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Holinger, Dorothy Powe, Ph.D.

The University of Michigan, 1990

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BRAIN POTENTIALS AND COGNITIVE DYSFUNCTION IN SCHIZOPHRENIA

by

Dorothy Powe Holinger

A dissertation submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy
(Psychology)
in The University of Michigan
1990

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To Bill

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CHAPTER I

GENERAL INTRODUCTION

Some of the earliest attempts to conceptualize schizophrenia focused on cognitive dysfunction. In 1911, Bleuler described a "fragmentation of the thinking process" as one of the primary symptoms of the disorder. Since then, efforts to understand schizophrenia from the perspective of cognitive dysfunction or thought disorder have occupied a prominent place in the theoretical conceptualizations and clinical descriptions of schizophrenia (Bleuler, 1911; Freud, 1911; Cameron, 1944; Goldstein, 1944; Von Domarus, 1944; Vygotsky, 1962; Chapman and Chapman, 1973; Andreasen, 1974, 1979, Magaro, 1980; Cancro, 1985; Harrow and Quinlan, 1985; Holzman, Shenton, and Solovay, 1986; Marengo and Harrow, 1986). Moreover, conceptualizations of cognitive dysfunction in schizophrenia have resulted in a number of views, some of which include: 1) a breakdown in formal logic (Von Domarus, 1944; Arieti, 1974); 2) looseness of associations in thinking (Bleuler, 1911; Chapman and Chapman, 1973); 3) over-inclusive thinking (Cameron, 1944); 4) a regression to a primary process level of thinking (Freud, 1900; Kris, 1952; Holt, 1967b); and 5) a deficit in abstract thinking and reliance on concrete thinking (Benjamin, 1944; Goldstein, 1941, 1944; Gorham, 1956; Chapman, 1960; Vygotsky, 1962; Cancro, 1969; Chapman and Chapman, 1973; Arieti, 1974; Harrow, Adler, Hanf, 1974;

Pishkin, Lovallo, Lenk, and Bourne, 1977; Pishkin and Bourne, 1981; Harrow and Quinlan, 1985; Liddle, 1987). From Bleuler's classic view that schizophrenic thinking was characterized by breaks in the logical flow of thought (a view that came to be known as "loose associations"), to more recent models that conceptualize schizophrenic thinking in terms of positive and negative symptoms (Crow, 1985; Andreasen, 1985; Cornblatt, Lenzenweger, Dworkin, and Erlenmeyer-Kimling, 1985; Pogue-Guille and Harrow, 1985; Strauss, 1985), attempts to understand the nature of the cognitive disturbance in schizophrenia have continued to interest researchers.

Since the pioneering work of Kraepelin (1919) and Bleuler (1911), which described and classified schizophrenia and its symptoms, the study of this disorder has been based on three fundamental models: the descriptive, the psychological, and the biological (Carpenter, 1987). The descriptive model, which laid the foundation for the medical/disease model of schizophrenia, is based on a phenomenological/social/environmental perspective of schizophrenia. This model has included areas that range from symptom descriptions relevant to diagnosis (Bleuler, 1911; Kraepelin, 1919; Schneider, 1959; Feighner, Robins, Guze, Woodruff, Winokur, and Munoz, 1972; Wing, Cooper, and Sartorius, 1974; Andreasen, 1985; Crow, 1985; American Psychiatric Association, 1987) to disturbances in communication and interactive family dynamics (Bateson, Jackson, Haley, and Weakland, 1956; Vaughan and Leff, 1976; Wynne, Singer, Bartko, Toohey, 1977; Doane, Goldstein, Rodrick, and Jones, 1981). The psychological model, on the other hand, laid the initial groundwork for causal explanations of the disorder based on the work of Freud (1900; 1911,) and Bleuler (1911). Two branches that developed from the psychological model are the psychodynamic and the cognitive. These approaches attempted to conceptualize possible causes of the disorder, causes ranging from disturbances in ego functioning (Freud, 1933; Bellak and Loeb, 1968; Arieti, 1974; Kernberg, 1975; Harrow and

Quinlan, 1985; Weiner, 1985) to deficits in attention (McGhie and Chapman, 1961; Shakow, 1962; Magaro, 1980; Gjerde, 1983; Nuechterlein and Dawson, 1984).

The biological model laid the foundation for investigations of various levels of brain dysfunctions in schizophrenia. Research efforts to discover brain abnormalities associated with schizophrenia have waxed and waned since Kraepelin (1911) and Bleuler's (1919) early postulations that an organic component existed in the disorder. Today, the biological study of schizophrenia has resulted in a number of models, some of which include theories related to neurochemical and neurophysiological abnormalities in schizophrenia.

The most enduring and widely accepted theory of abnormality in schizophrenia is a neurochemical one, the dopamine hypothesis (Carlsson and Lindqvist, 1963; Andreasen, 1988). This theory posits that functional hyperactivity in the dopaminergic system in schizophrenia is associated with the symptoms of the disorder. The endurance of the dopamine hypothesis is based on several lines of evidence: a reduction of symptomotology by the action of neuroleptic medication, and an exacerbation of symptomotology by dopamine agonists (Carlsson, 1978; Andreasen et al., 1988). There are two types of dopamine receptors in the CNS, D_1 and D_2 (Kebabian and Calne, 1979). Data from postmortem studies have shown that the D_2 receptors were found in higher densities in schizophrenic brains than in control brains (Seeman, Chau-Wong, Tedesco, and Wong, 1975; Owen, Cross, Crow, Longden, Poulter, and Riley, 1978; MacKay, Bird, Spokes, Rossor, and Iversen, 1980). These data were initially thought to be related to the dopamine abnormality in schizophrenia. However, questions were raised concerning the effect neuroleptic use might have on D_2, namely that the increase in these receptors might be a response to neuroleptic blockade of D_2 receptors. As a result, subsequent in vivo studies used positron emission tomography (PET) to investigate D_2 receptors in drug-naive schizophrenics. Although two separate groups looked at the neostriatum in drug-naive schizophrenics, the data reported by each group

were discrepant; one study found increased D_2 receptors (Wong et al., 1986), while the other study found no increase (Farde, Hall, Ehrin and Sedvall, 1986). Careful examination of each group's methodology revealed several critical differences. For example, different radioligand binding techniques were used. C-N-Methylspiperone was used by one group (Wong et al., 1986), and C-Raclopride by the other (Farde et al., 1986). One explanation for the discrepancy could be that these ligands are not equally sensitive to D_2 receptors. Raclopride, the ligand that was used in the study that found no increase in D_2 receptors, may not have the same action on D_2 receptors that Methylspiperone has. Other methodological issues, which may have contributed to the disparate results, included differences in analyses (dynamic, nonequilibrium model vs. equilibrium distribution model), sampling strategies, age, phenomenology, and stages of the disorder (Andreasen et al., 1988). Further investigations using comparable methodology should help to resolve the present ambiguities. Finally, until recently it has not been possible to test the dopamine hypothesis directly. However, with the development of PET and radioligand techniques it has been possible to study neuroleptic binding sites. Data from a recent study showed that 65-89% of D_2-dopamine receptor sites are occupied by standard neuroleptic drugs (Farde, 1989). Although these data show direct evidence to support the dopamine hypothesis, the relationship between D^2-dopamine receptor occupancy and the effect of neuroleptic medication will need to be studied in more detail.

Efforts to discover brain abnormalities in schizophrenia have also used neurophysiological approaches which include electrophysiological measures such as electroencephalography (EEG), evoked potentials (EPs), and event-related potentials (ERPs). Since the first EEG recordings by Berger (1929), the analysis of changes in the brain's electrical activity at rest or related to external stimuli has become more sophisticated. Today, routine clinical EEGs, which are continuous measurements of brain electrical activity that can be recorded from milliseconds to hours, are used to

relate a broad pattern of topographical change, e.g., rapid fluctuations in electrical activity to particular brain areas (Gale and Edwards, 1983). The EEG has been useful as a diagnostic tool in determining the status or presence of a number of neurological disorders, e.g., epilepsy. However, clinical EEG results have yielded limited information about the nature of brain dysfunction in relation to psychopathology (Fenton, 1980). Although reports of routine EEG tests in schizophrenia have shown some abnormalities (high frequency, low amplitudes, and irregular, choppy rhythms [Small, 1983]), interpretation of these results has generally been regarded as non-specific (Pincus and Tucker, 1985).

The long history of the study of the relationship between scalp-recorded electrical activity and human behavior sparked the expectation that brain potentials would provide a "window to the mind" in normal and disturbed subjects (Callaway, 1975). Indeed, despite the rapid advances in new technology applied to neuroscience in recent years (e.g., PET, Magnetic Resonance Imaging [MRI], and Magnetoencephalography [MEG]), electrophysiology remains a promising and accessible method of investigation in schizophrenia for a number of reasons: recording electrical activity from the scalp is non-invasive; it is far less costly than methods such as PET; it does not involve radioisotope administration; and it can be repeatedly used without risk (Buchsbaum and Haier, 1987). Moreover, there is a significant literature in electrophysiological studies of schizophrenia (cf. Shagass, 1983; Pritchard, 1986; Holzman, 1987).

In contrast to the unstimulated conditions and global behaviors (eyes open or closed) under which EEGs are usually recorded, evoked-brain responses are recorded under stimulated/cognitive decision-related conditions. Evoked-brain responses, which include evoked potentials (EPs) and event-related potentials (ERPs), are techniques that are used to study the relationship between the biology of electrical phenomena and the psychology of discriminative performance; these techniques measure the

correspondence between changes in scalp-recorded electrical activity and specific behavioral performance tasks. Evoked-brain responses are changes in electrical activity of the brain that are time-locked to an external stimulus or event of interest. These responses are low voltage signals that are embedded within the larger EEG voltage and need to be extracted from the "noise" of the background EEG. The usual procedure is to present subjects with a number of stimulus trials which are subsequently averaged. As a result of signal averaging the larger voltage of the random EEG is canceled and the low voltage of the evoked response is enhanced.

Evoked-brain responses are characterized by "components" or peaks which can be negative or positive deflections of the waveform. EP and ERP components are conceptualized as either exogenous or endogenous. Exogenous components, which generally occur < 100 msec after the stimulus, are sensory-locked to the stimulus, e.g., a response to a light flash. These components are the brain's "hard-wired" response to the physical properties of the stimulus. In contrast, endogenous components are independent of stimulus properties, and occur in response to the psychological demands of the paradigm. Endogenous components, which usually occur > 250-1000 msec (Donchin, Ritter, and McCallum, 1978), are thought to index cognitive updating about an event (Donchin and Coles, 1988), e.g., a change in a hypothesis about a cognitive event in response to a stimulus. Finally, the attention-sensitive components (Callaway, 1976; Coles, Gratton, and Fabiani, 1988), which usually occur > 100 and < 250 msec, are thought to index encoding of stimulus and stimulus features (Rockstroh, Elbert, Birbaumer, and Lutzenberger, 1982; Coles et al., 1988). These "middle" components are also instruction-dependent, and increase in response to instructions to attend to a stimulus. In sum, components of evoked-brain waveforms can be conceptualized in the following ways: 1) the exogenous, components are obligatory responses to orienting stimuli (Callaway, 1976); 2) the middle, attentional components are responses to perceptual demands of the stimulus; and 3) the later endogenous components are

responses that depend upon the cognitive demands of the paradigm (Donchin, et al., 1978; Donchin, Karis, Bashore, Coles, Gratton, 1986).

Several components that epitomize the range of peaks in the family of EP and ERP components include the N100, P200, P300, and N400 (see Figure 1). These components are characterized by their polarity, latency, and purported function. The N100, which is a negative deflection of a waveform has a latency range of 80-150 milliseconds. The negative increase in electrical activity of an N100 is dependent upon the experimental paradigm; that is, N100 can be a result of a sensory or an attentional response to a stimulus. For example, in studies where light flashes were presented, N100 amplitude was shown to be maximal at the Oz electrode (over the visual cortex) (Naatanen, 1982). In such paradigms N100 can clearly be described as a "hard-wired" component that is sensory-locked to the stimulus flash. However, in more complex paradigms, e.g., semantic categorization, the amplitude of N100 can vary depending upon the attention of the subject (Naatanen, 1982). The enhancing effect that attention has on N100 has also been referred to as the "Nd" or the selective attention effect (Hansen and Hillyard, 1980). In selective attention paradigms the N100 peak is usually found to be maximal at the Cz electrode (the vertex) in all modalities. In such cases the N100 is thought to index the encoding of features of the stimulus (Rockstroh et al., 1982; Ritter, Simson, and Vaughan, 1983). Thus, as a result of experimental conditions, N100 can function either as a sensory-locked component, or as an attention-related one.

The P200, another ERP component, is characterized by a positive potential shift that often occurs on the upward deflection of the N100, between 150 and 250 milliseconds post-stimulus onset. The P200 component is thought to index attention to the stimulus as a whole, i.e., stimulus recognition and storage (in contrast to the N100 which indexes stimulus feature encoding). Moreover, although the N100 and P200 components are often discussed separately, some researchers consider the N1-P2 a complex. In this context, the N1-P2 are thought to reflect: 1) selective filtering of

stimulus feature encoding, 2) stimulus set, and 3) initial selection of information for subsequent processing (Rockstroh et al., 1982). This complex, which also varies with attention, will usually be maximal at the vertex (Cz) when subjects are instructed to attend and largest over Oz when subjects do not attend to the visual stimulus. Overall, the N100 and the P200 are considered components that are sensory-determined or attention-related. These peaks are also modality specific, and can vary as a function of the task demands of the paradigm.

In the category of the later endogenous components there is a substantial literature on the relationship between cognitive events and changes in ERPs. For example, the P300 is an ERP component whose positive-going deflection occurs about 300 msec post-stimulus onset. The classic P300 is typically elicited in an auditory oddball paradigm in which the frequency of stimulus presentation differs in the context of task-dependent instructions. In an oddball paradigm, the amplitude of the P300 is inversely related to the probability of a rare stimulus occurring, i.e., the lower the probability of occurrence, the higher the P300 amplitude. Although the P300 can be elicited in paradigms other than an oddball one, the manipulation of the P300 amplitude is less predictable; as a result, its relationship to cognitive processing less well defined (cf. Donchin and Coles, 1988; Verleger, 1988).

Finally, the N400 component, which is a relatively new peak in the family of ERP components, is a negative deflection of an evoked waveform that occurs about 400 milliseconds post-stimulus. The fundamental work on the N400 (Kutas and Hillyard, 1980a, 1980b, 1980c, 1983) demonstrated that it could be elicited in a sentence-reading paradigm. Words that form a sentence were serially presented to subjects who were instructed to read silently in order to answer questions about the context of the sentence. If the terminal word in the sentence was semantically incongruous but syntactically correct, an N400 was elicited. In contrast, an N400 was not found when terminal words were congruous.

In sum, the N100 and P200 are early and mid-latency components that are related to attention and are thought to index stimulus feature encoding and stimulus storage, respectively. The P300 and the N400, in contrast, are later, endogenous components. The P300 is related to cognitive processing and is typically associated with stimulus probability (in oddball paradigms and in the context of task relevance). The N400, on the other hand, while also related to cognitive processing, is associated with semantic incongruity. Overall, the components of an evoked waveform can be conceptualized as indices of particular stages of information processing; the more complex the processing, the later the component appears in time.

While there is a substantial literature on the temporal, spatial, and functional characteristics of evoked-brain responses, much effort is being directed toward determining the neural generators of ERP components in humans. Although not conclusive, data from lesion, excision, MEG, and equivalent dipole modelling studies have suggested possible generators for several ERP components. For example, rather than the result of a unitary process attributable to a single generator source and area, the auditory N100 is thought to have several generators (Naatanen and Picton, 1986). The "hard-wired" auditory N100, which is a sensory response to the physical and temporal features of the stimulus, is thought to be generated from the supratemporal plane of the primary auditory cortex (Naatanen and Picton, 1986). MEG data (e.g., Hari, 1987) and spatiotemporal dipole modelling (Scherg and Von Cramon, 1986) generally support this view. Recent MEG data, however, show that the cortical area most responsible for the auditory N100 includes not only the superior temporal planum, but also extends into the temporoparietal area (Reite, Teale, Goldstein, Whalen, and Linnville, 1989). Moreover, other data show that at least six generators exist for the auditory N100 (cf. Naatanen and Picton, 1986). That several different neural generators are thought to contribute to the N100 is congruent with the sensory/attentional functions of this component. However,

the issue of which generators are associated with which N100 will need to be further investigated.

Other ERP components, such as the P300, are also thought to be associated with different brain generators, but these data are also not conclusive. For example, data based on stroke-induced lesions in the superior temporal gyrus showed an absence of the P300 elicited in an auditory paradigm (Knight, Scabini, Woods, and Clayworth, 1988). Other data based on depth recordings in chronic epileptic subjects being evaluated for surgical therapy also suggest that the P300 is generated from temporal lobe structures (Smith, Stapleton, and Halgren, 1986). However, other data do not support this view. ERP recordings from patients who had undergone anterior temporal lobe (ATL) lobectomy, which included removal of the hippocampus, uncus, and basolateral amygdala did not show P3 amplitude differences when compared to normals (e.g., Stapleton, Halgren, and Mareno, 1987). Because several temporal lobe structures were removed and no P300 reduction resulted, the ATL data suggest that temporal lobe structures are not the major generators of P300. However, because brain tissue excision changes the nature of the impedance from the skull, the P300 amplitude in ATL subjects might be an artifact resulting from the surgery. While such speculations about these ATL data do not seem likely, caution does need to be exercised in interpreting results based on different techniques. With the continuing development of methods such as current source density analysis (CSD), and with the expanding data base in MEG studies, the location of neural generators of ERP components should be clarified.

One of the most consistent EP findings in the literature is that schizophrenics' evoked responses to stimuli in all modalities 100 msec post-stimulus have usually been reduced when compared to normals (Shagass, 1983; Pritchard, 1986; Holzman, 1987). For example, one of the most robust findings of a biological deficit in schizophrenia is that, when compared to normals, these subjects show a reduction in P300 amplitudes in auditory oddball paradigms. Moreover, results from a number of studies have shown

that there are electrical brain correlates which index particular deficits in schizophrenia. These findings range from deficits in sensory gating (e.g., a lack of reduction in P50 [Adler, Waldo, and Freedman, 1985]) to attentional and perceptual dysfunctions (reduced P300). Thus, while electrophysiological studies have contributed important data to schizophrenia research, these studies have also laid an extensive groundwork for investigations of more complex cognitive dysfunction in schizophrenia.

Despite the large number of EP studies of schizophrenia, little work has been done to investigate the relationship between ERPs and cognitive dysfunction in this disorder. This lack stands in sharp contrast to the significant literature on ERPs and cognition in normals where, in the emerging field of cognitive psychophysiology, ERPs are considered markers of specific stages of information processing (Mirsky and Duncan, 1986). Current schizophrenia research, however, includes efforts in several directions: 1) to discover biological markers of the disorder (Meltzer, 1987), 2) to develop paradigms that could link biological dysfunction (using electrophysiological measures) with cognitive dysfunction (Donchin and Bashore, 1980; Fenton, 1980; Begleiter and Porjesz, 1984; Pritchard, 1986), and 3) to use ERPs as markers of deficits in information processing in schizophrenia (Mirsky and Duncan, 1986). Thus, investigations to determine whether there are EP and ERP correlates of cognitive dysfunction in schizophrenia are warranted. The studies in the following chapters are consistent with the present direction in schizophrenia research. These studies are part of a programmatic research design in which the level of cognitive complexity increases with each study to determine whether there are ERP correlates of cognitive dysfunction in schizophrenia.

Since few studies have used visual-semantic paradigms to determine whether a relationship between P300 and cognitive dysfunction in schizophrenia exists, the primary hypothesis of the study in Chapter II was that schizophrenic subjects would show a reduction in P300 amplitude compared to normals in a visual-semantic oddball

paradigm. Subjects were presented with stimuli which required categorization based on semantic features (Kutas and Donchin, 1978).

The study in Chapter III, on the other hand, was based on an integration of research from clinical, cognitive, and electrophysiological domains. From a clinical perspective, the abstract-concrete view of thought disorder in schizophrenia has a long history, (Benjamin, 1944; Goldstein, 1944; Gorham, 1956; Chapman, 1960; Vygotsky, 1962; Cancro, 1969; Chapman and Chapman, 1973; Arieti, 1974; Harrow, Adler, Hanf, 1974; Pishkin, Lovallo, Lenk, and Bourne, 1977; Pishkin and Bourne, 1981; Harrow and Quinlan, 1985; Liddle, 1987). This perspective is based on clinical observations that schizophrenics show a reduced ability to think abstractly and often rely on concrete thinking. Thus, although the abstract-concrete approach has been clinically useful in the study of schizophrenia, this view has been criticized for not withstanding empirical scrutiny (Carson, 1962; Cancro, 1969; Pavy, 1968; Reed, 1968; Shimkunas, 1970; Chapman and Chapman, 1973; Harrow, Adler, and Hanf, 1974; Harrow and Quinlan, 1985). However, recent converging data from animal, developmental, and cognitive research has made it possible to define both abstract and concrete thinking in more rigorous operational terms. Therefore, the primary aim in Chapter III was that, when abstract thinking was indicated, schizophrenic subjects would use concrete thinking more often than normals. An additional aim was to determine whether there would be ERP correlates of slippage to concrete thinking in the schizophrenic group. The study in Chapter III used a visual-semantic categorization paradigm to investigate the relationship between cognitive dysfunction and ERPs in schizophrenia. Abstract thinking was represented by superordinate categorization, and concrete thinking by basic-level categorization. Visual stimuli were presented to subjects on slides in a Stimulus 1 (S1) and Stimulus 2 (S2) sequence. S1 presented the name of a category; S2 presented three words that named items which could belong to the category named on

the first slide. Subjects were required to decide whether the items named on S2 belonged to the category named on S1.

