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P50 abnormalities in schizophrenia: relationship to clinical and neuropsychological indices of attention

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Abstract

While the P50 component (50–60-ms latency) of the auditory evoked potential has been reported as abnormal in schizophrenia, few studies have examined the relationship between this abnormality and clinical or neuropsychological measures. To examine these possible relationships, mid-latency auditory evoked potentials were recorded at the CZ recording site of 47 patients with schizophrenia in response to binaural clicks presented at three stimulus rates: 1, 5 and 10/sec. A sub-sample of patients were then divided into high- ($n=15$) and low-P50 abnormality ($n=16$) groups based on a median split of the P50 amplitude at a rate of 10/sec (a greater amplitude at this rate suggests a greater abnormality in recovery) of the entire sample. Only those patients with complete neuropsychological and clinical data and who were reasonably matched on demographic dimensions were included. A multivariate analysis of variance of 11 neuropsychological function profile scores showed a significant group × global score interaction (Hotelling $t=3.97$, $p<0.005$). The high-abnormality group had relatively greater deficits for attention profile scores than for the remaining neuropsychological measures. An analysis of global subscores for SAPS and SANS clinical measures revealed a significant difference only for the SANS attention subscale ($p<0.05$). The high-abnormality group was rated as more severe on the attention measure. These convergent findings across both phenomenological and neuropsychological measures suggest that abnormalities in P50 recovery may be linked to deficits in attention processes in schizophrenia.

Keywords: P50; P1; Attention; Schizophrenia; Auditory; Evoked potentials

1. Introduction

The recovery cycle of the P50 component (50–70-ms latency) of the mid-latency auditory evoked potential (MAEP) has been reported as abnormal in schizophrenia by a number of investigators [see Freedman et al. (1991) for a review]. This abnormality consists of a lack of suppression of the P50 when auditory stimuli are presented close together in time using either a paired stimulus [pairs of stimuli with a brief interstimulus interval (500 ms) and a long intertrial interval (10 s)] or a stimulus train (stimuli presented at constant rates) protocol. Recent evidence suggests that this abnormality is a possible marker of a genetic defect in schizophrenia (Freedman et al., 1997). However,

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relatively little is known about the relationship between this abnormality and clinical and neuropsychological deficits in these patients.

Initial studies, using paired stimulus protocols, did not find any relationship between P50 abnormalities in schizophrenia and clinical measures (Adler et al., 1982; Freedman et al., 1983; Baker et al., 1990), suggesting that the abnormality was a trait deficit. Studies in our laboratory (Erwin et al., 1991, 1994), using the stimulus train method, showed P50 abnormalities similar to those reported by Freedman and colleagues, although the abnormalities appeared more variable and sensitive to the effects of medication exposure (Erwin et al., 1994). These findings suggested that our protocols, which also employed different filter settings and ISIs than Freedman et al., were tapping into mechanisms that reflected relatively greater state deficits rather than trait deficits in schizophrenia. Consistent with this, we initially reported (Erwin et al., 1991) that a lack of P1 amplitude suppression was positively correlated with an index of symptoms relatively more specific to schizophrenia derived from the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham, 1980). However, we were unable to replicate this finding in a more recent study (Erwin et al., 1994). While these findings suggested that the relationship between P50 abnormalities and phenomenological measures was weak or perhaps non-existent, it may be that a specific dimension of symptomatology is more strongly associated with P50 abnormalities in schizophrenia.

One dimension of symptomatology that might be predicted to be associated with P1 amplitude is attention. Several studies have reported that patients with schizophrenia have attentional deficits related to vigilance, selective attention, attention switching and visual orienting [for reviews, see Gold and Harvey (1993) and Nuechterlein and Dawson (1984)]. Some have related deficits to clinical phenomenology (Ward et al., 1991) and to medication status (Harvey et al., 1990). In addition, attentional deficits have been observed in childhood schizophrenia (Strandburg et al., 1990) and in children at risk for schizophrenia (Schreiber et al., 1991, 1992). More recent work has suggested left hemisphere dysfunction in attentional processes in schizophrenia (Posner et al., 1988; Nestor et al., 1992).

