any "X" observed, thereby causing more effortful processing to be employed to prevent unwanted responses to mismatch-target Xs, maximizing the likelihood of false alarms. Hence, Shelley et als (1996) paradigm placed greater demands on WM resulting in more evident differences between groups (Shelley et al., 1996). In the present study the 1-back WM task was most similar to the measure employed by Shelley et al. (1996), albeit Shelley's (1996) task was more difficult due to a strong expectancy bias and longer ISI. The current data (see Figure 16) suggests that when the 1-back WM results are observed in isolation, the data appear similar to those of Shelley (1996). In the more effortful 1-back long ISI (3.6 sec) task, patient performance suggests possibly larger P3 amplitude (see Figure 16), lending some support to the hypothesis that disinhibition in schizophrenic patients would be manifest as paradoxically larger P3 amplitudes to catch trial stimuli. One explanation for this observation being non-significant is that the paradigm was not designed to maximally manipulate stimulus expectancy on the catch trials. Additionally, Shelley et al. (1996) employed a long ISI of 5 sec, whereas in the current study long ISI was only 3.6 sec. It is plausible that the parameters of stimulus expectancy and delay periods employed in the present study resulted in a smaller effect size and lower power. A study with more subjects may have yielded significant results. Alternatively, employing a paradigm producing a larger effect size, such as Shelley et als. (1996), would likely elicit significant findings with the current sample size. The fact that the present lower inhibition load produced a small P3 amplitude effect, and Shelley et als. (1996) high

inhibition load produced a larger effect, indicates that there may be a linear relationship between inhibition load and the paradoxical P3 amplitude increases observed in schizophrenic patients.

The current schizophrenic data indicating larger N1 amplitudes, more FAs, and paradoxically larger P3 amplitude to catch trial stimuli, suggests dysfunctional inhibition in the patient group. Since N1 amplitude, FA responding, and paradoxically larger P3 amplitudes have all been related to frontal lobe functioning, the inhibitory deficits observed in the present study are likely attributable to a disturbance of frontal cortex

**Patterns of Brain Dysfunction**

There were clear differences in scalp topography between tasks for the P3 component in both groups. Changes in scalp topography in response to changing cognitive demands has been reported previously (Johnson, Jr., 1993; Johnson, Jr. & Fedio, 1987). Such changes indicate that either different neural generators are activated, or the relative contributions of generators underlying a component are changing. N1 differences in topography were present across tasks for both groups, indicating that early sensory registration is affected by task demands. These N1 topographical changes suggest that neuronal recruitment patterns were different from task to task, but not between groups.

More pertinent to the present study is the assessment of brain activation of schizophrenic patients in comparison to controls. The current data indicate that P3 distribution does not differ between patients and controls overall. However, inspection of Figure 12 suggests that patients P3 topography, in response to target Xs in WM tasks,

displays larger amplitudes at frontal leads relative to parietal leads, when compared to the distributions generated by controls. This indicates that the pattern of neural generators contributing to the P3 response may differ amongst groups. This does not necessarily imply that different neural generators are activating in schizophrenic patients, but could mean that similar generator sites are activating differentially. The significance of a frontal shift in P3 in terms of its relation to WM has been provided by Fabiani et al. (1995). In a WM experiment designed to quantify P3 topography between young and old subjects an auditory oddball paradigm was employed. Older subjects displayed a P3 distribution to deviant target-stimuli that was displaced frontally (Fabiani & Friedman, 1995). The author suggested that since the frontal lobes are involved in the maintenance of WM, the elderly may require increased frontal activity because of more rapid memory decay (Fabiani et al., 1995). The results were thought to be consistent with decreased ability of the elderly to maintain the templates needed for stimulus categorization (Fabiani & Friedman 1995). Although not as compelling as the data presented by Fabiani et al. (1995), the indication of a more frontal P3 distribution in the present study may suggest that schizophrenic subjects have more difficulty maintaining representations of context, necessitating recruitment of frontal cortex during WM tasks.

The current finding of no difference in N1 distribution between groups, and only trend level group differences in P3 distribution, indicates that there are not sharp focal dysfunctions present in the schizophrenic sample. Rather a generalized brain dysfunction appears to be present, with perhaps somewhat greater involvement of the frontal lobes suggested by P3 amplitude distribution in WM tasks. This pattern of brain dysfunction

corresponds with the neuropsychological profiles that have been reported in schizophrenic patients who show generalized cognitive deficits with perhaps greater compromise of memory and executive functions (Bilder et al., 2000; Goldberg, Gold, & Braff, 1990).

## CONCLUSIONS

Domains of cognitive functioning such as general intelligence, language, memory, and executive functioning, have all been shown to have at least some level of impairment in schizophrenia (Bilder et al., 2000). Therefore, it is clear that WM is not the sole affected component of cognition in the disorder. Although WM deficits likely compound other cognitive functions, the fact that cognitive deficits abide in so many different domains in schizophrenia is indicative of a broad deficit in information processing. The lack of effect of manipulating WM load in the current experiment suggests that higher-order cognitive functioning in schizophrenia is not specifically impaired. How then can one explain the pervasive deficits seen in this experiment, and many others. The N1 amplitude data obtained in this study may shed some light on this question. Schizophrenic patients displayed a greater degree of neuronal recruitment during the early registration of sensory material. The behavioral results of accuracy and RT data indicate that the abnormal N1 amplitude effects can only be interpreted as deleterious to WM performance. It is then evident that information processing is affected at early stages in schizophrenia which is congruent with earlier theories of filtering deficits. Such early distortion of information most likely results in a cascading effect that becomes manifest as performance deficits in multiple cognitive domains. WM deficits in schizophrenia

may be viewed as the result of early imprecise processing of information, supporting the hypothesis of a processing imprecision in schizophrenia (Javitt et al., 1997), and could account for multi modal deficits (Park et al., 1992). Disinhibition of PFC on multiple primary sensory cortices would be consistent with such findings.

The current study supports the notion of both auditory-verbal and visual-verbal WM deficits in schizophrenia, confirming the work of others (Gold et al., 1997; Strandburg et al., 1999; Shelley et al., 1996). It is interesting to note that the effect sizes for the auditory verbal WM task (i.e. Letter Number Span) and the visual-verbal WM tasks (1-back and 2-back combined) appear similar. In the Letter Number Span patients produced 76.4% as many correct responses as controls, and in the AX-CPT tasks patients, on average, produced 82.7% as many correct responses as controls, a difference of only 6.3%. This suggests that the relative deficits in the two systems are roughly equivalent. Future research specifying the relative contributions of these two WM modalities could help researchers better understand the cognitive risk profile for schizophrenia and better plan cognitive remediation strategies. It would also be of interest to examine sensory precision in multiple modalities to determine if a correlation exists between sensory precision, and other higher-order cognitive processes.

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