Finally, the growth of research on the N400 as an index of semantic incongruity in normals is in sharp contrast to the paucity of N400 research in schizophrenics. The aim of the study in Chapter IV was to determine whether schizophrenic subjects, when compared to normals, would show differences in their N400 responses to incongruities in superordinate categorization. The rationale to use a categorization paradigm to test N400 differences between normals and schizophrenics (rather than an N400 sentence paradigm) was in keeping with the focus of the programmatic research design in these studies, namely cognitive dysfunction (vs. language disturbance) in schizophrenia.

The studies in the following chapters are noteworthy in several respects. First, these studies use a cognitive psychophysiological paradigm to investigate ERPs and cognitive dysfunction in schizophrenia. Second, they could lay the groundwork for more objective measures of cognitive dysfunction in schizophrenia. Finally, these studies could prove valuable in the evaluation of various treatment modalities.

In conclusion, current studies of schizophrenia show a number of neurophysiological abnormalities. In light of these promising data, the development and use of cognitive psychophysiological paradigms (such as the ones used in the following studies) to demonstrate ERP correlates of cognitive dysfunction in schizophrenia would be a step in the direction of integrating the descriptive, psychological, and biological models of the disorder.

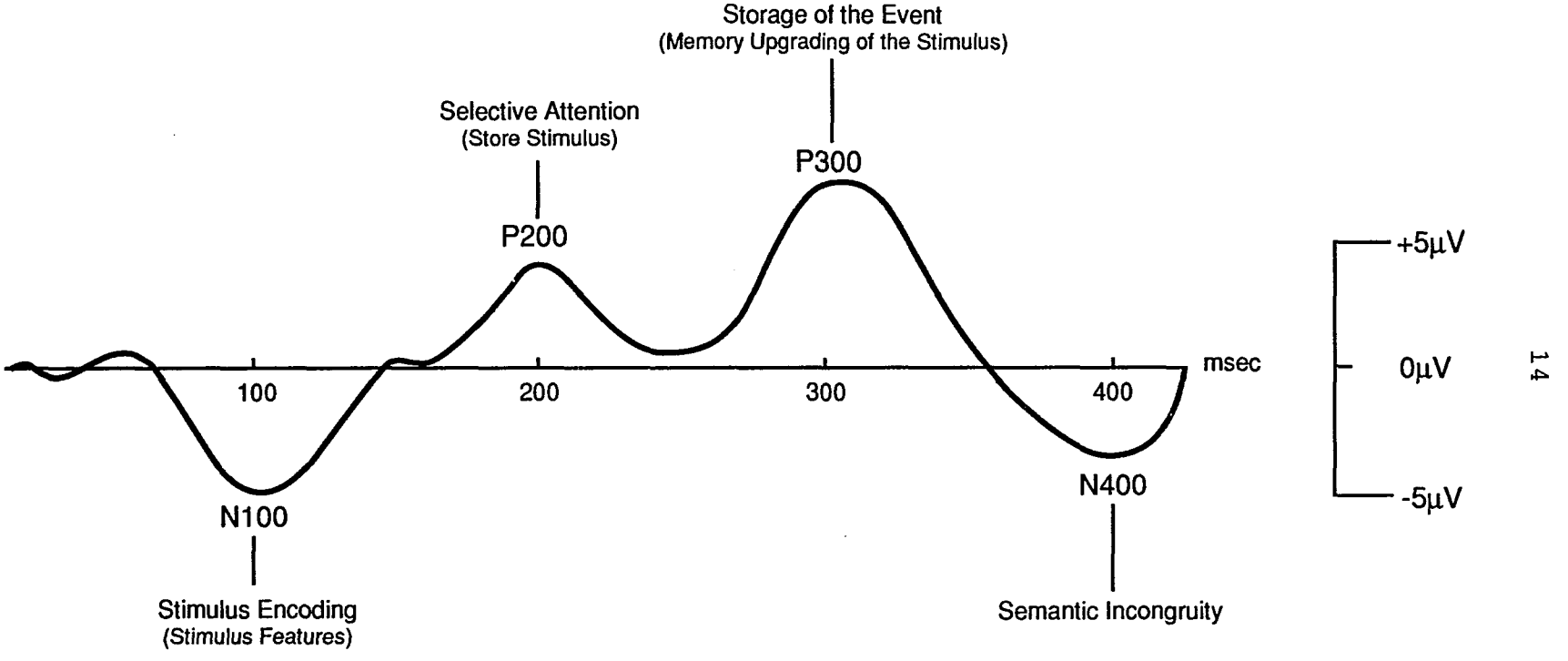

Figure 1: ERP Waveform Illustrating Idealized N100, P200, P300, and N400 Components
(Adapted from Rockstroh, Elbert, Birbaumer, and Lutzenberger, 1982)

CHAPTER II

P300: SCHIZOPHRENIC RESPONSES TO "ODDBALL" SEMANTIC CATEGORIZATION STIMULI

Introduction

Research on the P300 component of the human event-related potential (ERP) has burgeoned since its discovery was first reported in a guessing paradigm by Sutton, Braren, Zubin, and John (1965). The P300 of an event-related brain potential, which is a broad positive deflection of a waveform, is characterized by maximum positivity at centro-parietal scalp locations. The latency of this component was first observed to occur about 300 milliseconds after stimulus onset. Since then, P300 latency has been observed to vary within a relatively long period, a time window that spans 300 to 1,000 msec (Kutas and Donchin, 1978; Kutas, 1988). Moreover, the conditions under which this component can be elicited have expanded considerably since the early work. Today, the P300 can be elicited in response to a wide variety of tasks that are related to a number of psychological variables (Pritchard, 1981; Sutton and Ruchkin; 1984; Donchin and Coles, 1988; Verleger 1988). Some of these variables include: 1) stimulus probability (Picton and Stuss, 1980); 2) subjective probability and task relevance (Donchin, 1979; Donchin and Coles, 1988); and 3) context updating (Donchin and Coles, 1988).

Although a number of psychological variables can elicit a P300, the most replicated experimental condition in which the relationship between the amplitude of P300 and stimulus events is most visible is the signal detection paradigm. Signal detection studies, which are usually called oddball after the classic oddball paradigm, consistently show a robust P300 (Duncan-Johnson and Donchin, 1977). In oddball paradigms, subjective probability and task relevance are manipulated (Duncan-Johnson and Donchin, 1977; Donchin, 1979; Johnson, 1984; Donchin and Coles, 1988). Probabilities that are typically used for stimulus presentation in oddball studies are .20 (rare) and .80 (frequent). Task relevance, on the other hand, relates to the instructions given to the subject to classify the rare stimulus (e.g., count the number of high tones in a stream of low tones). Data from oddball studies have demonstrated that, when subjects are instructed to attend to the rare stimulus, the lower the probability of the rare stimulus occurring, the higher the P300 amplitude (Fabiani, Gratton, Karis, and Donchin, 1987; Donchin and Coles, 1988).

In contrast to the robust relationship between P300 and oddball stimuli, P300 amplitude differences in other paradigms are less clear and less predictable. Despite suggestions that cognitive variables that manipulate P300 amplitude be assigned to dimensions that control for subjective probability and information about the task (Johnson, Jr., 1984), considerable debate continues, which relates to the functional significance of P300 (Donchin and Coles, 1988; Verleger, 1988), and to the various types of P300 (Sutton and Ruchkin, 1984). From an overall view, research has shown that the P300 is a complex ERP component that is characterized by a number of features: 1) it can be elicited by a number of psychological variables; 2) its latency increases as task complexity increases (Kutas and Donchin, 1978; Kutas, 1988); and 3) it can have different scalp distributions (e.g., frontal versus centro-parietal) (cf. Sutton and Ruchkin, 1984).

Although there is a substantial literature on the temporal, spatial, and purported functional characteristics of the P300, efforts are presently being directed to locate the neural generators of this ERP component. While the data are not conclusive, it is presumed that P300 has multiple brain generators. These data are based on depth recordings, dipole modelling (Scherg and Von Cramon, 1986), lesion, and excision work. The prevailing view has been that the primary generator of P300 is in the medial temporal area from structures like the hippocampus (and other structures) (e.g., Halgren, Stapelton, Smith, and Altafullah, 1986). However, data on patients who had undergone anterior temporal lobe lobectomy suggest that the medial temporal area is not the major generator of the P300 (e.g., Stapelton, Halgren, and Mareno, 1987). These neuroanatomical data support the notion that P300 does not index a unitary phenomenon, but that it is a multi-faceted component that changes depending upon experimental manipulation. Given the extensive data base that studies of P300 have generated, and the lively and continued interest in its functional significance, this peak has become the quintessential component in the cognitive psychophysiological literature.

The extensive research on P300 has also generated considerable interest in its clinical application to psychiatric disorders. Roth and Cannon (1972) first reported that schizophrenic subjects showed significantly lower P300 amplitudes than normals in auditory oddball paradigms. This finding has been successfully replicated by a number of researchers (Levit, Sutton, and Zubin, 1973; Verleger and Cohen, 1978; Roth, Pfefferbaum, Horvath, Berger, and Koppel, 1980; Shagass, Roemer, Straumanis, and Amadeo, 1978; Baribeau-Braun, Picton, and Gosseline, 1983; Brecher and Begleiter, 1983; Morihisa, Duffy, and Wyatt, 1983; Morstyn, Duffy, and McCarley, 1983; Duncan-Johnson, Roth, and Koppel, 1984; Duncan, Perlstein, and Morihisa, 1987; Faux, Torello, McCarley, Shenton, and Duffy, 1987; Faux, Torello, McCarley, Shenton,

and Duffy, 1988). In sum, the attenuation of P300 is one of the most robust findings of biological deficits in schizophrenia (Begleiter and Porjesz, 1986).

The P300 amplitude reduction in schizophrenia has been attributed to a number of behavioral deficits in attention, information processing, and cognition (e.g., Pfefferbaum, Ford, White, and Roth, 1989). However, the auditory oddball P300 might actually lie on the interface between early, sensory processing and later cognitive processing, and thus more aptly be described as a deficit in perceptual processing. While some researchers have referred to the P300 reduction in auditory oddball studies as an ERP correlate of perceptual deficit (e.g., Begleiter and Porjesz, 1986), discriminations between loud and soft tones have not usually been referred to as perceptual tasks. Similarly, little work has been done to determine whether there are ERP correlates of cognitive dysfunction in schizophrenia. Interest in the study of the relationship between ERPs, particularly the P300, and cognitive deficits in schizophrenia has recently been expressed (Begleiter and Porjesz, 1986; Mirsky and Duncan, 1986). In addition, it has been suggested that cognitive psychophysiological paradigms be developed to use as diagnostic tools in schizophrenia (Donchin and Bashore, 1980; Pritchard, 1986). Therefore, efforts to discover whether there are P300 correlates of cognitive dysfunction in schizophrenia are warranted.

There were two hypotheses in the present study. The first hypothesis was that there would be P300 amplitude differences between two groups, normals and schizophrenics, in the rare condition of an oddball visual-semantic paradigm. The second hypothesis was that schizophrenic and normal subjects would show amplitude and latency differences in N100 and P200, components that are purported to index stimulus feature and storage, respectively (Rockstroh, Elbert, Birbaumer, and Lutzenberger, 1982). This study used a visual modality to present semantic stimuli in an oddball design to subjects (based on Kutas and Donchin, 1978).

Methods

General Criteria for Subject Selection

Fifteen subjects were included in this study: nine normal subjects (6 females and 3 males) and six schizophrenic subjects (4 females and 2 males). Normal subjects ranged in age from 19-54 (mean age = 28); schizophrenic subjects ranged in age from 19-32 (mean age = 27.6). All subjects were right-handed (The Edinburgh Inventory, Oldfield, 1971) and none had a history of head injury, alcohol abuse, or neurological disorder. Vision tested 20/20 (corrected as indicated) for all subjects (Rosenbaum Pocket Vision Screener) who were included in the study. I.Q. measures for normal subjects ranged from average to superior (mean = high average); I.Q. measures for schizophrenic subjects ranged from low average to high average (mean = average). The State-Trait Anxiety Inventory (STAI), which was used to control for level of anxiety, was administered before and after laboratory procedures. STAI results showed that subjects were not anxious (Spielberger, 1983).

Diagnostic Selection Criteria

The Schedule for Affective Disorders and Schizophrenia (SADS) (Endicott and Spitzer, 1978) was used to make a Research Diagnostic Criteria (RDC) (Spitzer, Endicott, and Robins, 1977) diagnosis of schizophrenia for the schizophrenic group. Five schizophrenic subjects were inpatients (who were discharged shortly after testing) and one was an outpatient (who had been recently discharged). The Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962) was used to assess symptom level. All schizophrenic subjects whose data were included in the final analysis scored less than 45 on the BPRS. Two BPRS assessments were done within several days of each other: one by the experimenter (a clinical psychologist trained in the use of the BPRS) on the day of electrophysiological testing, the other by a research assistant (trained by

the experimenter) on the day of cognitive tests administration. Interrater reliability for BPRS was 0.94 (Intraclass correlation coefficient [Winer, 1971]).

Normal subjects, who were recruited from an existing pool, had no history of psychiatric hospitalization themselves or among their first-degree relatives. I.Q. for normals was measured with the WAIS-R Vocabulary Subtest (Wechsler, 1981); normal functioning was assessed with Minnesota Multiphasic Personality Inventory (MMPI) (no elevation above 70 on any subscore) or with the Schedule for Affective Disorders (SADS) (no history of mental disorder). Two BPRS assessments of normals were also done within several days of each other, one by the experimenter on the day of electrophysiological testing, the other by a research assistant on the day that the cognitive tests were administered (see below).

Cognitive Measures: Thought Disorder and I.Q. Assessments

In addition to meeting the clinical criteria for diagnosis of schizophrenia or never mentally ill, all subjects who were included in the study had been cognitively assessed to determine whether there was evidence of cognitive dysfunction (defined as thought disorder in this study). Cognitive function versus dysfunction (i.e., thought disorder) was measured on Bizarre-Idiosyncratic Thinking (B-I) dimensions (Harrow and Quinlan, 1985). Evaluation of B-I Thinking involves an assessment of the major phenomena that can be grouped into the category of "positive thought disorder" (Marengo and Harrow, 1986). The five dimensions on which subjects' thinking were assessed include: 1) linguistic form and structure; 2) content of the statement; 3) intermixing; 4) relationship between question and response; and 5) behavior (cf. Harrow and Quinlan, 1985). The following measures were used to assess thought disorder: the Comprehension subtest on the Wechsler Adult Intelligence Scale, Revised (WAIS-R) (Wechsler, 1981); the Benjamin Proverbs Test (Benjamin, 1944); and the Object Sort Test (Goldstein and Sheerer, 1941). All tests were scored separately by two raters

(experimenter and research assistant). Each subject's B-I score was compared to the Thought Disorder rating scale and given a Thought Disorder score (Harrow and Quinlan, 1985). The scores on this scale ranged from 1 to 5 with the following divisions: **1-2** = no thought disorder; **3** = definite thought disorder; and **4-5** = severe thought disorder. Normals who scored >3, which indicated definite thought disorder (1 subject), were not included in the study. Similarly, schizophrenics who scored <3, which indicated no thought disorder (2 subjects), were also not included in the study. The Vocabulary subtest of the WAIS-R (Wechsler, 1981) was used as an estimate of I.Q. because it has the highest correlation (.96) with a full I.Q. score of any WAIS-R verbal subtest (Wechsler, 1981). Finally, interrater reliability (experimenter and research assistant) for scoring of all cognitive measures was .82 for B-I thinking and .98 for Vocabulary (Intraclass correlation coefficient [Winer, 1971]). Means and standard deviations for B-I scores, I.Q. scores, and ages of normal and schizophrenic subjects are presented in Table 1.

Medication and Other Considerations

Some studies suggest that medicated and unmedicated schizophrenics show similar levels of thought disorder in the early acute phase of an episode (Harrow, Grossman, Silverstein, and Meltzer, 1982). Moreover, while the initial effects of medication can reduce the acute symptomatology of schizophrenia, there is data that also suggest that improvement in thinking from the effects of medication, e.g., phenothiazines, can take 1 to 1-1/2 weeks or longer (Harrow and Quinlan, 1985). Because subject participation in this study included three phases (diagnostic assessment, cognitive assessments, and electrophysiological procedures) patient subjects needed to be relatively symptom-free in order to complete all phases of the study. Thus, all schizophrenic subjects included in the analysis were not in episode, were on psychotropic medication, had an RDC diagnosis of schizophrenia (based on SADS

interview), and had scores of definite thought disorder on the B-I thinking scale. Normals were not on medication, had scores of no thought disorder on the B-I thinking scale, and had an MMPI/SADS assessment of never mentally ill.

Histories and Miscellaneous Criteria

Medication and previous treatment histories, and demographic information were taken on all subjects. Confidentiality and protection of subjects' rights were taken into consideration. After consent forms were signed, only ID codes were used to identify subjects. All subjects were informed they could stop at any point of the procedure if they wished. All non-patients were compensated (inpatients were not compensated in accordance with hospital policy that patients are not paid for participation in hospital research). Approval for participation of hospitalized subjects was obtained from the Human Use Committee at the University of Michigan Hospital. Patients were asked a number of questions to check for: 1) adverse reactions to medications; and 2) new medications (or change in dosage). Finally, a special details checklist was administered to schizophrenic subjects to determine whether any situation of note needed to be addressed during or after laboratory procedures. Subjects in both groups completed all diagnostic, cognitive, and laboratory phases of the study.

Experimental Procedures

Subjects were seated in a dimly lit, sound attenuated room. They sat facing a projection screen (placed 65 cm. away) and viewed visual-semantic oddball stimuli. There were two experimental conditions during which male and female names were presented to subjects on slides. The male name, David (the "rare" condition), was presented with a .20 probability. The female name, Nancy (the "frequent" condition), was presented with a .80 probability. Subjects were instructed to count the number of male names and told that they would be asked how many names they counted at the end

of the experiment. Two blocks of 36 trials were presented to subjects. Trials occurred within a variable interval (2 1/2 seconds or longer depending on patient status or equipment difficulty).

Stimuli were projected onto a rear projection screen (Daylight Screens) using an Ectographic slide projector. A second Ectographic slide projector was used to project a fixation slide. The fixation slide was continuously projected to maintain a background with the same brightness as stimulus slides in order to minimize flash/blink responses when stimuli were presented. Room illumination was maintained at 2.5 ft. lamberts and fixation slide (dot was centered in the middle) at 2.5 ft. lamberts. Stimuli were presented for 100 msec at an intensity of 3.5 ft. lamberts (measured with an 40 X Opto-Meter). Stimulus words, when presented, were centered on the fixation dot. All stimulus words were white upper and lower case letters on a blue background centered on 2" x 2" slides.

Data Collection, Equipment, and Analysis

EEG was recorded from 3 midline electrode locations: Fz, Cz, and Pz (10-20 International System). All electrodes were referred to linked mastoids. Nicolet EEG Surface silver cup electrodes, which were attached with collodion, were used for scalp recordings and the ground electrode (placed mid-forehead). Eye movements were monitored by electrodes placed above and below the left eye (attached with paste). Impedances were maintained <4 kOhms.

The Nicolet Pathfinder I Electrodiagnostic System was used to amplify, filter, store, average, and plot the data. The Pathfinder I model can record eight channels of data; it has a 10 megabyte Winchester hard drive (to which individual trials were stored for off-line analysis) and two floppy drives.

The EEG and EOG were amplified with Pathfinder I SM200L amplifiers. Low bandpass filter was set at .01 Hz (time constant was 7-sec [-6 db roll-off] [Rockstroh,

Elbert, Birbaumer, and Lutzenberger, 1982]) and high bandpass filter at 30 Hz. Recording epoch was 1000 msec with a 206 msec pre-stimulus interval. With an analysis sweep (time) of 512 data points, data were sampled at 1.95 msec. Individual trials were stored to disk so that inspection of raw data could occur off-line. During ERP averaging, all trials were individually inspected prior to inclusion in the averaging. The decision to accept or reject was based on preset rejection criteria, e.g., trials with artifacts such as eye movements >65 μV were rejected.

Simultaneous presentation of each trial and initiation of EEG data collection were manually triggered by the experimenter (who monitored the status of patient subjects) from a Grass Stimulator (S88). An automatic timing mechanism (Vincent Associates, 4 msec open/shut time) was attached to the shutter of the stimulus projector for preset timed presentations of stimuli.

ERPs were averaged for two conditions: rare and frequent. Measurement of P300 was computed with respect to the averaged pre-stimulus recording period to the highest peak within the designated P300 time window (300-440 msec).

Results

Means and standard deviations were performed for all subjects on ERP amplitudes and latencies, thought disorder, age, and I.Q. (Tables 1-5; 10-13). Univariate 2x2x3 factor repeated-measures analyses of variance using BMDP2V were performed on the amplitudes of N100 (Table 6), P200 (Table 7), and P300 amplitude (Table 8). Analyses were also performed on the latencies of N100 (Table 14), P200 (Table 15), and P300 (Table 16). Diagnostic group (normal and schizophrenic subjects) was the between-subjects factor; within-subject factors were electrode position (Pz, Cz, and Fz) and experimental condition (rare and frequent). A full ANOVA model (2x2x3) was

used to assess the effect of each factor in the experiment (diagnosis x condition x electrode) on component amplitude.

The repeated-measures ANOVAs, which were used to analyze all the amplitude and latency data, incorporated The Greenhouse-Geisser correction for violations of sphericity of the variance-covariance matrix of repeated measures when the number of repeated measures levels is greater than two (Jennings, Cohen, Ruchkin, and Fridlund, 1987).

Analysis of the P300 data revealed three significant main effects for P300 amplitude: an effect of diagnosis ($F(1,13) = 5.97$, $p < 0.03$); of condition ($F(1,13) = 52.0$, $p < 0.001$); and of electrode ($F(2,26) = 3.39$, $p < 0.05$) (Table 8). A two-way significant interaction for P300 amplitude between condition and diagnosis ($F(1,13) = 5.33$, $p < 0.04$) reflects amplitude differences between schizophrenics and normals in the rare condition. Simple group contrasts were significant when the P300 amplitude means for both groups were collapsed across electrodes in the rare and frequent condition (13 df, $p < 0.02$) (Table 9). These data showed that normals' P300 amplitude was significantly higher than schizophrenics in the rare condition, as reflected in the condition by diagnosis interaction (Figure 1). Finally, group contrasts also showed that the largest P300 amplitude difference between schizophrenics and normals occurred at the Cz electrode (central electrode) in the rare condition.

There were two significant main effects for N100: effect of condition ($F(1,13) = 8.8$, $p = 0.01$); and electrode ($F(2,26) = 6.22$, $p = 0.006$) (Table 6) and a significant interaction of condition, electrode, and diagnosis: ($F(2,26) = 6.02$, $p = 0.007$). Group contrasts indicated that normals' N100 generally showed larger magnitude than schizophrenics in both the rare and frequent conditions. This effect was largest at Pz and Cz electrodes in the frequent condition, as reflected in the three-way interaction.

The P200 data, on the other hand, showed three significant main effects: diagnosis ($F(1,13) = 11.48$, $p = 0.005$); condition ($F(1,13) = 4.85$, $p < 0.05$); and

electrode ($F(2,26) = 11.26$, $p = 0.001$) and no interactions (Table 7). These results reflect the significant differences between normals and schizophrenics in the rare and frequent conditions at all electrode sites. When compared to normals, schizophrenics showed significantly lower P200 amplitudes at all electrodes in both conditions.

ANOVA analyses were also computed on the mean latencies of P300 (Table 16), P200 (Table 15), and N100 (Table 14). Results showed no main effects and no significant interactions for P300 or P200. However, there was a significant three-way interaction of condition, electrode, and diagnosis ($F(2,26) = 3.72$, $p < 0.04$) for N100. Group contrasts showed that the N100 of schizophrenics occurred significantly later than normals at Pz, Cz, and Fz in the rare condition, an effect reflected by the three way interaction.

Discussion

P300 differences have typically been reported in auditory oddball paradigms in schizophrenic and normal subjects. However, few studies have used visual-semantic oddball stimuli to test for P300 amplitude differences between normals and schizophrenics. Thus, the main hypothesis tested in this study was that schizophrenic and normal subjects would show P300 differences in the rare condition. Results supported the first hypothesis. Schizophrenic subjects' P300 to visual-semantic, oddball stimuli was significantly lower than normals in the rare condition. Moreover, while schizophrenics showed significantly reduced amplitude at all electrode sites in the rare condition, the reduction was largest at the Cz electrode.

Effects of visual and auditory oddball tasks on earlier components (such as N100 and P200) have also demonstrated reduced amplitude in schizophrenics compared to normals (Levit, Sutton, and Zubin, 1973; Baribeau-Braun et al., 1983; Barrett,

McCallum, and Pocock, 1986; Mukundan, 1986). Based on these data, the second hypothesis was that there would be N100 and P200 differences between schizophrenics and normals. Results supported the second hypothesis. However, although schizophrenic subjects showed significant reductions in N100 at Cz and Fz in the frequent condition, they showed no significant amplitude differences in N100 in the rare condition. In contrast, schizophrenic subjects showed significantly reduced P200 amplitudes in both the rare and frequent conditions at all electrodes when compared to normals. Finally, schizophrenic and normal subjects did not show latency differences for either P200 or P300. Schizophrenic subjects, however, did show a significantly later N100 at all electrodes in the rare condition, results that are consistent with other studies (e.g., Sandman, Gerner, O'Halloran, and Isenhart, 1987).

The primary finding in this study suggests that P300 amplitude differences between schizophrenic subjects and normals can be replicated with discrimination tasks that engage visual-semantic stimuli, i.e., counting the number of infrequently appearing male names in a succession of female names.

Theories of attentional selectivity have been described as including the following levels of processing: early, sensory filtering; stimulus encoding; stimulus storage; and response set (Treisman, 1964; Broadbent, 1970; Baribeau-Braun et al., 1983). ERP researchers have investigated these stages in attempts to find evoked brain response correlates of sensory, attentional, and perceptual deficits in schizophrenic subjects. For example, because N100, P200 and P300 are thought to reflect stimulus encoding, stimulus storage, and response set, respectively, reductions in any of these ERP components would suggest deficits in the stages these peaks are purported to index. Based on these data, the results of the present study suggest that, in the rare condition, schizophrenic subjects showed later deficits, at the stimulus storage (P200) and response set (P300) stages, rather than at the encoding stage (N100). These data are generally consistent with other research (Baribeau-Braun et. al, 1983).

Several caveats need to be addressed in the interpretation of the results of this study. First, while statistical analyses did show significant results in the expected directions, in the light of a small sample size and limited number of trials, caution needs to be exercised in the interpretation of these data. Therefore, although the positive results of this study warrant additional investigation, no definite conclusions can be reached. Second, that the schizophrenic subjects were thought-disordered compared to normals, who were not thought-disordered, might have contributed to the amplitude differences between the two groups. Preliminary analysis of several schizophrenic subjects who did not show thought disorder, and thus were not included in the present analysis, showed no P300 differences compared to the normal group. These data suggest that the P300 might prove to be a state marker of cognitive dysfunction in schizophrenia, a finding that is supported by other research (Pfefferbaum, Roth, and Koppel, 1979; Begleiter and Porjesz, 1986; Duncan, Perlstein, and Morihisa, 1987). Thus, the hypothesis that P300 amplitude differences might reflect the presence of thought disorder in schizophrenia is an important issue for future study. And third, future studies need to resolve the issue of whether subjects were discriminating stimuli on the basis of physical features (the first letter of each name) or were semantically categorizing the male versus female names. In future work, if an additional condition, which included variable names, was added to the existing series, it could be stated with more confidence that subjects were categorizing stimuli on the basis of semantic meaning.

Implications for future research based on data from the present study suggest several directions. For example, it would be important to determine whether a link exists between brain dysfunction (P300 reduction) and cognitive dysfunction (thought disorder) in schizophrenia. And if so, whether P300 reduction relates to the presence of thought disorder in other groups, e.g., depressives, or if thought disorder and reduced P300 are unique to schizophrenia. Moreover, the relationship between the earlier and

later components, N100 compared to P200 and P300, could also be studied more directly. The N100 occurred significantly later for schizophrenic subjects in the rare condition, but not in the frequent condition. Further, schizophrenic subjects showed no P300 reduction in the rare condition. These data suggest that the schizophrenics encode the stimulus features, but that it takes them longer. Delay in encoding for schizophrenic subjects might impact on subsequent stages of stimulus storage and response set, which is suggested by the reductions in P200 and P300. Thus, whether it is a delay in stimulus encoding that results in subsequent deficits in stimulus storage and response set in schizophrenia is another hypothesis that would important to pursue.

In conclusion, the results of the present study suggest that the P300 amplitude differences are related to the cognitive dysfunction which was present in the schizophrenic subjects. Whether the P300 could function as a marker of thought disorder in schizophrenia, and whether it would reflect thought disorder in disorders other than schizophrenia, are among some of the important issues for future research.

TABLE 1.

MEANS AND STANDARD DEVIATIONS: THOUGHT DISORDER INDICES, INTELLIGENT QUOTIENTS, AND AGES OF NORMAL AND SCHIZOPHRENIC SUBJECTS

		TDI[a]		IQ[b]		AGE	
Diagnosis	n	x	s	x	s	x	s
Normal	9	1.22	.44	3.00	.71	29.56	9.29
Schizophrenic	6	3.50	.84	2.33	1.21	27.00	5.87

Note: x = mean. s = standard deviation.

[a]1 = absent, 2 = mild, 3 = definite, 4 = severe, 5 = very severe.
[b]1 = low average, 2 = average, 3 = high average, 4 = superior, 5 = very superior.

TABLE 2.

MEANS AND STANDARD DEVIATIONS: PEAK AMPLITUDES FOR NORMAL SUBJECTS IN RARE CONDITION

	N100		P200		P300	
Electrode	x	s	x	s	x	s
Pz	-15.40	4.41	15.21	5.24	18.06	5.99
Cz	-17.76	4.26	20.08	4.92	22.36	6.40
Fz	-12.76	5.03	18.80	5.15	19.99	6.58

Note: n = 9. x = mean amplitude in μV. s = standard deviation.

TABLE 3.

MEANS AND STANDARD DEVIATIONS: PEAK AMPLITUDES FOR SCHIZOPHRENIC SUBJECTS IN RARE CONDITION

	N100		P200		P300	
Electrode	x	s	x	s	x	s
Pz	-11.86	3.82	7.77	4.83	11.68	3.13
Cz	-15.28	8.34	11.91	6.49	13.81	4.83
Fz	-10.03	7.79	12.04	7.17	12.97	4.20

Note: n = 6. x = mean amplitude in μV. s = standard deviation.

TABLE 4.

MEANS AND STANDARD DEVIATIONS: PEAK AMPLITUDES FOR NORMAL SUBJECTS IN FREQUENT CONDITION

	N100		P200		P300	
Electrode	x	s	x	s	x	s
Pz	-13.46	4.50	12.90	3.85	13.37	5.22
Cz	-14.73	4.25	16.36	3.60	15.38	6.79
Fz	-9.30	4.12	15.01	4.16	12.54	4.65

Note: n = 9. x = mean amplitude in μV. s = standard deviation.

TABLE 5.

MEANS AND STANDARD DEVIATIONS: PEAK AMPLITUDES FOR SCHIZOPHRENIC SUBJECTS IN FREQUENT CONDITION

	N100		P200		P300	
Electrode	x	s	x	s	x	s
Pz	-7.06	2.70	6.96	2.16	9.17	1.06
Cz	-10.55	3.02	10.05	3.63	10.57	3.98
Fz	-8.96	5.95	10.31	4.32	9.00	3.32

Note: n = 6. x = mean amplitude in μV. s = standard deviation.

TABLE 6.

ANOVA SUMMARY: N100 AMPLITUDES FOR RARE AND FREQUENT CONDITIONS

	SS	df	MS	F	p
Main Effects					
Diagnosis	224.55	1	224.54	3.00	NS
Condition	224.91	1	224.91	8.80	.01
Electrode	284.13	2	142.06	6.22	.006
Interactions					
Diag. x Cond.	3.69	1	3.69	.14	NS
Diag. x Elec.	42.59	2	21.29	.93	NS
Cond. x Elec.	11.58	2	5.78	2.44	NS
Diag. x Elec. x Cond.	28.61	2	14.30	6.02	.007

Note: n = 15.

TABLE 7.

ANOVA SUMMARY: P200 AMPLITUDES FOR RARE AND FREQUENT CONDITIONS

	SS	df	MS	F	p
Main Effects					
Diagnosis	927.33	1	927.33	11.48	.005
Condition	121.63	1	121.63	4.85	.046
Electrode	254.86	2	127.43	11.26	.001
Interactions					
Diag. x Cond.	17.63	1	17.63	.70	NS
Diag. x Elec.	8.47	2	8.47	.37	NS
Cond. x Elec.	7.07	2	7.07	1.05	NS
Diag. x Elec. x Cond.	.30	2	.14	.04	NS

Note: n = 15.

TABLE 8.

ANOVA SUMMARY: P300 AMPLITUDES FOR RARE AND FREQUENT CONDITIONS

	SS	df	MS	F	p
Main Effects					
Diagnosis	713.92	1	713.92	5.97	.029
Condition	499.68	1	499.68	52.00	.0001
Electrode	96.05	2	48.02	3.39	.049
Interactions					
Diag. x Cond.	53.11	1	53.11	5.53	.035
Diag. x Elec.	9.30	2	4.64	.33	NS
Cond. x Elec.	17.02	2	8.51	3.19	NS
Diag. x Elec. x Cond.	2.51	2	1.25	.47	NS

Note: n = 15.

TABLE 9.

MEANS OF P300 AMPLITUDES COLLAPSED ACROSS ELECTRODES: NORMAL AND SCHIZOPHRENIC SUBJECTS IN EACH CONDITION

Condition	RARE	FREQUENT
Normals	20.14	13.76
Schizophrenics	12.82	9.58

Note: Mean amplitude measured in μV.

(13 df, p = .01)

TABLE 10.

MEANS AND STANDARD DEVIATIONS: LATENCIES FOR NORMAL SUBJECTS IN RARE CONDITION

	N100		P200		P300	
Electrode	x	s	x	s	x	s
Pz	137.11	9.80	209.11	13.93	367.33	41.57
Cz	131.11	10.73	203.78	14.29	362.67	26.91
Fz	124.89	20.10	211.33	21.68	358.00	33.32

Note: n = 9. x = mean amplitude in μV. s = standard deviation.

TABLE 11.

MEANS AND STANDARD DEVIATIONS: LATENCIES FOR SCHIZOPHRENIC SUBJECTS IN RARE CONDITION

	N100		P200		P300	
Electrode	x	s	x	s	x	s
Pz	151.33	13.31	215.00	14.28	355.00	33.82
Cz	147.00	16.09	215.00	13.25	347.33	31.18
Fz	146.67	18.79	207.67	20.99	348.00	29.29

Note: n = 6. x = mean amplitude in μV. s = standard deviation.

TABLE 12.

MEANS AND STANDARD DEVIATIONS: LATENCIES FOR NORMAL SUBJECTS IN FREQUENT CONDITION

	N100		P200		P300	
Electrode	x	s	x	s	x	s
Pz	131.33	19.44	209.11	9.75	355.11	15.43
Cz	129.56	15.89	207.56	9.58	355.33	14.78
Fz	129.11	27.00	208.22	17.36	358.00	13.64

Note: n = 9. x = mean amplitude in μV. s = standard deviation.

TABLE 13.

MEANS AND STANDARD DEVIATIONS: LATENCIES FOR SCHIZOPHRENIC SUBJECTS IN FREQUENT CONDITION

	N100		P200		P300	
Electrode	x	s	x	s	x	s
Pz	145.33	122.40	216.33	20.45	348.33	29.35
Cz	136.33	16.17	212.00	8.39	349.00	27.68
Fz	131.67	19.24	210.00	12.96	350.00	25.64

Note: n = 6. x = mean amplitude in μV. s = standard deviation.

TABLE 14.

ANOVA SUMMARY: N100 LATENCIES FOR RARE AND FREQUENT CONDITIONS

	SS	df	MS	F	p
Main Effects					
Diagnosis	3395.03	1	3395.03	3.04	NS
Condition	725.70	1	725.70	2.84	NS
Electrode	993.70	2	496.85	2.76	NS
Interactions					
Diag. x Cond.	489.25	1	489.25	1.91	NS
Diag. x Elec.	29.26	2	14.62	.08	NS
Cond. x Elec.	1.97	2	.98	.02	NS
Diag. x Elec. x Cond.	325.35	2	162.67	3.72	.038

Note: n = 15.

TABLE 15.

ANOVA SUMMARY: P200 LATENCIES FOR RARE AND FREQUENT CONDITIONS

	SS	df	MS	F	p
Main Effects					
Diagnosis	433.81	1	433.81	.54	NS
Condition	1.06	1	1.06	.00	NS
Electrode	167.57	2	83.78	1.01	NS
Interactions					
Diag. x Cond.	0.00	1	0.00	0.00	NS
Diag. x Elec.	323.84	2	161.91	1.95	NS
Cond. x Elec.	4.31	2	2.15	.02	NS
Diag. x Elec. x Cond.	139.24	2	69.62	.78	NS

Note: n = 15.

TABLE 16.

ANOVA SUMMARY: P300 LATENCIES FOR RARE AND FREQUENT CONDITIONS

	SS	df	MS	F	p
Main Effects					
Diagnosis	2072.90	1	2072.90	.64	NS
Condition	305.25	1	305.25	.29	NS
Electrode	161.88	2	80.94	1.77	NS
Interactions					
Diag. x Cond.	164.45	1	164.45	.16	NS
Diag. x Elec.	12.73	2	6.36	.14	NS
Cond. x Elec.	401.97	2	200.98	1.68	NS
Diag. x Elec. x Cond.	44.10	2	22.05	.18	NS

Note: n = 15.

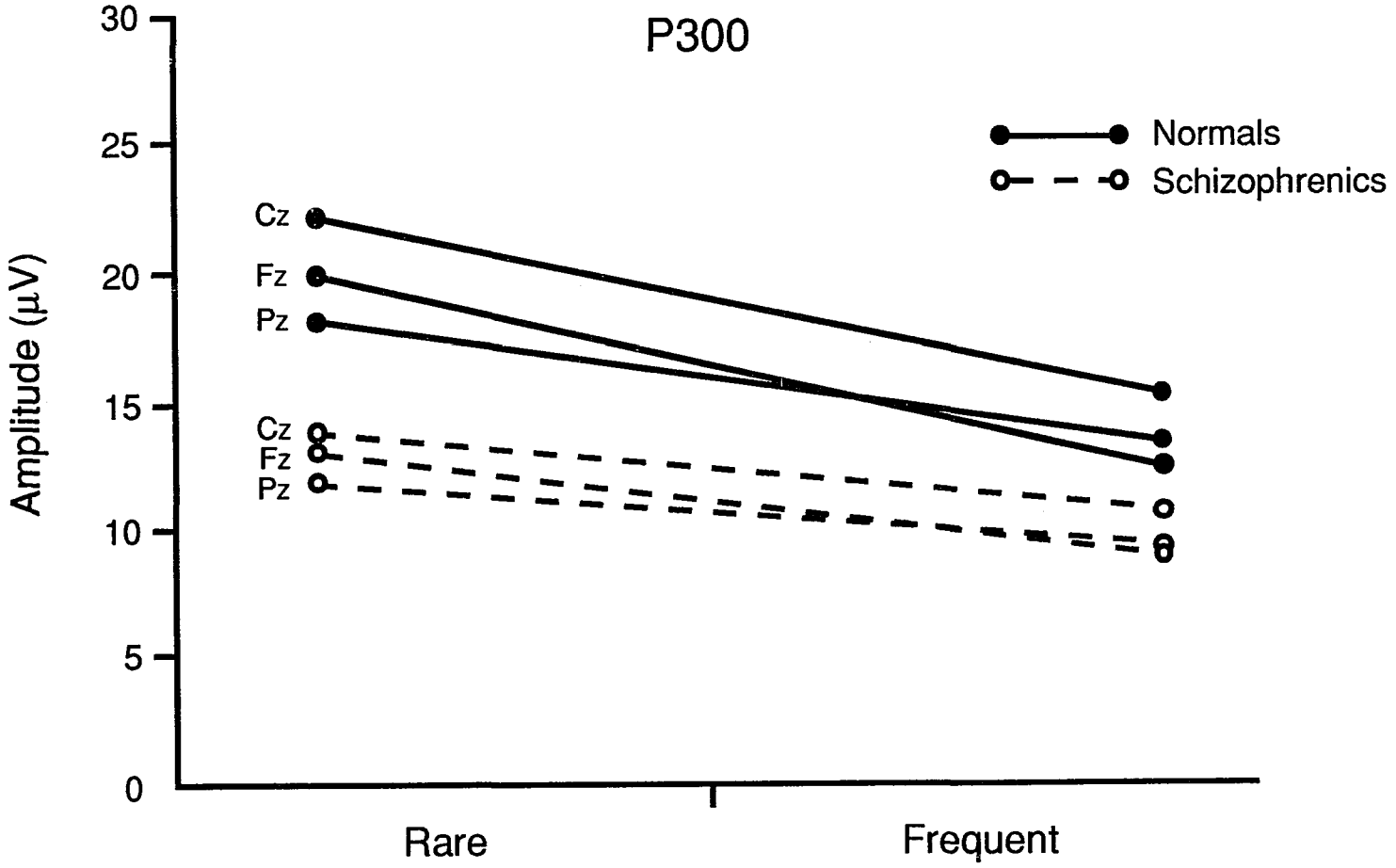

Figure 1: Comparison of Normals and Schizophrenics in Rare and Frequent Conditions

CHAPTER III

EVENT-RELATED POTENTIAL AND BEHAVIORAL CORRELATES OF COGNITIVE DYSFUNCTION IN SCHIZOPHRENIA

Introduction

Electrophysiology studies using the electroencephalogram (EEG) and evoked potentials (EPs) have made important contributions to schizophrenia research (Roth and Cannon, 1972; Levit, Sutton and Zubin, 1973; Rappaport, 1975; Verleger and Cohen, 1978; Lifshitz, 1979; Roth, Horvath, Pfefferbaum, Berger, and Koppel, 1980; Baribeau-Braun, Picton, and Gosselin, 1983; Brecher and Begleiter, 1983; Morihisa, Duffy and Wyatt, 1983; Morstyn, Duffy and McCarley, 1983; Shagass, 1983; Duncan-Johnson, Roth and Koppel, 1984; Levin, 1984; Pritchard, 1986; Holzman, 1987; Duncan, Perlstein and Morihisa, 1987; Faux, Torello, McCarley, Shenton and Duffy, 1987; Faux, Torello, McCarley, Shenton and Duffy, 1988). The focus of these studies has generally been on the relationship between changes in electrical brain activity and attentional deficits in schizophrenia rather than on cognitive dysfunction. In normal subjects, on the other hand, there is an extensive literature on the correspondence between changes in scalp-recorded electrical activity and cognitive events. In

response to the lack of data on ERPs and cognitive dysfunction in schizophrenia, researchers have suggested several directions in electrophysiology research in schizophrenia: 1) that cognitive psychophysiological paradigms be developed and used to study cognitive deficits in schizophrenics (Fenton, 1980); and 2) that such paradigms replace the clinical paradigms used in electrophysiological studies of attention in schizophrenia (Donchin and Bashore, 1980; Begleiter and Porjesz, 1986; Pritchard, 1986). In short, rather than using brain recordings as an aid to the clinical diagnosis of schizophrenia, the development of a cognitive psychophysiological paradigm, using semantic stimuli, would be a step in the direction of using ERPs to detect cognitive dysfunction in schizophrenia. In addition, such ERPs could also be used as early indicators of cognitive deficits before psychotic symptoms develop.

Cognitive dysfunction, which is also referred to as thought disorder, has traditionally been considered one of the diagnostic hallmarks of schizophrenia. The earliest efforts to understand the characteristics of schizophrenia focused on thought disturbances. For example, Bleuler (1911) described schizophrenic thought disorder in terms of breaks in the logical flow of thought, a view that came to be known as "looseness of association." Later views of cognitive dysfunction in schizophrenia used several different perspectives. One approach, the abstract-concrete view, conceptualized thought disorder as an impairment in abstract thinking that resulted in a reliance on concrete thinking (Benjamin, 1944; Goldstein, 1944; Vygotsky, 1962; Arieti, 1974; Harrow, Adler and Hanf, 1974; Harrow and Quinlan, 1985). The reliance on concrete thinking in schizophrenia has been described by clinicians as childlike, imagistic and unrestrained. Theoretically, the abstract-concrete view of thought disorder was thought to be a "regression" from an abstract level of thinking to a concrete one. The regression hypothesis (Chapman and Chapman, 1973) was based on theories of cognitive development in children (Bolles and Goldstein, 1938; Vygotsky, 1962;) and on psychoanalytic theories of secondary and primary process thinking (Freud, 1900; Kris,

1952; Fenichel, 1945; Rapaport, 1960a). Goldstein (1944) was one of the several theorists (Benjamin, 1944; Vygotsky, 1962; Arieti, 1974) who considered concreteness to be the essence of the schizophrenic disorder, and thought that the regression to concreteness was a protective mechanism against anxiety that was rooted in earlier developmental stages. Vygotsky, on the other hand, considered the schizophrenic inability to think abstractly as the core of the disorder and described thought disorder as a "regression to a more primitive level called thinking in concrete complexes" (Vygotsky, 1962). Although research has shown that children (Olver and Hornsby, 1966; Markman and Callanan, 1984) and adults (Freud, 1933; Brenner, 1957; Holt and Havel, 1965; Bellak, 1966; Blatt and Ritzler, 1974; Quinlan and Harrow, 1974; Johnson and Quinlan, 1980) will often shift to "easier," concrete levels of thought when anxiety or task demands escalate beyond tolerance or ability levels, the difference in this shift between children and adults and schizophrenics, is the schizophrenics' greater reliance on concrete thinking. In other words, if given a choice between abstract and concrete thought tasks, schizophrenics will use concrete thinking more frequently than normals. Within the theoretical framework and clinical descriptions of schizophrenia, the abstract-concrete view came to occupy a prominent place (Benjamin, 1944; Goldstein, 1944; Gorham, 1956; Chapman, 1960; Vygotsky, 1962; Cancro, 1969; Chapman and Chapman, 1973; Arieti, 1974; Harrow, Adler, Hanf, 1974; Pishkin, Lovallo, Lenk and Bourne, 1977; Pishkin and Bourne, 1981; Harrow and Quinlan, 1985; Liddle, 1987).

While the abstract-concrete view proved useful as a clinical and descriptive construct, it has been criticized for not withstanding empirical scrutiny (Carson, 1962; Pavy, 1968; Reed, 1968; Cancro, 1969; Shimkunas, 1970; Chapman and Chapman, 1973; Harrow, Adler and Hanf, 1974; Harrow and Quinlan, 1985). One of the difficulties that contributed to the compromised results in this research is the discrepancy in the definition of abstract and concrete thinking (Harrow and Quinlan,1985). Since the conceptual underpinning upon which any model of thought disorder is based is, how

"thinking" is defined, this difficulty is particularly salient in the context of dysfunctional thinking in schizophrenia research. Given the numerous processes that the term "thinking" subsumes (attention, perception, intention, judgment, planning, categorization, memory, learning, etc.), "normal thought" has traditionally eluded definition. Therefore, it is not surprising that definitions of thought disorder from any perspective have created difficulties in schizophrenia research, particularly in the operational definitions of abstract-concrete thinking.

Several measures have been developed that purport to define and assess abstract and concrete thinking in schizophrenia; two such tests that are frequently used are the Proverbs Test (Benjamin, 1944; Gorham, 1956) and the Object Sort Test (Goldstein and Scheerer, 1941). The Proverbs test is a verbal test, which measures abstract and concrete thinking by asking subjects to interpret a number of proverbs; a response is scored as concrete if key words from a proverb are used in the subject's response. (For example, a concrete interpretation of the proverb, "Shallow brooks are noisy," would be "The water hits the rocks and makes noises" [Harrow and Quinlan, 1985]). The Object Sort Test, on the other hand, is a performance test, which measures abstract and concrete thinking by asking subjects to sort objects into groups; it is scored on the basis of the subject's ability to group objects into concrete or abstract categories. (The subject is confronted by an array of objects [e.g., ball, hammer, screwdriver] and is required to group objects together based on the instruction, "Why do these objects go together?" If, after grouping a hammer and screwdriver together, this group is labeled "tools" by a subject, this response would be scored abstract on the basis that "tools" is a superordinate category.)

Comparison of the Proverbs Test to the Object Sort Test reveals a discrepancy; to give an abstract interpretation of a proverb verbally is a different cognitive task than to sort objects into abstract categories physically. Not only are different facets of concrete-abstract thought tapped by the Object Sort and Proverbs Tests (performance versus verbal) (Harrow and Quinlan, 1985), but the stimuli in each test are presented to subjects

in different modalities (visual versus auditory). Consequently, measurement of abstract-concrete thought under these different circumstances may not be equivalent. In sum, difficulties in the theoretical and operational definitions of the abstract-concrete view of thought disorder may be factors that contributed to the results which have been criticized in the literature (Carson, 1962; Cancro, 1969; Pavy, 1968; Reed, 1968; Shimkunas, 1970; Chapman and Chapman, 1973; Harrow, Adler and Hanf, 1974; Harrow and Quinlan, 1985).

Converging findings from experimental animal, developmental, and cognitive studies suggest that there is a level of concrete processing that is shared by animals and by children and human adults. Data show that experimental animals have a discriminating ability based on feature perception; they are able to discriminate and classify based on concrete features and to generalize from these differences to form rules of classification (Davenport and Rogers, 1971; Davenport, Rogers and Russell, 1975). Pigeons, for example, have been trained not only to discriminate between pictures with and without trees (Herrnstein, 1979), but also to classify diverse pictures of cats, flowers and chairs and to generalize from the learned categories to new instances (Bhatt, Wasserman, Reynolds and Knauss, 1988). The object discrimination that has been described in pigeons and is based on concrete feature perception, is similar to a developmental level of cognition in children (excluding language) that researchers have termed "ikonic" (Olver and Hornsby, 1966). The ikonic stage of cognition, which precedes development of symbolic thought stages, has been described as thought "depicted in images" (Olver and Hornsby, 1966). As with the experimental animal research cited above, this stage of processing is based on discrimination by concrete feature similarity. (An example of feature discrimination at an ikonic level would be to group a number of objects together because they are all yellow).

Research in cognitive psychology has identified a concrete level of categorization called "basic-level" (Rosch, Mervis, Gray, Johnson and Boyes-Broem, 1976) that is

congruent with both the perceptual discrimination described by animal researchers and the ikonic stage described by developmental researchers. Basic-level categorization, which is the easiest, fastest and most frequently used of all category levels, is also the basic-level of lexical representation in American Sign Language (ASL) (Newport and Bellugi, 1978). Moreover, maximum information with the least cognitive effort is conveyed at the basic-level of categorization (Rosch, 1976). Finally, basic-level has been identified as playing a central role in much of cognition (Markman and Callanan, 1984). Thus, the level of concrete processing that seems common to experimental animals, children, adult and deaf humans seems best described by "basic-level" research (see below for more discussion). Furthermore, as a construct of concrete thought, basic-level categorization could be particularly useful in schizophrenia research.

Since the introduction of Goldstein and Scheerer's Object Sort Test (1941), categorization has been used by clinicians to study cognitive dysfunction in schizophrenia. Similarly, categorization has been used to study thinking in normal subjects. As a construct of cognition, categorization is viewed as the capacity to discriminate among things that are different and to classify objects into equivalent groups (Bruner, Goodnow and Austin, 1956). Recent research has broadened the study of categorization by distinguishing classification at the basic-level of natural categories as well as at the superordinate level. Superordinate and basic-levels of categorization, however, are based on different principles of organization. The organizing principle for basic-level categorization is feature similarity (based on perceptual rules). In contrast, symbolic similarity (based on universal rules) is the organizing principle for superordinate categorization; superordinate categorization relies on an understanding of the asymmetric relations between concepts (Markman and Callanan, 1984). For example, "furniture" is a superordinate category that is made up of different objects which have asymmetric features, functions and shapes. Chairs and tables look different and have different functions, yet they belong to the same category of furniture. Basic-

level categorization, on the other hand, is based on local, perceptual rules of matching (Olver and Hornsby, 1966). Objects in basic-level categories are symmetrical; they have features and functions that match. For example, although the basic-level category 'chair' is made of different ***types*** of chairs, all chairs in the category of chairs have the same basic features and function. Moreover, response time has been shown to be shortest at basic-level (e.g., car), longest at superordinate level (e.g., vehicle) and mid-way between superordinate and basic-levels at a subordinate level (e.g., sedan) (Murphy and Brownell, 1985). In the context of cognitive dysfunction in schizophrenia, the relevance of superordinate and basic-level categorization research is particularly important because it provides a way to define thinking more rigorously; concrete and abstract thought can be operationally defined as basic-level and superordinate categorization, respectively.

Finally, the substantial literature on the relationship between cognition and changes in event-related brain potentials in normal subjects has expanded considerably since the classic work on P300 (Sutton, Braren, Zubin and John, 1965), which ushered in the era of cognitive psychophysiology. As a result, the use of brain potentials as indices of cognition has become more sophisticated and more widely applied. ERPs are components of brain electrical activity whose latencies are time-locked to stimuli that require cognitive effort. The P300, for example, is a positive-going deflection of an ERP waveform that occurs about 300 msec post-stimulus. A prominent P300 is typically elicited in oddball paradigms. In oddball paradigms, stimuli from all modalities differ in frequency of occurrence in the context of subjective probability (cf. Chapter II). Other ERP components include the N100 and the P200. The N100 is a negative deflection of an ERP waveform that peaks between 90 and 150 msec post-stimulus onset; this component is thought to index the encoding of stimulus features. The P200, on the other hand, is a positive potential shift which generally occurs between 150 and 230 msec post-stimulus onset. The P200 is thought to index selective attention to the stimulus, i.e., stimulus recognition and storage.

To recapitulate: the lack of data on the correspondence between ERPs and cognitive dysfunction in schizophrenia has urged researchers to suggest that cognitive psychophysiological paradigms be developed. These paradigms would replace the clinical ones that have been used in most electrophysiology studies of schizophrenia (Donchin and Bashore, 1980; Fenton, 1980; Begleiter and Porjesz, 1986; Pritchard, 1986). Used in this way, ERPs could not only detect cognitive dysfunction in schizophrenia, but could also detect early cognitive deficits before psychotic symptoms developed.

In light of converging research from psychology and biology in clinical, cognitive and electrophysiological domains, this study is based on three conceptual underpinnings: 1) an abstract-concrete view of thought disorder; 2) categorization research; and 3) event-related brain potentials. In addition, given that semantic categorization paradigms have frequently been used in the ERP research in normal subjects (Kutas and Donchin, 1978; Sanquist, Rohrbaugh, Syndulko and Lindsley, 1980; Polich, 1985; Boddy, 1981; 1986), the present study used an S1-S2 semantic categorization paradigm to determine whether there were ERP and behavioral correlates of cognitive dysfunction in schizophrenia based on the abstract and concrete view of thought disorder. Superordinate categorization and basic-level categorization were used as operational definitions of abstract and concrete thinking. That is, superordinate categorization responses demonstrated abstract thinking and basic-level categorization responses demonstrated concrete thinking. There were two hypotheses: 1) when abstract thinking was required (superordinate categorization responses), it was predicted that schizophrenics would use concrete thinking (basic-level categorization responses) more often than normals; and 2) that schizophrenic and normal subjects' ERPs (N100, P200 and P300) would reflect amplitude differences similar to those reported in other evoked-response studies.

Methods

General Criteria for Subject Selection

Data were collected on ten subjects, five normal subjects (4 females and 1 male) and five schizophrenic subjects (3 females and 2 males). Normal subjects ranged in age from 24-38 (mean age = 29.8); schizophrenic subjects ranged in age from 19-35 (mean age = 27.6). All subjects were right-handed (The Edinburgh Inventory, Oldfield, 1971) and none had a history of head injury, alcohol abuse, or neurological disorder. Vision tested 20/20 (corrected as indicated) (Rosenbaum Pocket Vision Screener) for all subjects whose results were included in the analysis. The WAIS-R Vocabulary Test (Weschler, 1981) was used as a measure of I.Q. Intelligence quotient measures for normal subjects ranged from average to superior (mean = high average); I.Q. measures for schizophrenic subjects ranged from low average to superior (mean = average). The State-Trait Anxiety Inventory (STAI), which was used to control for level of anxiety, was administered before and after laboratory procedures. STAI results showed that subjects were not anxious (Spielberger, 1983).

Diagnostic Selection Criteria

The Schedule for Affective Disorders and Schizophrenia (SADS) (Endicott and Spitzer, 1978) was used to make a Research Diagnostic Criteria (RDC) (Spitzer, Endicott and Robins, 1977) diagnosis of schizophrenia for the schizophrenic group. Three schizophrenic subjects were inpatients (who were discharged shortly after testing) and two were outpatients (who had been recently discharged). The Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962) was used to assess symptom level. The BPRS is a widely used instrument developed to provide an assessment of symptom severity and frequency. All schizophrenic subjects whose data were included in the final analysis scored <35 on the BPRS. Two BPRS assessments were done within several days of each

other: one by the experimenter (a clinical psychologist) on the day of electrophysiological testing, the other by a research assistant (trained by experimenter) on the day of cognitive tests administration. Interrater reliability for BPRS was .94 (Intraclass correlation coefficient [Winer, 1971]).

Normal subjects, who were recruited from an existing pool, had no history of psychiatric hospitalization themselves or among their first-degree relatives. I.Q. for normals was measured with the WAIS-R Vocabulary subtest (Wechsler, 1981) and normal functioning had been assessed with the Minnesota Multiphasic Personality Inventory (MMPI) (no elevation above 70 on any subscore) or with the Schedule for Affective Disorders (SADS) (no history of mental disorder). In addition, as with the schizophrenic group, two BPRS assessments of normals were done within several days of each other, one by the experimenter on the day of electrophysiological testing, the other by a research assistant on the day that the cognitive tests were administered (see below). Interrater reliability for BPRS was .94 (Intraclass correlation coefficient [Winer, 1971]).

Cognitive Measures: Thought Disorder and I.Q. Assessments

All normal and schizophrenic subjects who were included in the study had been cognitively assessed to determine whether there was evidence of cognitive dysfunction (defined as thought disorder in this study). Cognitive function versus dysfunction was measured on Bizarre/Idiosyncratic Thinking (B-I) dimensions (Harrow and Quinlan, 1985; Harrow and Marengo, 1986). Bizarre/Idiosyncratic Thinking is a construct that is purported to measure thought disorder on several dimensions, some of which include linguistic form and structure and content of the statement (cf. Harrow and Quinlan, 1985). The following measures were used to assess thought disorder on B/I dimensions: 1) the Comprehension subtest on the Weschler Adult Intelligence Scale, Revised (WAIS-R) (Weschler, 1981); the Benjamin Proverbs Test (Benjamin, 1944); and the Object Sort Test (Goldstein and Sheerer, 1941). All tests were separately scored by two raters

(experimenter and research assistant). Each subject's B-I score was compared to Harrow's Thought Disorder rating scale and given a Thought Disorder score. The scores on this scale ranged from 1 to 5 with the following divisions: **1-2** = no thought disorder; **3** = definite thought disorder; and **4-5** = severe thought disorder. Normals who scored >3, which indicated definite thought disorder (1 subject), were not included in the study. Similarly, schizophrenics who scored <3, which indicated no thought disorder (2 subjects), were not included in the study. The Vocabulary subtest of the WAIS-R was used as an estimate of I.Q. level because this subtest has the highest correlation (.96) with I.Q. score of any WAIS-R verbal subtest (Weschler, 1981). Finally, interrater reliability (experimenter and research assistant) for scoring of all cognitive measures was .82 for B/I thought and .98 for Vocabulary (Intraclass correlation coefficient [Winer, 1971]) (Means and standard deviations for B/I scores, I.Q. scores and ages of normal and schizophrenic subjects are presented in Table 1.)

Medication and Other Considerations

Some studies suggest that medicated and unmedicated schizophrenics show similar levels of thought disorder in the early acute phase of an episode (Harrow, Grossman, Silverstein and Meltzer, 1982). Although the initial effects of medication can reduce the acute symptomatology of schizophrenia, some data suggest that improvement in thinking from the effects of medication, e.g., phenothiazines, can take 1-1 1/2 weeks or longer (Harrow and Quinlan, 1985). Because subject participation in this study included three phases (diagnostic assessment, cognitive assessments and electrophysiological procedures), patient subjects needed to be relatively symptom-free in order to complete all phases of the study. Thus, all schizophrenic subjects included in the analysis were not in an acute episode, were on psychotropic medication, had an RDC diagnosis of schizophrenia (based on a SADS interview) and had scores of definite thought disorder on the B/I thinking scale (>3). Normals were not on medication, had an MMPI/SADS

assessment of normal functioning and had scores of no thought disorder on the B/I thinking scale (<3).

Histories and Miscellaneous Criteria

Medication and previous treatment histories and demographic information, were taken on all subjects. Confidentiality and protection of subjects' rights were taken into consideration. After consent forms were signed, only ID codes were used to identify subjects . All subjects were informed they could stop at any point of the procedure if they wished. All non-patients were compensated (inpatients were not compensated in accordance with hospital policy). Approval for participation of hospitalized subjects was obtained from the Human Use Committee at the University of Michigan Hospital. Patients were asked a number of questions in order to check for: 1) adverse reactions to medications and 2) new medications (or change in dosage). Finally, questions about special details were asked of patient subjects to determine whether any situation of note needed to be addressed during or after laboratory procedures. Subjects in both groups completed all diagnostic, cognitive and laboratory phases of the study.

Experimental Procedures

Subjects were seated in a dimly lit, sound attenuated room. They sat facing a projection screen (placed 63.5 cm. away from subjects) and performed visual, semantic S1-S2 categorization tasks. Subjects were told they would see two slides in rapid succession. On Slide 1 they would see one word (S1) that named a category (e.g., **Furniture**); on Slide 2 (S2) they would see three vertically-presented words that named objects that might or might not be members of the S1 category (e.g., **Chair**, **Chair**, **Table**). Subjects' task was to decide whether all the objects named on S2 belonged to the category named on S1. A response box was placed in front of subjects. The second, third and fourth fingers of the right hand were used to press buttons 1, 2 and 3, whereas

the left index finger was used to press the A button. If subjects decided that S2 object names belonged to the category named on S1, they were instructed to press **A** button (all belong). On the other hand, if they decided one object didn't belong, they were instructed to press the button that corresponded to the number of the word in the list. For example, if the first word on S2 didn't belong to the category named by S1, the response button marked **1** (corresponding to the first word) should be pressed (and so forth for the second and third words). Subjects were given practice trials until they reached an 80% level of accuracy (number of practice trials ranged from 10-30; means for practice trials: normals = 12; schizophrenics = 20.25).

S1 and S2 were each presented for 200 msec for normals with a 1000 msec interstimulus interval (ISI) between S1 and S2. Subjects were told to respond within the 1000 msec for the response to be recorded (epoch=2600 msec [including pre-stimulus time]). During pilot testing it became clear that schizophrenic subjects needed a longer stimulus presentation time in order to reach an accuracy level of 80%. The need to increase the time of stimulus presentation in order to reach a set criterion level of performance has been addressed as a specific deficit in schizophrenia (Chapman and Chapman, 1973). Thus, based on the pilot work, S1 and S2 were presented for 400 msec for schizophrenics with a 1000 msec ISI and 1200 msec to respond (epoch=3200 msec [including pre-stimulus time]).

S2 words in the regular superordinate condition were manipulated so that one of the four choices would be a slip to basic-level (concrete thinking). For example, if an **S1** word were **Furniture** (a superordinate category) and **S2** words were **Table, Table, Chair** (members of the furniture category), a superordinate level response (abstract thinking) would be to chose **A** (all belong). However, a basic-level response (concrete thinking) would be to chose **3** (**chair** does not belong). This choice would be considered a slip to concrete thinking because choosing chair as not belonging implies that chair

does not belong to the category of tables. Finally, if buttons **1** or **2** were chosen, these response were scored as errors, i.e., no categorization occurred.

The two categorization conditions, regular superordinate and regular basic-level, corresponded to abstract and concrete thinking, respectively. Two additional conditions were also included, an incongruous superordinate and a match concrete. The incongruous superordinate condition was included to be sure that subjects were reading the category words and not just responding randomly. (This condition was also included to test for categorization incongruity [cf. Chapter IV]). Finally, a match concrete condition (all basic-level) was included to insure that the "**A**" button (all belong choice) could be pressed a corresponding number of times equal to the number of times this button could be pressed in the superordinate condition.

Category words that were presented for S1 and S2 consisted of 64 high frequency nouns. (See Appendix A for category lists.) Stimuli were presented on slides projected onto a rear projection screen (Daylight Screens) using an Ectographic slide projector. A second Ectographic slide projector was used to project a fixation slide. (The fixation slide was continuously projected to minimize flash/blink responses when stimuli were presented.)

Subjects were instructed to focus on a dot that was in the middle of the fixation slide whenever a trial was to be initiated. Room luminance was maintained at 2.5 ft lamberts; fixation slide and stimulus slides were maintained at 2.5 and 3.5 ft. lamberts, respectively (measurements were made with UDT 40X Opto-Meter). Stimulus words, when presented, were centered on the fixation dot. All stimulus words were white upper and lower case letters on a blue background on 2" x 2" slides. Visual angle for words ranged from 1.7^0 for the shortest word to 3.4^0 for the longest word. Frequency of words (length ranged from 3 to 9 letters) averaged 43 per million (Francis and Kucera, 1967).

S1 and S2 were presented at approximately one pair/25 seconds. The length of time between stimuli included time to store trial to disk, monitor ongoing EEG, check on

the subject and attend to any difficulties. Thus, the presentation of 2 blocks of 64 stimulus pairs in random order required an average of 1 hour. The entire length of time to complete all laboratory procedures ranged from 2 to 3 hours.

Data Collection, Equipment and Analysis

EEG was recorded from three midline electrode locations: Fz, Cz and Pz (10-20 International System). All electrodes were referred to linked mastoids. Nicolet EEG Surface silver cup electrodes were used for the scalp recordings, for the ground (attached with collodion), which was placed mid-forehead and for electro-ocular recording activity (EOG). Eye movements were monitored by EOG electrodes placed above and below the left eye (attached with paste). Impedences were maintained <5 Kohm.

The Nicolet Pathfinder I Electrodiagnostic System was used to amplify, filter, average, store and plot the data. The Pathfinder I model has a 10 megabyte Winchester drive (to which individual trials were stored for off-line analysis) and 2 floppy drives.

The EEG and EOG were amplified with Pathfinder I SM200L amplifiers. Low band pass filter was set at .01 Hz (at -6 db roll-off, the time constant is about 7 seconds [Rockstroh, Elbert, Birbaumer and Lutzenberger, 1982]) and high band pass filter was set at 30 Hz. With an analysis sweep (time) set at 512 data points, data were sampled at 5.1 msec for normals (2600 msec epoch) and at 6.3 msec for schizophrenics (3200 msec epoch). Individual trials were stored to disk so that inspection of raw data could occur off-line. During ERP averaging, all trials were individually inspected prior to inclusion in the averaging. The decision to accept or reject was based on preset rejection criteria, e.g., trials with artifacts such as eye movement >65 uv were rejected.

The S1 and S2 sequence for each trial was manually triggered by the experimenter (who monitored the status of patient subjects) from a Grass Stimulator (S88). An automatic timing mechanism (Vincent Associates, 4 msec open/shut time) was attached to the shutter of the stimulus projector for preset timed presentations of S1 and

S2. Stimulus 1 and 2 onset and offset were measured by a photocell, which was placed at the edge of the shutter opening of the slide projector. Thus, the channels of data that were recorded for each trial included the Pz, Cz and Fz electrode channels, the EOG channel and the stimulus marker channel.

ERPs were averaged across all correct trials (after contaminated trials were excluded) for superordinate and basic-level conditions for normals and schizophrenics. In addition to the superordinate condition averages, two separate ERP averages were computed only for schizophrenics: for no-slip responses (correct superordinate categorization responses) and for slip responses (basic-level categorization responses when superordinate was indicated). ERP averages, therefore, were computed for the abstract and concrete conditions for normal and schizophrenic subjects and for slip and no-slip responses for schizophrenic subjects.

To accommodate the potential drift that often occurs using a longer time constant, all individual trials were baseline corrected before averaging. Within the designated time windows for N100 (70-175 msec), P200 (180-280 msec) and P300 (300-580 msec), the highest amplitudes for these peaks were computed with respect to a prestimulus baseline (mean value for the 160 msec prior to Stimulus-2 presentation)

Results

Means and standard deviations for all subjects' ERP amplitudes, thought disorder, age and I.Q. are presented in Tables 1-5. Univariate 2x2x3 factor repeated-measures analyses of variance using BMDP2V were performed on the amplitudes of N100 (Table 6), P200 (Table 7) and P300 (Table 8). Diagnostic group (normals and schizophrenics) was the between-subject factor, within-subject factors were electrode position (Pz, Cz and Fz) and experimental condition (abstract and concrete). A full ANOVA model was

used to assess the effect of each factor (diagnosis x condition x electrode) on component amplitudes.

For the slip and no-slip responses for schizophrenics, means and standard deviations are presented in Tables 9-10. Univariate 2x3 factor repeated-measures analyses of variance using BMDP2V were performed on the amplitudes of N100 (Table 11), P200 (Table 12) and P300 (Table 13). In this case, within-subject factors were type of responses (slip and no-slip) and electrode position (Pz, Cz and Fz). Full model ANOVAs were used to assess the effect of schizophrenics' slip and no-slip responses on the three components at each electrode site.

The repeated-measures ANOVAs, which were used to analyze all the amplitude data, incorporate The Greenhouse-Geisser correction for violations of sphericity of the variance-covariance matrix of repeated measures (Jennings, Cohen, Ruchkin, and Fridlund, 1987) when the number of repeated measures levels is greater than two (electrode position).

Analysis of the abstract and concrete conditions for the normal and schizophrenic groups showed two main effects for N100: a significant main effect for condition ($F(1,8) = 5.66$, $p = .04$) and a marginally significant one for diagnosis ($F(1,8) = 4.95$, $p = .056$). These results suggest that stimulus recognition in the abstract condition requires more activation (evident in the larger N100) than in the concrete condition (Figure 1). The main effect for diagnosis where schizophrenics showed more activation for N100 is in accord with other studies where schizophrenic subjects have shown greater activation in the early components than normal subjects (cf. Shagass, 1983).

In the analysis of the P200 and P300 data, there was only one significant main effect for electrode ($F(2,16) = 3.54$, $p = .05$) for P200. Although schizophrenic subjects' P200 and P300 were generally lower than normals, the lack of a condition main effect -- no difference between groups -- is probably due to the nature of the tasks. Since P300 is most influenced by oddball or missing stimuli task variables, increasing the complexity

of tasks increases its latency (Kutas, 1988) and reduces its amplitude. Because this paradigm was not specifically designed to elicit a robust P300 effect, the lack of a prominent P300 is therefore not surprising (cf. Chapter II for P300 visual-semantic paradigm).

The analyses of the N100, P200, and P300 components of schizophrenic subjects' slip and no-slip responses showed one main effect for N100, a significant main efffect for condition ($F(1,2) = 55.70$, $p = .02$). This finding reflected an N100 amplitude difference between the slip and no-slip responses, which averaged 5.1 uV greater for the slip responses than for no slips (Figure 2). This result shows that greater activation of N100 occurred when schizophrenics slipped to concrete thinking rather than when they chose correct no-slip responses.

Behavioral Results

Statistical analyses were performed on the following behavioral variables for schizophrenics and normals: 1) comparison of the differences in the number of slip and no-slip responses and 2) correct number of responses for the four categories.

A Likelihood Ratio X^2 Test (Williams, 1982) was used to test whether there was a significant difference in slip responses (to concrete thinking) between normals and schizophrenics (Table 14). This chi-square test is a likelihood ratio statistic that uses a binomial model, which is a conservative test that assumes over-dispersion (unequal variances) between the two diagnostic groups. Results, which were significant (X^2 (1df) $= 4.54$, $p = .019$), showed that schizophrenics responded concretely rather than abstractly significantly more often than normals.

Means and standard deviations for normal and schizophrenics' number of correct responses for the four types of categorization tasks: regular superordinate (abstract condition), basic-level (concrete condition), incongruous superordinate and match concrete (see Appendix for category lists) are presented in Table 15.

A 2x4 factor repeated-measures analysis of variance using BMDP2V was performed on correct responses (Table 16). Diagnostic group (normals and schizophrenics) was the between-subject factor; categories was the within-subject factor (regular superordinate [abstract], basic-level [concrete], incongruous superordinate and match concrete).

ANOVA results for correct responses showed two main effects; an effect of diagnosis that was almost significant ($F(1,8) = 4.65$, $p = .06$) and an effect of category that was highly significant ($F(3,24) = 10.22$, $p = .001$). Furthermore, there was a significant two-way interaction between diagnosis and category ($F(3,24) = 3.95$, $p = .02$). Schizophrenics made fewer correct response than normals in three out of the four categories: the regular superordinate, incongruous superordinate and match concrete categories. However, in the basic-level category (regular concrete), the number of correct choices for schizophrenics and normals was almost the same.

Discussion

The present study investigated the correspondence between changes in the brain's electrical activity and deficits in abstract thinking in schizophrenia, an area in which little research has been done. The conceptual underpinning of this study rests on the abstract-concrete view of thought disorder in schizophrenia, a view which proposes that schizophrenics suffer from an impairment in abstract thinking and rely on concrete thinking. Although clinically useful, the abstract-concrete view has been difficult to define in operational terms. Converging data from several areas, particularly the work on basic-level categorization (Rosch et al., 1976), has provided a way to define abstract and concrete thought more rigorously. Thus, concrete and abstract thought were

operationalized as correct responses to basic-level and superordinate categorization, respectively.

Given this background, the first hypothesis posited that when abstract thinking was required, schizophrenics would slip to concrete thinking more often than normals. Results supported the hypothesis; schizophrenic subjects chose concrete responses (when abstract responses were correct) significantly more often than normals. These behavioral findings support the abstract-concrete view of thought disorder in schizophrenia, namely that abstract thinking in schizophrenia is impaired and results in a reliance on concrete thinking.

The second hypothesis posited that, when compared to normals, schizophrenics would show attenuated ERP responses to abstract and concrete thinking tasks. For example, studies have shown that schizophrenics consistently demonstrate reduced amplitudes in auditory oddball paradigms when compared to normals. More recent work has shown that similar differences (attenuated P300) also emerge when a visual-semantic categorization oddball paradigm is used (cf. Chapter II). The hypothesis was that when compared to normals, schizophrenics would show attenuated N100, P200 and P300 amplitudes in the concrete and abstract conditions. Results did not support the second hypothesis; P200 and P300 components were not selectively affected by the abstract and concrete conditions. However, the findings for N100 in both the abstract and concrete conditions and for the slip versus no-slip responses showed several interesting effects. First, schizophrenic subjects did not show the expected N100 attenuation, but showed greater N100 activation than normals in the abstract and concrete conditions. Second, schizophrenic subjects showed greater N100 activation when they slipped to concrete thinking compared to when they did not slip. These findings suggest that schizophrenics did not show deficits in the early, encoding stage in both the abstract and concrete conditions, but used more attentional resources than normals in the early processing of these categories. Greater N100 activation for schizophrenic subjects could be a reflection

of how attention is associated with thought disorder in schizophrenia, i.e., using more attentional resources earlier could result in later cognitive dysfunction.

In sum, since no group differences occurred for P200 or P300 and N100 results occurred in the opposite direction, the second hypothesis was not supported. However, the finding that N100 was greater for schizophrenic subjects in the slip versus no-slip responses merits some additional discussion. Both N100 and basic-level categorization are purported to index stimulus feature encoding (ERP and behavioral correlates) in the following ways. Basic-level categorization is characterized by feature similarity grouping, i.e., encoding stimulus features. Similarly, the N100 is thought to index stimulus feature encoding. Thus, when schizophrenic subjects chose a basic-level categorization response when superordinate was required (slips), this choice was represented by greater activation of N100. This result demonstrates a link between a behavioral and an ERP response. It remains to be determined, however, whether increased activation at N100 results from slipping to a different level of processing, i.e., concrete, in the context of an abstract level. Whether in fact, it is the process of slipping that results in greater N100 activation. If so, then slipping to concrete thinking in a situation that requires abstract thinking might account for thought disorder in schizophrenic subjects.

The behavioral data, namely the number of appropriately correct responses for the four categories, showed a main effect for category. This effect reflects a pattern that is consistent with other schizophrenia research which shows that schizophrenics generally make fewer correct responses than normals. However, schizophrenic subjects made significantly fewer correct choices in three out of four categories, but not for regular concrete. These results suggest that schizophrenic subjects recognized abstract, incongruous and identical categories with lower frequency than normals, but that discrimination based on feature similarity was not impaired. These data also suggest that

thought-disordered schizophrenic subjects have difficulties with conceptual organization rather than with concrete organization that is based on stimulus feature discrimination.

Several caveats need to be addressed in the context of this study's results. First, because of the small number of subjects, caution needs to be exercised in the interpretation of these data. Thus, it is important to see whether these intriguing results will be replicated with a larger group of schizophrenic subjects. Second, schizophrenics were on medication for clinical control of symptoms of recent acute episodes. Harrow and Quinlan (1985) suggest medication results in an improvement in abstract thinking compared to cognition measured during an acute illness. However, since schizophrenics chose concrete thinking responses more often than abstract responses suggests that medication did not have an effect on their abstract performance, a pattern that was also reflected in their thought disorder score.

Finally, another aspect of this study is that the schizophrenic subjects study scored definite thought disorder, in contrast to normals who scored no thought disorder. Thought disorder as inclusion criteria for the schizophrenics, however, provides additional support for this study's results. Since schizophrenics were neither intellectually impaired (no significant difference compared to normals), nor behaviorally impaired (they completed all tasks), the reliance on concrete thought results does not translate to general impairment in intellectual functioning, but only to a specific impairment in abstract thinking. Overall, schizophrenic subjects showed three specific deficits in this study: 1) an impairment in abstract thought, 2) an N100 correlate of cognitive dysfunction (slips to concrete thought) and 3) fewer correct responses than normals.

In conclusion, the cognitive psychophysiology paradigm used in this study resulted in findings that are in accord with data from other research (cf. Chapter II), which showed that a visual-semantic paradigm can be used to demonstrate ERP correlates of cognitive dysfunction in schizophrenia. Such results are consistent with the

direction of EP and ERP investigations of schizophrenia that researchers have suggested. The suggested direction has been to develop cognitive psychophysiology paradigms that could be used to measure cognitive deficits in schizophrenia and also, to detect early cognitive dysfunction before psychotic symptoms develop. Thus, this study has demonstrated that a cognitive psychophysiology paradigm can be successful in eliciting specific cognitive deficits in schizophrenia, namely deficits in abstract thinking, that are reflected in ERP changes. Because this paradigm has been useful in demonstrating behavioral and ERP correlates of cognitive dysfunction in schizophrenia, continued efforts to develop and use such paradigms in the study of more complex cognitive dysfunction in schizophrenia seem justified.

TABLE 1.

MEANS AND STANDARD DEVIATIONS: THOUGHT DISORDER INDICES, INTELLIGENT QUOTIENTS, AND AGES OF NORMAL AND SCHIZOPHRENIC SUBJECTS

		TDI[a]		IQ[b]		AGE	
Diagnosis	n	x	s	x	s	x	s
Normal	5	1.2	.2	2.8	.7	29.8	6.3
Schizophrenic	5	3.2	.2	2.4	1.8	27.6	6.4

Note: x = mean. s = standard deviation.

[a]1 = absent, 2 = mild, 3 = definite, 4 = severe, 5 = very severe.
[b]1 = low average, 2 = average, 3 = high average, 4 = superior, 5 = very superior.

TABLE 2.

MEANS AND STANDARD DEVIATIONS: PEAK AMPLITUDES FOR NORMAL SUBJECTS IN ABSTRACT[a] CONDITION

	N100		P200		P300	
Electrode	x	s	x	s	x	s
Pz	-4.75	1.22	8.95	3.80	7.41	5.13
Cz	-5.31	2.95	9.96	4.44	8.68	4.95
Fz	-4.69	3.25	8.63	3.48	8.58	6.48

Note: n = 5. x = mean amplitude in μV. s = standard deviation.

a = Superordinate Categorization.

TABLE 3.

MEANS AND STANDARD DEVIATIONS: PEAK AMPLITUDES FOR SCHIZOPHRENIC SUBJECTS IN ABSTRACT[a] CONDITION

	N100		P200		P300	
Electrode	x	s	x	s	x	s
Pz	-4.78	3.19	5.53	2.74	4.52	2.88
Cz	-7.47	2.57	9.18	4.68	7.14	3.37
Fz	-7.61	3.77	8.54	4.93	8.06	5.68

Note: n = 5. x = mean amplitude in μV. s = standard deviation.

a = Superordinate Categorization.

TABLE 4.

MEANS AND STANDARD DEVIATIONS: PEAK AMPLITUDES FOR NORMAL SUBJECTS IN CONCRETE[b] CONDITION

	N100		P200		P300	
Electrode	x	s	x	s	x	s
Pz	-2.74	2.18	10.37	1.26	11.10	5.14
Cz	-3.11	2.68	12.02	1.64	12.96	3.94
Fz	-2.73	2.35	12.69	2.63	11.53	6.78

Note: n = 5.

b = Basic-level Categorization.

TABLE 5.

MEANS AND STANDARD DEVIATIONS: PEAK AMPLITUDES FOR SCHIZOPHRENIC SUBJECTS IN CONCRETE[b] CONDITION

	N100		P200		P300	
Electrode	x	s	x	s	x	s
Pz	-2.40	2.39	5.59	1.54	7.23	4.86
Cz	-5.01	1.85	8.99	2.23	9.15	6.70
Fz	-5.62	2.63	7.34	7.06	7.58	6.39

Note: n = 5.

b = Basic-level Categorization.

TABLE 6.

ANOVA SUMMARY: N100 AMPLITUDES FOR ABSTRACT[a] AND CONCRETE[b] CONDITIONS

	SS	df	MS	F	p
Main Effects					
Diagnosis	38.06	1	38.06	4.95	.056
Condition	70.61	1	70.61	5.66	.04
Electrode	31.09	2	15.54	2.50	NS
Interactions					
Diag. x Cond.	.18	1	.18	.01	NS
Diag. x Elec.	24.88	2	12.43	2.00	NS
Cond. x Elec.	.33	2	.16	.03	NS
Diag. x Elec. x Cond.	.073	2	.03	.01	NS

Note: n = 10.

a = Superordinate Categorization.
b = Basic-Level Categorization.

TABLE 7.

ANOVA SUMMARY: P200 AMPLITUDES FOR ABSTRACT[a] AND CONCRETE[b] CONDITIONS

	SS	df	MS	F	p
Main Effects					
Diagnosis	126.71	1	126.78	3.95	NS
Condition	16.02	1	16.02	.77	NS
Electrode	62.05	2	31.02	3.54	.05
Interactions					
Diag. x Cond.	32.77	1	32.77	1.58	NS
Diag. x Elec.	12.38	2	6.19	.71	NS
Cond. x Elec.	1.26	2	.62	.09	NS
Diag. x Elec. x Cond.	10.41	2	5.20	.76	NS

Note: n = 10.

a = Superordinate Categorization.
b = Basic-Level Categorization.

TABLE 8.

ANOVA SUMMARY: P300 AMPLITUDES FOR ABSTRACT[a] AND CONCRETE[b] CONDITIONS

	SS	df	MS	F	p
Main Effects					
Diagnosis	114.48	1	114.48	.97	NS
Condition	95.71	1	95.71	4.33	NS
Electrode	38.96	2	19.47	1.93	NS
Interactions					
Diag. x Cond.	18.57	1	18.57	.84	NS
Diag. x Elec.	3.39	2	1.69	.17	NS
Cond. x Elec.	12.57	2	6.28	1.18	NS
Diag. x Elec. x Cond.	3.77	2	1.88	.35	NS

Note: n = 10.

a = Superordinate Categorization.
b = Basic-level Categorization.

TABLE 9.

MEANS AND STANDARD DEVIATIONS: PEAK AMPLITUDES FOR SCHIZOPHRENIC SUBJECTS IN SLIPS TO CONCRETE[a] THINKING

	N100		P200		P300	
Electrode	x	s	x	s	x	s
Pz	-7.50	5.31	6.17	2.16	2.29	2.72
Cz	-9.23	4.02	8.70	2.78	2.01	2.71
Fz	-8.27	5.35	8.73	2.31	.85	2.68

Note: n = 3.

a = Basic-Level Categorization.

TABLE 10.

MEANS AND STANDARD DEVIATIONS: PEAK AMPLITUDES FOR SCHIZOPHRENIC SUBJECTS FOR NO SLIP[b] RESPONSES

	N100		P200		P300	
Electrode	x	s	x	s	x	s
Pz	-1.42	3.48	3.55	3.15	3.24	2.20
Cz	-4.25	4.43	5.96	3.15	4.33	3.96
Fz	-4.16	4.63	5.96	3.50	2.05	1.64

Note: n = 3.

b = Superordinate Categorization.

TABLE 11.

ANOVA SUMMARY: SCHIZOPHRENIC N100 AMPLITUDES FOR SLIP AND NO-SLIP RESPONSES

	SS	df	MS	F	p
Main Effects					
Condition	115.11	1	115.11	55.70	.02
Electrode	17.06	2	8.53	1.86	NS
Interaction					
Cond. x Elec.	2.91	2	1.45	1.62	NS

Note: n = 3.

TABLE 12.

ANOVA SUMMARY: SCHIZOPHRENIC P200 AMPLITUDES FOR SLIP AND NO-SLIP RESPONSES

	SS	df	MS	F	p
Main Effects					
Condition	27.26	1	27.26	6.28	NS
Electrode	28.95	2	14.47	2.81	NS
Interaction					
Cond. x Elec.	.43	2	.21	.23	NS

Note: n = 3.

TABLE 13.

ANOVA SUMMARY: SCHIZOPHRENIC P300 AMPLITUDES FOR SLIP AND NO-SLIP RESPONSES

	SS	df	MS	F	p
Main Effects					
Condition	14.05	1	14.05	2.25	NS
Electrode	15.39	2	7.69	1.93	NS
Interaction					
Cond. x Elec.	1.55	2	.77	3.69	NS

Note: n = 3.

TABLE 14.

LIKELIHOOD RATIO χ^2 TEST[a]: DIFFERENCES BETWEEN NORMAL AND SCHIZOPHRENIC SUBJECTS IN SLIPS TO CONCRETE THINKING

	SLIPS[b]	NO SLIPS[c]
Normals	18	157
Schizophrenics	43	74

Note: n = 10.

χ^2 (1df) = 4.54.
p-value = .019.

a = Likelihood ratio χ^2 test is based on a binomial model with over-dispersion due to correlated observations.
b = Basic-level Categorization Responses.
c = Superordinate Categorization Responses.

TABLE 15.

MEANS AND STANDARD DEVIATIONS: NUMBER OF CORRECT RESPONSES FOR NORMAL AND SCHIZOPHRENIC SUBJECTS IN ALL CONDITIONS

	RS[a]		FS[b]		RC[c]		MC[d]	
Diagnosis	x	s	x	s	x	s	x	s
Normal	25.20	3.27	27.00	2.55	26.60	3.13	31.20	.84
Schizophrenic	10.60	9.92	23.20	8.11	24.00	7.04	25.00	8.41

Note: n = 5. x = mean. s = standard deviation.

a = Regular Superordinate.
b = Incongruous Superordinate.
c = Regular Concrete.
d = Match Concrete.

TABLE 16.

ANOVA SUMMARY: CORRECT RESPONSES FOR NORMAL AND SCHIZOPHRENIC SUBJECTS

	SS	df	MS	F	p
Main Effects					
Diagnosis	462.40	1	462.40	4.65	.06
Category	568.80	3	18.96	10.22	.001
Interaction					
Diag. x Cat.	219.60	3	73.20	3.95	.02

Note: n = 10.

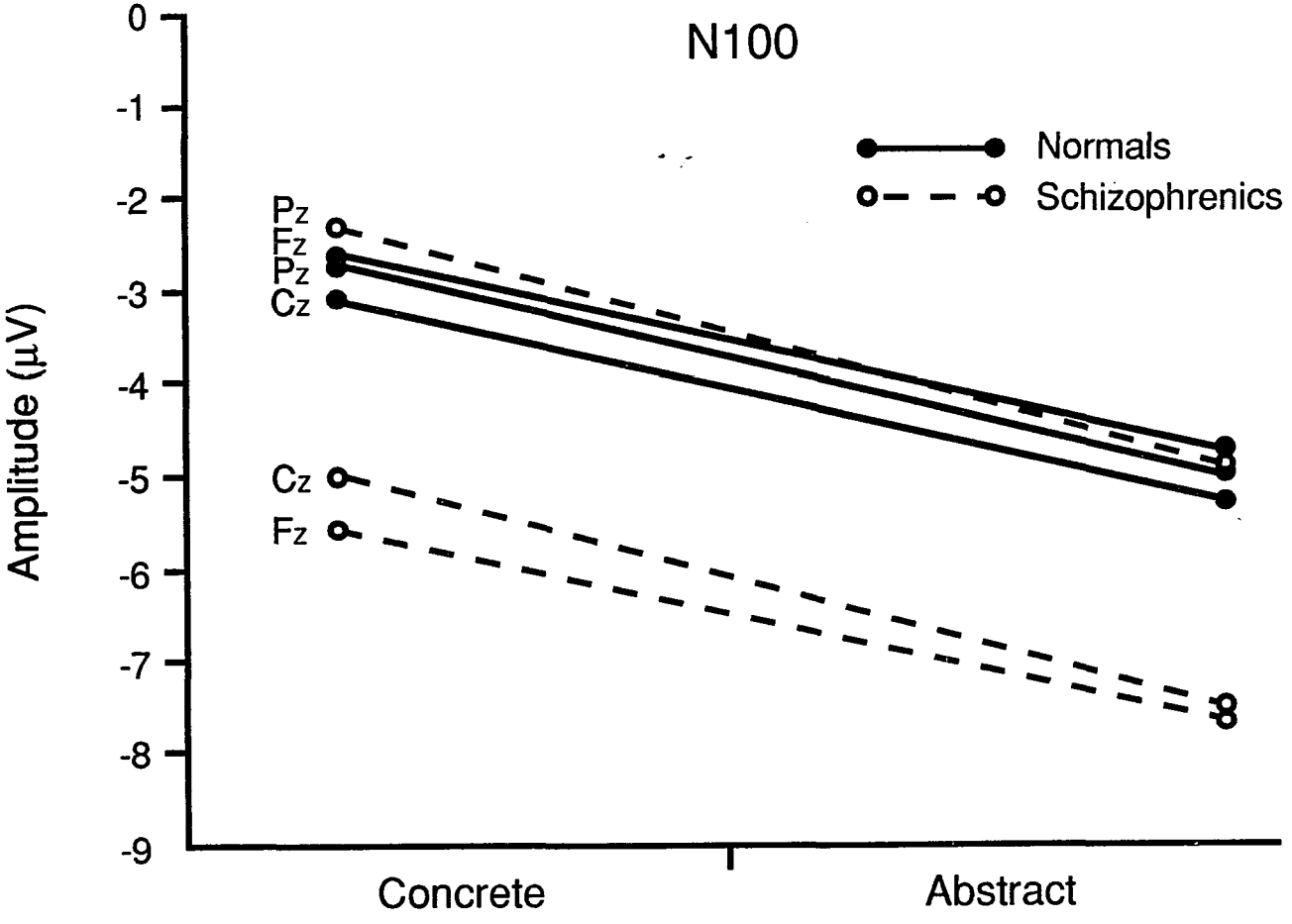

Figure 1: Comparison of Normals and Schizophrenics in Concrete and Abstract Conditions

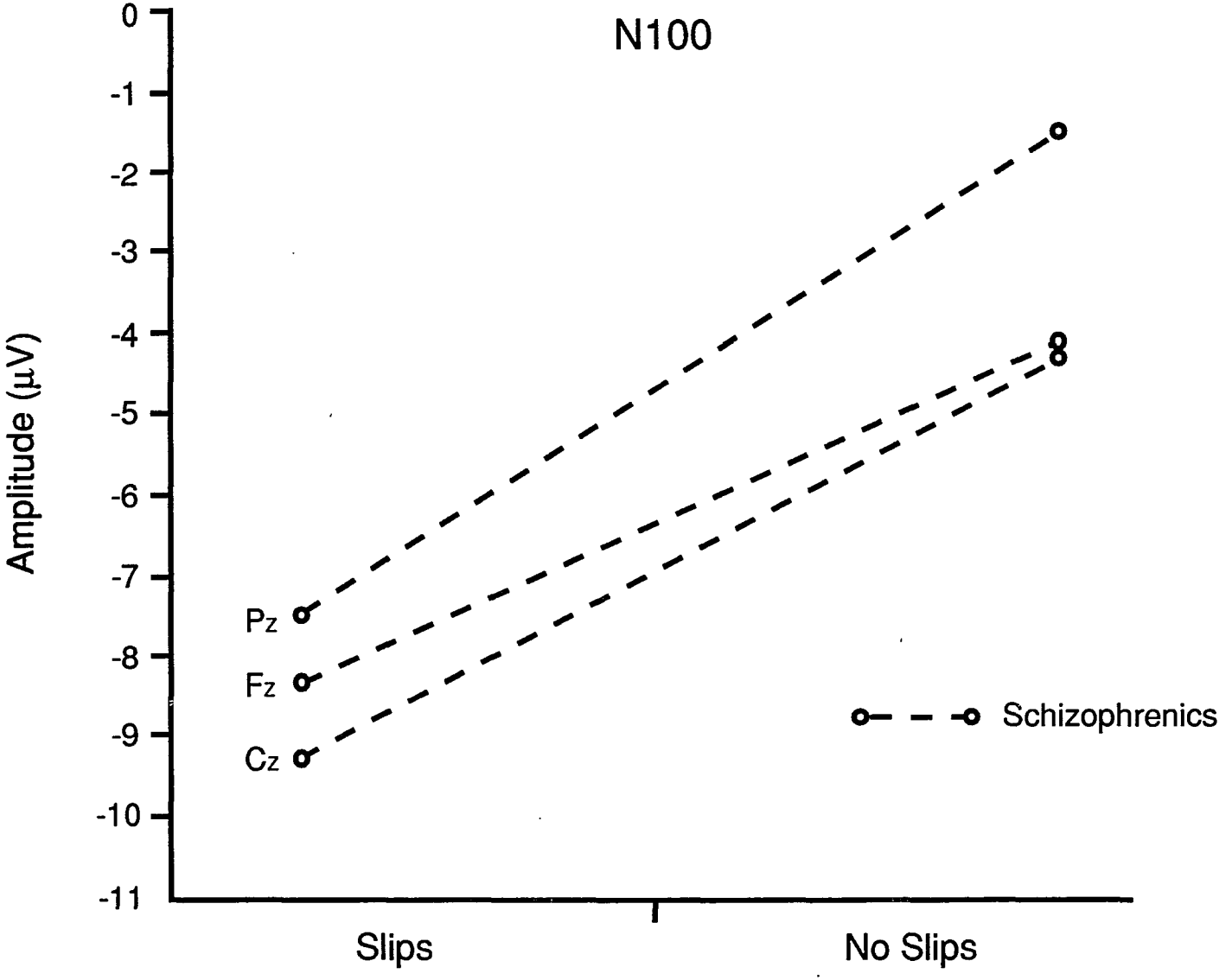

Figure 2: Comparison of Slip and No Slip Responses for Schizophrenics

CHAPTER IV

N400: SCHIZOPHRENIC AND NORMAL SUBJECTS' RESPONSES TO SEMANTIC CATEGORIZATION DIFFERENCES

Introduction

There is a significant literature on the relationship between cognitive events and changes in event-related brain potentials (ERPs) in normal subjects. Since the classic work on the P300 (Sutton, Braren, Zubin, and John, 1965) ushered in the era of cognitive psychophysiology, research on ERP components has become increasingly sophisticated and more widely applied. The N400, which is a relatively new addition to the family of ERP components, was first described by Kutas and Hillyard (1980a). The N400 component is a negative-going deflection of a waveform whose peak latency occurs about 400 milliseconds post-stimulus onset. Kutas and Hillyard's (1980a) fundamental work on the N400 demonstrated that this component could be elicited in a sentence-reading paradigm; words that form a sentence are serially presented (visually) to subjects who are instructed to read silently in order to answer questions about the context of the sentence. If the terminal words in the sentences are semantically incongruous (but syntactically correct), an N400 is elicited that is more negative than if the terminal words are congruous. For example, the sentence, "He spread the bread with warm socks," elicits a large N400 compared to the sentence, "He spread the bread with warm butter,"

which elicits no negativity (Kutas and Hillyard, 1980a). Subsequent N400 research has shown that the amplitude of N400 is inversely related to the subjects' expectancy of the final word in the sentence, and that an N400 is not elicited in response to other sentence constraints, such as physical deviance (e.g., the terminal word appearing in large print). Thus, the more unlikely the final word in the context of the meaning of the sentence (cloze probability), the larger the amplitude of the N400 (Kutas and Hillyard, 1984). In general, research has shown that the degree of semantic relatedness is a significant determinant of the N400 (Coles, Gratton, Fabiani, 1988).

In addition to the sentence-reading tasks that have been used to elicit the N400, semantic priming and sentence-verification paradigms have also been used. In sentence verification designs, subjects are asked to determine whether statements are positive or negative or whether they are true or false. For example, "A robin is a tree," elicits a large negativity (Fischler, Bloom, Childers, Roucos, and Perry, 1983). Overall, paradigms which set up subjects' semantic expectancies and then violate them will elicit a significant N400. The N400 research suggests that this ERP component is a brain response that indexes semantic incongruity.

Electrophysiological (EEG and EP) studies have made important contributions to schizophrenia research (Roth and Cannon, 1972; Levit, Sutton, and Zubin, 1973; Rappaport, 1975; Verleger and Cohen, 1978; Lifshitz, 1979; Roth, Horvath, Pfefferbaum and Koppel, 1980; Baribeau-Braun, Picton, and Gosselin, 1983; Brecher and Begleiter, 1983; Morihisa, Duffy, and Wyatt, 1983; Morstyn, Duffy, and McCarley, 1983; Shagass, 1983; Duncan-Johnson, Roth, and Koppel, 1984; Levin, 1984; Pritchard, 1986; Holzman, 1987; Duncan, Perlstein, and Morihisa, 1987; Faux, Torello, McCarley, Shenton, and Duffy, 1987; Faux, Torello, McCarley, Shenton, and Duffy, 1988). The focus of these studies, however, has generally been on the relationship between changes in electrical brain activity and attentional deficits, rather than on

cognitive dysfunction in schizophrenia. Similarly, there is an extensive literature on event-related potentials (ERPs) and cognitive events in normals. However, little work has been done to investigate the relationship between ERPs and cognitive dysfunction in schizophrenia. This situation has prompted researchers to suggest two directions in electrophysiology research in schizophrenia: 1) to develop and use cognitive psychophysiological paradigms to study cognitive deficits in schizophrenics (Fenton, 1980; Pritchard, 1986); and 2) to replace the clinical paradigms used in electrophysiology studies of attention in schizophrenia with cognitive psychophysiological ones (Donchin and Bashore, 1980; Begleiter and Porsjez, 1984; Pritchard, 1986). Thus, rather than as an aid to clinical diagnosis, the development of a cognitive psychophysiological paradigm using ERPs would be a way to detect specific cognitive deficits in schizophrenia. In light of these recommendations, N400 research could prove to be a promising area in terms of its clinical application to psychiatric disorders. Such an application would be similar to the P300 research, which has proved to be a robust biological phenomenon (Begleiter and Porsjez, 1986) in schizophrenia. Indeed, N400 research related to semantic anomalies in schizophrenia is in the beginning stages of investigation (Adams, Faux, McCarley, Marcey, and Shenton, 1989). The study of N400 in relation to cognitive dysfunction in schizophrenia could be particularly useful in determining whether brain responses to semantic incongruity in schizophrenia differ from those of normals.

Paradigms that set up violations of semantic expectancies have included sentence-reading and sentence-verification designs to elicit N400 components in normal subjects (Fischler, Bloom, Childers, Roucos, and Perry, 1983; Polich, 1985) and in schizophrenic subjects (Adams, Faux, McCarley, Marcey, and Shenton, 1989). However, to date no one has used a semantic categorization paradigm related to cognitive processing to determine whether schizophrenic subjects show N400 response differences from normals to incongruities in categorization. The present study, therefore, used an S1-S2 paradigm

to see whether ERP recordings would show N400 differences between normals and schizophrenics in response to categorization incongruities. The aims of this study were to see whether normals would show N400 differences between regular superordinate categorization (e.g, S1: **Furniture** and S2: **Chair, Chair, Desk**) and incongruous superordinate categorization (e.g., S1: **Tool** and S2: **Vise, Vise, Egg**), and also to see whether there would be N400 differences between normal and schizophrenic subjects.

Methods

General Criteria for Subject Selection

Data were collected on ten subjects, five normal subjects (4 females and 1 male) and five schizophrenic subjects (3 females and 2 males). Normal subjects ranged in age from 24-38 (mean age = 29.8); schizophrenic subjects ranged in age from 19-35 (mean age = 27.6). All subjects were right-handed (The Edinburgh Inventory, Oldfield, 1971) and none had a history of head injury, alcohol abuse, or neurological disorder. Vision tested 20/20 (corrected as indicated) (Rosenbaum Pocket Vision Screener) for all subjects whose results were included in the analysis. The WAIS-R Vocabulary Test (Weschler, 1981) was used as a measure of I.Q. I.Q. measures for normal subjects ranged from average to superior (mean = high average); I.Q. measures for schizophrenic subjects ranged from low average to superior (mean = average). The State-Trait Anxiety Inventory (STAI), which was used to control for level of anxiety, was administered pre and post laboratory procedures. STAI results showed that subjects were not anxious (Spielberger, 1983).

Diagnostic Selection Criteria

The Schedule for Affective Disorders and Schizophrenia (SADS) (Endicott and Spitzer, 1978) was used to make a Research Diagnostic Criteria (RDC) (Spitzer, Endicott, and Robins, 1977) diagnosis of schizophrenia for the schizophrenic group. Three schizophrenic subjects were inpatients (who were discharged shortly after testing) and two were outpatients (who had been recently discharged). The Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962) was used to assess symptom level. The BPRS is a widely used instrument developed to provide an assessment of symptom severity and frequency. All schizophrenic subjects whose data were included in the final analysis scored <35 on the BPRS. Two BPRS assessments were done within several days of each other: one by the experimenter (a clinical psychologist trained in the use of the BPRS) on the day of electrophysiological testing, the other by a research assistant (trained by experimenter) on the day of cognitive tests administration. Interrater reliability for BPRS was .94 (Intraclass correlation coefficient [Winer, 1971]).

Normal subjects were recruited from an existing pool. These subjects had no history of psychiatric hospitalization themselves or among their first-degree relatives. I.Q. had been measured with the WAIS-R and normal functioning had been assessed with the Minnesota Multiphasic Personality Inventory (MMPI) (no elevation above 70 on any subscore) or with the Schedule for Affective Disorders (SADS) (no history of mental disorder). In addition, as with the schizophrenic group, two BPRS assessments of normals were done within several days of each other: one by the experimenter on the day of electrophysiological testing, the other by a research assistant on the day that the cognitive tests were administered (see below). Interrater reliability for BPRS was .94 (Intraclass correlation coefficient [Winer, 1971]).

Cognitive Measures: Thought Disorder and I.Q. Assessments

All normal and schizophrenic subjects who were included in the study had been cognitively assessed to determine whether they showed any evidence of cognitive dysfunction (defined as thought disorder in this study). Cognitive function vs. dysfunction (i.e., thought disorder) was measured on Bizarre/Idiosyncratic Thinking (B-I) dimensions (Harrow and Quinlan, 1985; Harrow and Marengo, 1986). Bizarre/Idiosyncratic Thinking is a construct that purports to measure thought disorder on several levels, some of which include linguistic form and structure and content of the statement. The following measures were used to assess thought disorder on B/I dimensions: 1) the Comprehension subtest on the Weschler Adult Intelligence Scale, Revised (WAIS-R) (Weschler, 1981); the Benjamin Proverbs Test (Benjamin, 1944); and the Object Sort Test (Goldstein and Sheerer, 1941). All tests were separately scored by two raters (experimenter and research assistant). Each subject's B-I score was compared to Harrow's Thought Disorder rating scale and given a Thought Disorder score. The scores on this scale ranged from 1 to 5 with the following divisions: **1-2** = no thought disorder; **3** = definite thought disorder; and **4-5** = severe thought disorder. Normals who scored >3, which indicated definite thought disorder (1 subject), were not included in the study. Similarly, schizophrenics who scored <3, which indicated no thought disorder (2 subjects), also were not included in the study. The Vocabulary subtest of the WAIS-R was used as an estimate of I.Q. level because this subtest has the highest correlation (.96) with the full I.Q. score of any WAIS-R verbal subtest (Weschler, 1981). Finally, interrater reliability (experimenter and research assistant) for scoring of all cognitive measures was .82 for B/I thought and .98 (Intraclass correlation coefficient [Winer, 1971]) (Means and standard deviations for thought disorder scores, I.Q. scores, and ages of normal and schizophrenic subjects are presented in Table 1).

Medication and Other Considerations

Some studies suggest that medicated and unmedicated schizophrenics show similar levels of thought disorder in the early acute phase of an episode (Harrow, Grossman, Silverstein, and Meltzer, 1982). Although the initial effects of medication can reduce the acute symptomatology of schizophrenia, some data suggest that improvement in thinking from the effects of medication, e.g., phenothiazines, can take 1-1 1/2 weeks or longer (Harrow and Quinlan, 1985). Because subject participation in this study included three phases (diagnostic assessment, cognitive assessments, and electrophysiological procedures), patient subjects needed to be relatively symptom-free in order to complete all phases of the study. Thus, all schizophrenic subjects included in the analysis were not in an acute episode, were on psychotropic medication, had an RDC diagnosis of schizophrenia, and had scores of definite thought disorder on the B/I thinking scale (>3). Normals were not on medication, had an MMPI/SADS assessment of normal functioning, and had scores of no thought disorder on the B/I thinking scale (<3).

Histories and Miscellaneous Criteria

Medication and previous treatment histories, and demographic information were taken on all subjects. Confidentiality and protection of subjects' rights were taken into consideration. After consent forms were signed, only ID codes were used to identify subjects. All subjects were informed they could stop at any point of the procedure if they wished. All non-patients were compensated (inpatients were not compensated in accordance with hospital policy). Approval for participation of hospitalized subjects was obtained from the Human Use Committee at the University of Michigan Hospital. Patients were asked a number of questions in order to check for: 1) adverse reactions to medications, and 2) new medications (or change in dosage). Finally, questions about special details were asked of patient subjects to determine whether any situation of note

needed to be addressed during or after laboratory procedures. Subjects in both groups completed all diagnostic, cognitive, and laboratory phases of the study.

Experimental Procedures

Subjects were seated in a dimly lit, sound attenuated room. They sat facing a projection screen (placed 63.5 cm away from subjects) and performed visual, semantic S1-S2 categorization tasks. Subjects were told they would see two slides in rapid succession. On Slide 1 they would see one word that named a category; on Slide 2 they would see three words (presented vertically) that named objects that might or might not be members of the S1 category. Subjects' task was to decide whether all the objects named on S2 belonged to the category named on S1. A response box was placed in front of subjects. The second, third, and fourth fingers of the right hand were used to press buttons 1, 2, and 3, whereas the left index finger was used to press button A. If subjects decided that S2 object labels belonged to the category named on S1, they were instructed to press **A** button (all belong). If, on the other hand, they decided one word didn't belong, they were instructed to press the button which corresponded to the number of the word in the list. For example, if the first word on S2 didn't belong to the category named by S1, the response button marked **1** (corresponding to the first word) should be pressed (and so forth for second and third word). Subjects were given practice trials until they reached an 80% level of accuracy (number of practice trials ranged from 10-30; means for practice trials: normals = 12; schizophrenics = 20.25).

S1 and S2 were presented for 200 msec for normals with a 1000 msec interval between stimuli (ISI). Subjects needed to respond within the 1000 msec for response to be recorded (epoch=2600 msec [including pre-stimulus time]). During pilot testing it became clear that schizophrenic subjects needed a longer stimulus presentation time in order to reach an accuracy level of 80%. The need to increase the time of stimulus time in order to reach a set criterion level of performance has been addressed as a specific

deficit in schizophrenia (Chapman and Chapman, 1973). Thus, based on the pilot work, S1 and S2 were presented for 400 msec for schizophrenics with a 1000 msec ISI and 1200 msec to respond (epoch=3200 msec [including pre-stimulus time]).

There were two superordinate categorization conditions: regular superordinate and incongruous superordinate. The following instances are examples of incongruous and congruous trials. A congruous trial could be S1: **Animal,** S2: **Bear, Lion, Bear**. In contrast, an incongruous trial could be S1: **Vehicle,** S2: **Bus, Bus, Ice**. Two additional conditions were also included: a concrete level and a match level of categorization (cf. Chapter III). The match condition was included to insure that the "A" button (all belong choice) could be pressed a corresponding number of times equal to the number of times this button could be pressed in the superordinate condition.

Category words that were presented for stimulus 1 and 2 consisted of 64 high frequency nouns. (See Appendix A for category lists). Stimuli were presented on slides projected onto a rear projection screen (Daylight Screens) using an Ectographic slide projector. A second Ectographic slide projector was used to project a fixation slide. (The fixation slide was continuously projected to minimize flash/blink responses when stimuli were presented.)

Subjects were instructed to focus on a dot that was in the middle of the fixation slide whenever a trial was to be initiated. Room luminance was maintained at 2.5 ft lamberts; fixation slide and stimulus slides were maintained at 2.5 and 3.5 ft. lamberts, respectively (measurements were made with UDT 40X Opto-Meter). Stimulus words, when presented, were centered on the fixation dot. All stimulus words were white upper and lower case letters on a blue background centered on 2" x 2" slides. Visual angle for words ranged from 1.7^0 for the shortest word and 3.4^0 for the longest word. Frequency of words (length ranged from 3 to 9 letters) averaged 43 per million (Francis and Kucera, 1967).

S1 and S2 were presented at approximately one pair/25 seconds. The length of time between stimuli included time to store trial to disk, monitor ongoing EEG, check on the subject, and attend to any difficulties. Thus, the presentation of 2 blocks of 64 stimulus pairs in random order required an average of 1 hour. Entire length of time to complete all laboratory procedures ranged from 2 to 3 hours.

Data Collection, Equipment, and Analysis

EEG was recorded from 3 midline electrode locations: Fz, Cz, and Pz (10-20 International System). All electrodes were referred to linked mastoids. Nicolet EEG Surface silver cup electrodes were used for the scalp recordings, for the ground (attached with collodion), which was placed mid-forehead, and for electro-ocular recording activity (EOG). Eye movements were monitored by EOG electrodes placed above and below the left eye (attached with paste). Impedences were maintained <5 Kohm.

The Nicolet Pathfinder I Electrodiagnostic System was used to amplify, filter, average, store, and plot the data. The Pathfinder I model has a 10 megabyte Winchester drive, to which individual trials were stored for off-line analysis, and 2 floppy drives.

The EEG and EOG were amplified with Pathfinder I SM200L amplifiers. Low band pass filter was set at .01 Hz (at -6 db roll-off, the time constant is about 7 seconds [Rockstroh, Elbert, Birbaumer, and Lutzenberger, 1982]), and high band pass filter was set at 30 Hz. With an analysis sweep (time) set at 512 data points, data were sampled at 5.1 msec for normals (2600 msec epoch) and at 6.3 msec for schizophrenics (3200 msec epoch). Individual trials were stored to disk so that inspection of raw data could occur off-line. During ERP averaging, all trials were individually inspected prior to inclusion in the averaging. The decision to accept or reject was based on preset rejection criteria, e.g., trials with artifacts such as eye movement >65 uv were rejected.

The S1 and S2 sequence for each trial was manually triggered by the experimenter (who monitored the status of patient subjects) from a Grass Stimulator

(S88). An automatic timing mechanism (Vincent Associates, 4 msec open/shut time) was attached to the shutter of the stimulus projector for preset timed presentations of S1 and S2. Stimulus 1 and 2 onset and offset were measured by a photocell, which was placed at the edge of the shutter opening of the slide projector. Thus, the channels of data that were recorded for each trial included the Pz, Cz, and Fz electrode channels, the EOG channel, and the stimulus marker channel.

ERPs were averaged across all correct trials (excluding contaminated trials) for regular and incongruous superordinate conditions. ERPs were also averaged for abstract and concrete thinking choices within the superordinate condition (cf. Chapter III). To accommodate the potential drift that often occurs with a long time constant, all individual trials were baseline corrected before averaging. N400 was computed with respect to the averaged pre-stimulus 2 recording period (160 milliseconds prior to Stimulus 2) to the highest peak within the designated time window for N400 (350-580 msec).

Results

Means and standard deviations for all subjects' ERP amplitudes, thought disorder, age, I.Q., are presented in Tables 1-3. Subjects' behavorial measures for correct and error responses and also for reaction times for the regular and incongruous superordinate conditions are presented in Tables 5-6.

A univariate 2x2x3 factor repeated-measures analysis of variance using BMDP2V was performed on the amplitude of N400 (Table 4). Diagnostic group (normals and schizophrenics) was the between-subjects factor; within-subject factors were electrode position (Pz, Cz, and Fz) and experimental condition (regular and incongruous superordinate). A full ANOVA model (2x2x3) was used to assess the effect of each factor (diagnosis x condition x electrode) on N400 amplitude.

The repeated-measures ANOVA, which was used to analyze the amplitude data, incorporated The Greenhouse-Geisser correction for violations of sphericity of the variance-covariance matrix of repeated measures when the number of repeated measures levels is greater than two (Jennings, Cohen, Ruchkin, and Fridland, 1987).

Analysis of the N400 data showed one significant main effect for condition ($F(1,8) = 5.29$, $p = .05$) and three interactions. There were two significant two-way interactions: condition and diagnosis ($F(1,8) = 6.38$, $p = .03$); condition and electrode ($F(2,16) = 3.96$, $p = .04$), and one three-way interaction: condition and electrode and diagnosis ($F(2,16) = 5.75$, $p = .013$). These results showed that this paradigm was successful in eliciting the expected N400 difference between the two conditions for normals, an effect that was particularly striking at the Fz and Cz electrodes (Figure 1). Moreover, the condition by diagnosis effect shows that schizophrenics differed from normals in their responsiveness to the regular and incongruous conditions. Generally, schizophrenics showed little N400 difference in response to condition, an effect that contrasted with normals who showed a large effect. In sum, normals showed a large N400 response to the incongruous condition (an effect that was maximal at Fz) in contrast to schizophrenics who showed little difference between condition; this effect reflects the diagnosis x condition x electrode interaction.

Although there was little N400 change for schizophrenic subjects between conditions, the behavioral data show several effects. When compared to normals, schizophrenic subjects took longer to respond to both conditions than normals did (Table 6); however, their correct responses to the incongruous tasks differed only slightly from normals (Table 5). Thus, although this paradigm elicited small ERP differences between conditions for schizophrenic subjects, their behavioral responses indicate that they were engaged by the tasks, despite taking longer to respond. These data, therefore, suggest that the attenuated N400 effect might be an ERP expression of cognitive dysfunction in

schizophrenia, namely that incongruity might not be processed differently from congruity.

Discussion

Research has shown that the N400 is an endogenous ERP component which is thought to index semantic incongruity in normals. In the early work on N400, normal subjects showed a significant negativity of N400 in response to anomalous sentence endings. This effect was shown to be the result of semantic incongruity and not an effect of physical deviation (e.g., stimulus letter size) (Kutas and Hillyard, 1980c). Moreover, recent work on the N400 in schizophrenia, which was based on a sentence-reading paradigm similar to the original work (Kutas and Hillyard, 1980a; 1980b; 1980c), found that schizophrenic subjects showed a marked attentuation of N400 (Adams et al., 1989). In this light and based on the recommendation to investigate a possible correspondence between ERPs and cognitive dysfunction in schizophrenia, there were two aims in this S1-S2 semantic categorization study. The first aim was to determine whether normals would show N400 differences to categorization incongruities. The second aim was to see whether, when compared to normals, schizophrenics would show N400 differences to incongruities in categorization.

Overall, results emerged in the expected directions. Normals showed greater N400 activation in the incongruous condition than in the regular (congruous) condition, an effect that was maximal at Fz. Furthermore, schizophrenic subjects generally showed a reduced N400 compared to normals in the incongruous condition. These results for normals are consistent with other findings (Kutas and Hillyard, 1980a, 1980b, 1980c; Neville, Kutas, Chesney, and Schmidt, 1986). Moreover, the attenuated ERP results for schizophrenics are in accord with other work (Adams et al., 1989), and are also

consistent with data from other paradigms based on categorization differentiation (cf. Chapter III).

In addition, these data show that there were no significant N400 effects for schizophrenic subjects in response to different types of categorizatio.. congruent vs. incongruent. That is, schizophrenics showed little change in N400 amplitude between conditions, compared to normals who did show a significant N400 change (Figure 1). This lack suggests that schizophrenic subjects may not have perceived any semantically incongruous difference between conditions, i.e., category incongruities were not perceived as incongruous. However, their behavioral responses suggest that they were processing the category members correctly (not belonging). These data suggest one of two interpretations: 1) that augmentation of N400 is not an essential aspect of incongruity, or 2) that incongruity in this paradigm may be recognized in more than one way. For example, in an incongruous trial such as S1: **Tool**, S2: **Vise, Vise, Plum**, schizophrenics may have processed only that plum did not belong to the category rather than that it violated semantic categorization expectancy. Thus, schizophrenics may not have determined that category members were semantically incongruous, only that they did not belong.

Finally, with the qualification that the ERP data was undersampled (only three electrodes) combined with a small number of subjects, the large effect for normals at Fz bears some discussion in light of other N400 work. In this study, the anterior scalp distribution of N400 of normals was not in accord with findings that showed a centro-parietal maximum (Kutas and Hillyard, 1980a, 1980b, 1980c). The process of recognizing categorization incongruity in this paradigm could result in a shift toward the frontal area in N400 activation for normals, the area that showed the largest N400 difference between conditions. In contrast, the small difference in N400 between conditions at Pz might result when processing for normals fits semantic expectancies (regular categorization). This discrepancy might be accounted for in several ways. The

sentence-reading paradigm that has typically been used in N400 studies is considerably different from the S1-S2 categorization paradigm used in this study. Another major difference is that other studies did not have a button press that allowed one out of four choices. Lastly, that schizophrenic subjects took longer to respond might indicate that a longer time window than was used in this study would be required for N400 identification.

In conclusion, this study revealed several interesting findings. First, this paradigm was successful in eliciting a N400 differences for normals at Fz and Cz (Figure 1). These effects reflect ERP correlates of two opposing processes, namely the processing of "expected" and congruous semantic categorization in contrast to "unexpected" and incongruous semantic categorization. Second, schizophrenics showed reduced N400 compared to normals in the incongruous condition. Third, schizophrenic subjects demonstrated little change in N400 between conditions. These findings are consistent with the research on normals (Kutas et al., 1980a, 1980b, 1980c; Polich, 1985) and with recent work on N400 in schizophrenia (Adams et al., 1989).

The results of this study have demonstrated that a cognitive psychophysiology paradigm can be a successful tool to study cognitive dysfunction in schizophrenia. The S1-S2 semantic categorization paradigm that was used resulted in data that showed subtleties in cognitive impairment not previously reported in schizophrenia research. However, these results need to be interpreted with caution because of the small sample and the limited number of electrodes. In addition, the group of schizophrenic subjects used in this study was a select one (relatively young subjects close to first hospitalization). Moreover, because this group did not show the generalized and early perceptual deficits usually reported suggests that early testing of cognitive dysfunction in schizophrenia could impact on treatment modalities. For example, specific deficits at particular stages of perceptual/cognitive processing could be identified. Therefore, in light of recommendations to develop paradigms that use ERPs to study cognitive

dysfunction in schizophrenia, the results of this study warrent research in several directions. First. it needs to be determined whether these data can be replicated with a larger group of schizophrenic subjects. Second, it will be important to determine whether other psychiatric disorders show similar N400 differences. And third, if this paradigm were used with a 28-electrode array, e.g., topographic brain-potential mapping, the hypothesis that incongruous categorization is processed more anteriorly by normals could be explored more effectively. Additional efforts in N400 research in schizophrenia could result in a promising area of investigation.

TABLE 1.

MEANS AND STANDARD DEVIATIONS: THOUGHT DISORDER INDICES, INTELLIGENT QUOTIENTS, AND AGES OF NORMAL AND SCHIZOPHRENIC SUBJECTS

		TDI[a]		IQ[b]		AGE	
Diagnosis	n	x	s	x	s	x	s
Normal	5	1.2	.2	2.8	.7	29.8	6.3
Schizophrenic	5	3.2	.2	2.4	1.8	27.6	6.4

Note: x = mean. s = standard deviation.

[a]1 = absent, 2 = mild, 3 = definite, 4 = severe, 5 = very severe.
[b]1 = low average, 2 = average, 3 = high average, 4 = superior, 5 = very superior.

TABLE 2.

MEANS AND STANDARD DEVIATIONS: N400 AMPLITUDES FOR SUBJECTS IN REGULAR SUPERORDINATE CONDITION

	NORMAL		SCHIZOPHRENIC	
	x	s	x	s
Pz	-5.20	2.60	-3.15	3.26
Cz	-2.32	2.39	-5.56	3.04
Fz	-0.92	3.06	-5.05	1.84

Note: n = 5.

TABLE 3.

MEANS AND STANDARD DEVIATIONS: N400 AMPLITUDES FOR SUBJECTS IN INCONGRUOUS SUPERORDINATE CONDITION

	NORMAL		SCHIZOPHRENIC	
	x	s	x	s
Pz	-3.75	4.84	-3.59	2.41
Cz	-6.88	4.13	-4.58	3.19
Fz	-8.17	2.73	-4.92	1.60

TABLE 4.

ANOVA SUMMARY: N400 AMPLITUDES FOR REGULAR AND INCONGRUOUS CONDITIONS

	SS	df	MS	F	p
Main Effects					
Diagnosis	.06	1	.06	.00	NS
Condition	39.11	1	39.11	5.29	.05
Electrode	10.26	2	5.12	.43	NS
Interactions					
Diag. x Cond.	50.56	1	50.56	6.83	.03
Diag. x Elec.	8.04	2	4.01	.34	NS
Cond. x Elec.	41.47	2	20.73	3.96	.04
Diag. x Elec x Cond.	60.30	2	30.15	5.75	.013

Note: n = 10.

TABLE 5.

MEANS FOR CORRECT AND ERROR RESPONSES:* NORMAL AND SCHIZOPHRENIC SUBJECTS IN REGULAR AND INCONGRUOUS SUPERORDINATE CONDITIONS

Condition	NORMAL		SCHIZOPHRENIC	
	Correct x	Error x	Correct x	Error X
Regular[a]	14	.1	10	1.5
Incongruous[b]	13	1.3	12	2.2

Note: n = 10.

[a] = Regular Superordinate Categorization.
[b] = Incongruous Superordinate Categorization.
x = Mean number of correct and error responses.

*Based on 16 responses.

TABLE 6.

MEANS FOR CORRECT AND ERROR REACTION TIMES: NORMAL AND SCHIZOPHRENIC SUBJECTS IN REGULAR AND INCONGRUOUS SUPERORDINATE CONDITIONS

Condition	NORMAL		SCHIZOPHRENIC	
	Correct x	Error x	Correct x	Error x
Regular[a]	780	972	1020	1167
Incongruous[b]	758	825	1020	1104

Note: n = 10.

[a] = Regular Superordinate Categorization.
[b] = Incongruous Superordinate Categorization.
x = Mean reaction time in milliseconds.

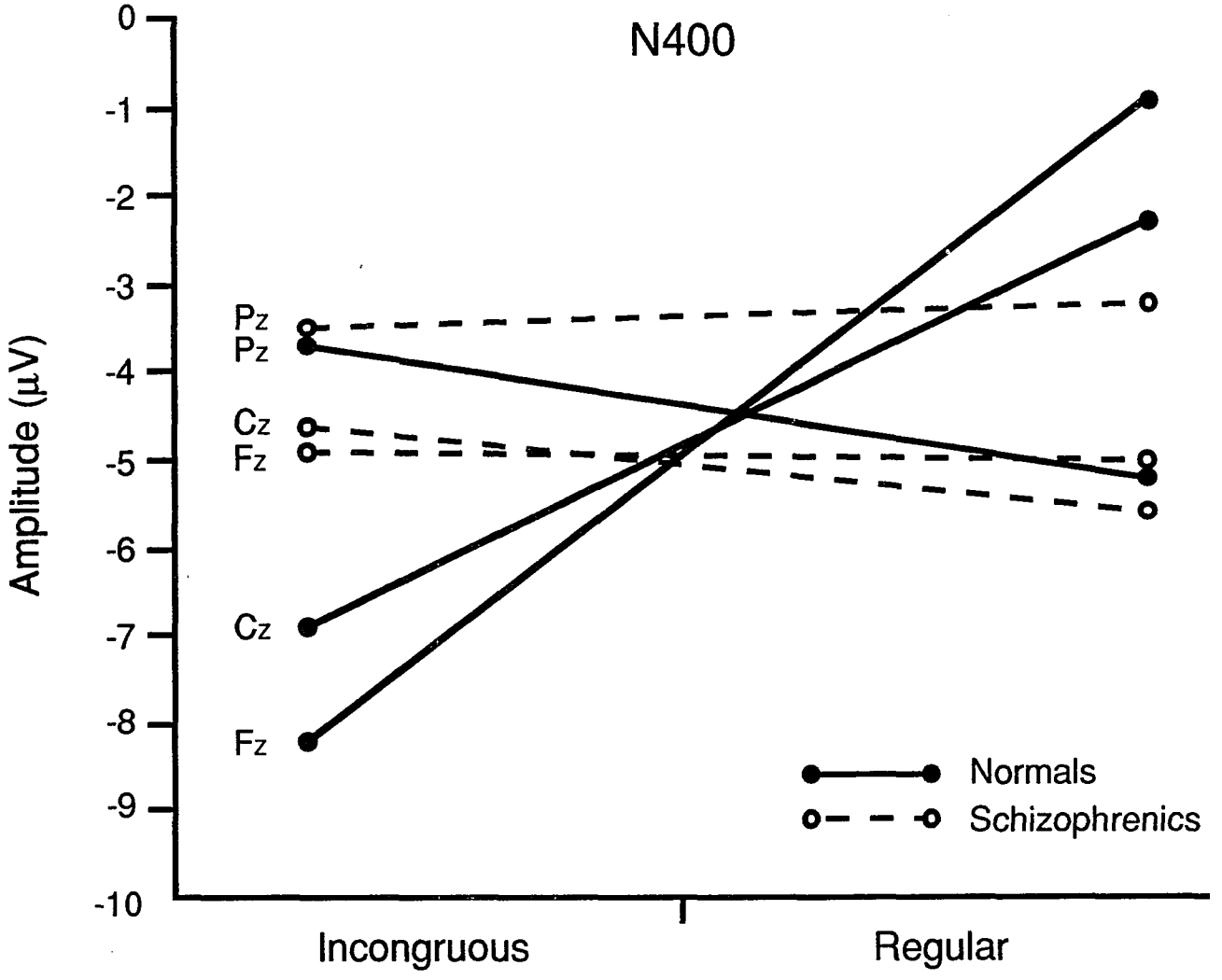

Figure 1: Comparison of Normals and Schizophrenics in Incongruous and Regular Superordinate Conditions

CHAPTER V

GENERAL CONCLUSIONS

Although EP studies of schizophrenia have made significant contributions to the literature (Shagass, 1983; Pritchard, 1986; Holzman, 1987), few studies have investigated ERPs and cognitive dysfunction in schizophrenia (e.g., Pfefferbaum, et. al, 1989). Understandably, the current direction of evoked brain response research is toward the development of cognitive paradigms that can be used to study ERPs and cognitive dysfunction in schizophrenia (Donchin and Bashore, 1980; Fenton, 1980; Begleiter and Porzjez, 1984; Pritchard, 1986; Mirsky and Duncan, 1987). The lack of research in this area, moreover, stands in sharp contrast to a significant literature on ERPs and cognition in normals where, in the emerging field of cognitive psychophysiology, ERPs are considered markers of specific stages of information processing (Rockstroh, Elbert, Birbaumer, and Lutzenberger, 1982; Mirsky and Duncan, 1986). Several ERP components that are purported to be markers of information processing include: N100 (stimulus feature encoding), P200 (stimulus recognition and storage), P300 (cognitive updating), and N400 (semantic incongruity).

Given this background, the studies in the preceding chapters were part of a programmatic research design in which the general aim was to determine whether there was a correspondence between changes in the brain's electrical activity and cognitive dysfunction in schizophrenia. The three studies were based on a newly-developed

cognitive psychophysiological paradigm in which the level of cognitive complexity increased with each study, so that each study was a logical extension of the one that preceded it. The increase in cognitive complexity progressed from simple semantic discrimination of female/male names in Chapter II, to more complex discrimination between abstract and concrete categories in Chapter III, to the most complex discrimination between incongruous and congruous categories in Chapter IV. The following discussion recapitulates the main findings, their implications, and directions for future research.

The study in Chapter II was based on the P300 literature in schizophrenia. Schizophrenic subjects have typically shown a robust P300 phenomenon, namely when compared to normals, they show a reduced P300 in response to auditory oddball stimuli (Roth and Cannon, 1972; Levit, Sutton, and Zubin, 1973; Verleger and Cohen, 1978; Roth, Horvath, Pfefferbaum and Koppel, 1980; Baribeau-Braun, Picton, and Gosseline, 1983; Brecher and Begleiter, 1983; Shagass, 1983; Duncan-Johnson, Roth, and Koppel, 1984; Morihisa, Duffy, and Wyatt, 1983; Morstyn, Duffy, and McCarley, 1983; Duncan, Perlstein, and Morihisa, 1987; Faux, Torello, McCarley, Shenton, and Duffy, 1987; Faux, Torello, McCarley, Shenton, and Duffy, 1988). Most of these P300 data have resulted from paradigms in which attentional/perceptual tasks were used. The specific aim of the study in Chapter II, therefore, was to determine whether in response to visual-semantic oddball stimuli, schizophrenics would show P300 reductions similar to the attenuations they've shown in response to perceptual oddball stimuli. The results were in the expected direction. Schizophrenic subjects showed a reduced P300 to the rare, semantic stimuli. In addition, they also showed a lower P200 and N100 to the target stimuli. The main finding in Chapter II, therefore, shows that P300 amplitude differences between schizophrenic and normal subjects can be replicated with discrimination tasks that engage visual-semantic stimuli.

In contrast to the simple categorization stimuli that were presented in Chapter II, the study in Chapter III was more complex; it was based on three conceptual underpinnings: 1) the abstract-concrete view of thought disorder in schizophrenia, 2) categorization research, and 3) ERP research. An S1-S2 semantic categorization paradigm was used to test two hypotheses, which predicted that schizophrenics would choose concrete thinking responses more often than normals when abstract responses were required, and that schizophrenics would show reduced ERP amplitudes compared to normals in the abstract and concrete conditions. The first hypothesis was supported. Schizophrenics did choose concrete responses significantly more often than normals. These behavioral results support the classic abstract-concrete view of thought disorder in schizophrenia, a view which posits that schizophrenics suffer from an impairment in abstract thinking and rely on concrete thinking (Benjamin, 1944; Goldstein, 1944; Vygotsky, 1962; Arieti, 1974; Harrow, Adler, and Hanf, 1974; Harrow and Quinlan, 1985). However, the second hypothesis was not supported; there were no between group differences or condition differences for P200 or P300. Furthermore, in contrast to the P300 increase that normals showed in the paradigm in Chapter II, which was based on an expectancy of oddball stimuli, normals did not show any P300 differences to the abstract-concrete stimuli in Chapter III. Rather, normals showed lower P300 amplitudes in response to these more complex stimuli than to the simpler stimuli in Chapter II.

There were several interesting results, however, that schizophrenic subjects showed for the N100 peak. First, schizophrenics generally showed more N100 activation than normals in both the abstract and concrete conditions. And second, schizophrenic subjects showed greater N100 activation when they slipped to concrete thinking compared to when they did not. When the N100 data for Chapter II and III are compared, the results are different. Schizophrenic subjects showed an N100 increase when more complex processing was needed to differentiate abstract-concrete stimuli, whereas when they showed no N100 increase when expectancy was used to differentiate

oddball semantic stimuli. The normals, on the other hand, did not show an increase in N100 in either paradigm. One implication of this difference is that schizophrenics do not show early processing effects when expectancy (Chapter II) is a variable, but do show differences when complex semantic processing is a variable (Chapter III). Furthermore, when compared to the lack of N100 increase that normals showed, the N100 increase in schizophrenic subjects is an inappropriate response. It suggests that, when faced with complex semantic stimuli, schizophrenic subjects use early attentional resources, which might significantly contribute to the thought disorder they often show, e.g., an impairment in abstract thinking. In contrast to the unexpected N100 findings, the behavioral data for schizophrenics (number of correct responses) reflect a pattern consistent with reports in the literature, that they make fewer correct responses than normals (e.g., Chapman and Chapman, 1973). In sum, the data in Chapter III indicate that there are ERP and behavioral correlates of abstract and concrete thinking in schizophrenia that are elicited in response to abstract-concrete stimuli. These findings, suggest that for schizophrenic subjects, cognitive processing of complex semantic stimuli has an effect on attention (an increase in N100), an effect that does not occur when perceptual processing is based on an expectancy of oddball stimuli (no increase in N100).

Finally, there is a growing body of research on a relatively new ERP component, the N400. The N400 has been shown to index semantic incongruity in sentence-reading paradigms (Kutas and Hillyard, 1980a, 1980b, 1980c; Polich, 1985). In contrast to the large P300 literature in schizophrenia, few studies have investigated N400 in schizophrenia (Adams, Faux, McCarley, Marcey, and Shenton, 1989). The two aims in Chapter IV, therefore, were to see whether normals would show greater N400 differences to the incongruous condition, and to see whether schizophrenics would show attenuated N400 differences compared to normals. The S1-S2 semantic categorization paradigm, which was used to determine whether subjects would show N400 differences

to categorization incongruities, generally showed effects in the expected direction. Normals showed greater N400 activation to the incongruous category members than to the congruent category members. And when compared to normals, schizophrenic subjects showed less negativity in N400 than normals in response to the incongruous condition. An additional finding in this study was that schizophrenics showed little N400 change between conditions compared to the differential effects that normals showed. Generally, these findings are consistent with the N400 literature on normals (Kutas and Hillyard, 1980a, 1980b, 1980c; Polich, 1985), and with the data on schizophrenics (Adams et al., 1989). Another finding that emerged in this study was that schizophrenics showed an opposite N400 effect compared to normals; they showed a lack of N400 activation to the incongruous condition. If, as the data on normals suggest, an increased N400 indexes semantic incongruity, and schizophrenics showed no N400 difference, they may not have processed the incongruous category members in the same way as normals did. Since schizophrenic subjects were engaged by the tasks (based on their correct behavioral responses), the lack of N400 activation does not indicate a lack of response. Rather, this lack could be an ERP difference that reflects a difference in cognitive strategy for schizophrenics, and also that in response to complex semantic processing, schizophrenics show later cognitive deficits. Furthermore, the failure to show a response in a later ERP component, the N400, might be linked to the slippage to concrete thinking and the increase in N100 that schizophrenic subjects showed in the study in Chapter III. That is, schizophrenics' use of early attentional resources could have the effect that resulted in later cognitive deficits. In short, the lack of N400 activation to the incongruous condition suggests that schizophrenics used different cognitive processing than normals whose N400 was activated in response to category incongruity.

The data from these three studies can be grouped into six main findings for normal and schizophrenic subjects. First, normals showed a significant increase in P300

amplitude in response to visual-semantic oddball stimuli in Chapter II (rare stimuli). And, when compared to normals, schizophrenic subjects showed a reduced P300 to the rare stimuli, a finding that was predicted based on P300 data from perceptual oddball studies. Second, in response to the more complicated S1-S2 semantic categorization tasks in Chapter III (which required behavioral responses [a button press]), the two unexpected findings that emerged for schizophrenic subjects were that they demonstrated more N100 activation than normals in both conditions (abstract and concrete), and that they showed a larger N100 when they slipped to concrete thought compared to when they did not. Third, the data from Chapter III indicated that schizophrenics also showed behavioral impairments in abstract thinking and a reliance on concrete thinking compared to normals who showed no impairment (Benjamin, 1944; Goldstein, 1944; Vygotsky, 1962; Arieti, 1974; Harrow, Adler, and Hanf, 1974; Harrow and Quinlan, 1985). Fourth, in the most complex categorization condition in Chapter IV, normals showed more N400 activation in response to the incongruous category condition than to the regular. Fifth, in comparison to normals, schizophrenics showed a reduced N400 in the incongruous category condition. And sixth, schizophrenics showed little change in N400 between the incongruous and regular conditions.

The newly-developed cognitive psychophysiological paradigm that was used in these studies provided a structure in which the cognitive complexity increased with each successive study. And, as the data in Chapters II, III, and IV indicate, this paradigm was successful in eliciting the expected effects. Furthermore, the findings for normals can be viewed as a template against which to compare the data for schizophrenic subjects. The data from these studies can also be viewed as a whole or as separate phenomena. From the perspective of separate studies, normals showed significant differential effects in P300 and N400, whereas schizophrenic subjects showed attenuated amplitudes in these components when compared to normals. As a whole, schizophrenic subjects showed

ERP and behavioral correlates of cognitive dysfunction compared to normal subjects who showed ERP effects that resulted from specific cognitive manipulation.

Another strength of this cognitive psychophysiological paradigm is that the conditions of each study clearly determined the results that emerged. The studies in Chapter II and IV, which were designed to affect P300 and N400, resulted in expected effects. Normals showed significant P300 and N400 differences to the target stimuli in contrast to the schizophrenic subjects who showed reductions. On the other hand, the S1-S2 abstract-concrete categorization paradigm in Chapter III resulted in mixed findings. There were significant behavioral effects, but no differential effects for the later ERP components. However, the N100 findings in this study, namely that schizophrenic subjects showed a larger N100 in both conditions, and especially when they slipped to concrete thinking, were unexpected and intriguing. These data suggest that N100 may be an ERP correlate of concrete thinking in schizophrenia. Thus, in light of the recommendation to develop cognitive psychophysiological paradigms to study ERPs and cognitive dysfunction in schizophrenia, this paradigm not only elicited the predicted P300 and N400 effects for normals and schizophrenics, but it also elicited robust behavioral effects and several unexpected N100 effects for schizophrenics.

With the caution that these studies were based on a small sample size, a limited number of electrodes, and a select group of schizophrenic subjects, these data point to several implications. That schizophrenics were able to perform the behavioral tasks indicates that they were not as cognitively impaired as many studies of schizophrenia have reported. However, because most ERP studies of schizophrenia have usually used simple perceptual tasks, these data may have resulted from simply using a more complex paradigm, i.e., as tasks become more complicated, schizophrenics may show later deficits. Thus, this paradigm may be useful to determine whether schizophrenic subjects show discrete deficits evident at particular stages of the disorder. However, it needs to be kept in mind that this paradigm was used with a group of patient subjects who were

young, had been recently diagnosed, and had a relatively high I.Q.. In sum, schizophrenic subjects were able to complete the behavioral tasks; they showed more errors and responded more slowly than normals; and they did not show early N100 deficits in response to complex cognitive stimuli, but did show later deficits in P200 and P300.

In conclusion, while it is important to determine whether these results can be replicated with a larger number of subjects. these data clearly demonstrate that research into cognitive dysfunction and ERPs in schizophrenia using a cognitive psychophysiological paradigm is a viable and justified endeavor. Because the paradigms used in these studies were generally successful and resulted in several intriguing findings, cognitive psychophysiology is an area that needs further exploration; similar paradigm need to be developed to use as tools for ERP studies of thought-disordered and non-thought-disordered schizophrenics. Furthermore, in light of the continuing difficulties in the psychiatric diagnosis of schizophrenia and the problematic attempts to relate early, exogenous components to schizophrenia, a paradigm similar to the one used in these studies might prove useful as a diagnostic tool in schizophrenia as well as in other patient populations. That is, subjects might be subdivided on the basis of their ERPs and the presence of thought disorder rather than on psychiatric diagnosis (Donchin and Bashore, 1980; Pritchard, 1986; Duncan, Perlstein, and Morihisa, 1987). These results further suggest that the paradigms used in these three studies could provide prototypes for future ERP research, not only to study cognitive dysfunction in schizophrenia, but also to provide more objective measures of thought disorder in schizophrenia and other psychiatric groups. Finally, complex cognitive paradigms might also prove clinically useful, not only in diagnosis, but in the evaluation of the effects of various treatment modalities.

APPENDIX A

Category Lists

Regular Superordinate

Animal	**Animal**	**Clothing**	**Clothing**
bear	fox	pants	coat
lion	fox	skirt	shoe
bear	pig	skirt	shoe
Fruit	**Fruit**	**Furniture**	**Furniture**
pear	grape	couch	table
plum	peach	bench	chair
plum	peach	bench	table
Tool	**Tool**	**Toy**	**Toy**
pliers	drill	ball	bike
chisel	vise	ball	bike
pliers	drill	sled	doll
Vegetable	**Vegetable**	**Vehicle**	**Vehicle**
corn	beans	boat	bus
peas	beans	boat	bus
corn	carrot	train	car

Incongruous Superordinate

Animal	**Animal**	**Clothing**	**Clothing**
shoe	desk	pants	coat
deer	lion	pants	lamp
deer	lion	sugar	coat
Fruit	**Fruit**	**Furniture**	**Furniture**
orange	moon	belt	chair
orange	pear	desk	chair
river	pear	desk	braid
Tool	**Tool**	**Toy**	**Toy**
drill	saw	doll	sled
dream	egg	hawk	sled
drill	saw	doll	pear
Vegetable	**Vegetable**	**Vehicle**	**Vehicle**
corn	carrot	ice	train
lock	eraser	bus	train
corn	carrot	bus	mouth

Regular Concrete

Ball	**Bear**	**Car**	**Cat**
ball	bear	car	ear
game	bear	seat	cat
ball	paw	car	cat
Celery	**Chair**	**Corn**	**Fork**
leaves	rung	corn	fork
celery	chair	husk	tong
celery	chair	corn	fork
Lamp	**Milk**	**Pants**	**Pepper**
cord	milk	cuff	pepper
lamp	milk	pants	pepper
lamp	glass	pants	shaker
Piano	**Sugar**	**Tea**	**Wagon**
piano	sugar	bag	wagon
piano	sugar	tea	wheel
bench	bowl	tea	wagon

Match Concrete

Apple	**Bear**	**Bed**	**Bus**
apple	bear	bed	bus
apple	bear	bed	bus
apple	bear	bed	bus
Cup	**Daisy**	**Dog**	**Dress**
cup	daisy	dog	dress
cup	daisy	dog	dress
cup	daisy	dog	dress
Flute	**Onion**	**Pear**	**Pliers**
flute	onion	pear	pliers
flute	onion	pear	pliers
flute	onion	pear	pliers
Rose	**Sled**	**Spoon**	**Table**
rose	sled	spoon	table
rose	sled	spoon	table
rose	sled	spoon	table

APPENDIX B

Protocol

Initial Criteria

1. Explanation of study to subject
2. Preliminary checklist (Right-Hand only)
3. Consent form
4. Handedness questionnaire

Diagnostic Criteria

5. SADS interview (RDC diagnosis)
6. MMPI

Histories

7. Medication history I and II
8. Demographics
9. Previous treatment history

Thought Disorder and I.Q. Indices

10. WAIS-R Vocabulary
11. WAIS-R Comprehension
12. Benjamin Proverbs Test
13. Object Sort Test

Miscellaneous

14. Special Details Checklist
15. Medications Checklist

Laboratory Procedures

16. BPRS
17. Subject to lab
18. STAI administration
19. Vision Check
20. Lab Subject Checklist
21. Equipment Checklist
22. Electrode Application
23. Experimental Procedures
24. Electrode Removal
25. STAI Administration
26. Debriefing

(Printed materials used in this thesis are available upon written request.)

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