Studies examining the effect of directly manipulating attention on P50 amplitude or suppression have reported mixed findings. Some studies found no effects on P50 amplitude or suppression (Waldo and Freedman, 1986; Jerger et al., 1992), whereas others reported a lack of supression to the second stimulus during attention tasks (Guterman et al., 1992). The primary methodological difference across these studies was the salience of the auditory stimuli to the tasks designed to engage attention. In the former studies, the second click (paired stimulus protocol) was either not salient (Waldo and Freedman, 1986), or was only minimally salient (i.e. detection of presence or absence; Jerger et al., 1992). In contrast, the second click was highly salient (detection of frequency difference during task conditions) in the Guterman et al. (1992) study. Thus, it appears that attentional manipulation can effect the suppression of the P50 to the second stimulus in normals but only when it is highly task-relevant. In patients with schizophrenia, abnormalities in P50 suppression have been positively correlated with deficits on neuropsychological measures of attention, including the digit span test of the WAIS-R (Wechsler, 1981), but not measures of verbal learning or memory (Cullum et al., 1993). All of the above studies used paired stimuli protocols. To our knowledge, no studies have examined the relationship between attention and P50 suppression measured using stimulus train protocols.

The purpose of the present study was to examine the relationship between phenomenological and neuropsychological measures and P50 abnormalities in schizophrenia assessed by stimulus train protocols. It was hypothesized that when patients were divided into high- and low-P50 abnormality groups, the high-abnormality group would show relatively greater and selective deficits on phenomenological and neuropsychological indices of attention.

2. Methods

2.1. Subjects

The initial sample consisted of 46 patients with the diagnosis of schizophrenia recruited through

the Mental Health Clinical Research Center in the Department of Psychiatry at the University of Pennsylvania. Participants underwent a medical, neurological and psychiatric evaluation using standard assessment procedures. The Structured Clinical Interview (SCID; Spitzer et al., 1994) was administered. All patients met DSM-IV criteria for schizophrenia. Participants had no other neurological or psychiatric history. Additional exclusion criteria were: significant visual or auditory impairment, history of head trauma with loss of consciousness, presence or history of substance abuse by DSM-IV criteria (assessed by SCID and toxic screen), previous electroconvulsive therapy, presence or history of any neurologic disease, age <18, pregnancy, and English not a native language. All patients were either neuroleptic-naïve or off medication for a minimum of 2 weeks prior to all assessment procedures. None of the previously medicated patients was on depot neuroleptics prior to cessation of medication. The patient sample included the subjects used in the Erwin et al. (1991, 1994) studies. Informed consent was obtained from all subjects prior to study.

2.1.1. Definition of high- and low-P50 abnormality groups

Patients were divided into low- and high-abnormality groups based on P50 amplitude at the 10/sec rate (a greater amplitude at this rate suggests a greater abnormality in recovery) using a median split based on the initial sample of 46 patients. Details of the procedures used to obtain P50 and its measurement are presented below. Of the total sample, both clinical and neuropsychological measures were available for 15 high-abnormality and 16 low-abnormality patients balanced as closely as possible on demographic dimensions (Table 1). Consistent with our previous report of greater P50 recovery abnormalities for neuroleptic-naïve patients, the high-abnormality group had a greater percentage of neuroleptic-naïve patients (47.7%) than the low-abnormality group (25%), although a Fisher's exact test of these data was not significant. For these sub-samples, P50 means and standard errors at stimulus rates of 1 and 10/sec are presented in Fig. 1. For comparison purposes, the same measures from the normal control group ($n=13$) used in the Erwin et al. (1994) study are also presented. Fig. 2 shows the waveforms for high- and low-abnormality groups at stimulus rates of 1 and 10/sec. Similar median splits and analyses as described below were conducted for the baseline (1/sec stimulus rate) and recovery ratio measures. No significant findings across groups based on these latter measures were obtained for either clinical or neuropsychological measures.

2.1.2. Evoked potential recording

MAEP recordings were obtained using a Biologic Systems Corporation Brain Atlas III with amplifier gain settings of 100 000, filter settings of 10–300 Hz (12 dB/octave Butterworth type analog filters) and a sampling rate of 2000 Hz over a

Table 1
Demographic and clinical dimensions for High ($n=15$) and Low ($n=16$) P50 Abnormality Groups

	Low P50 Abnormality	High P50 Abnormality
Age	Mean = 30.5; standard error = 1.9	Mean = 30.9; standard error = 1.5
Sex	Male = 13 female = 3	Male = 11 female = 4
Race	Caucasian = 9; Afro-American = 7	Caucasian = 11 ;Afro-American = 4
Education (years)	Mean = 12.8; standard error = .4	Mean = 13.3; standard error = .4
Parental education	Mean = 12.1; standard error = .4	Mean = 13.4; standard error = .6
Neuroleptic-naïve	4	7
Subtype	Paranoid = 11	Paranoid = 6
	Undifferentiated = 4	Undifferentiated = 7
	Other = 1	Other = 2
Duration of illness	Mean = 8.8; standard error = 1.2	Mean = 7.7; standard error = 1.1
Total BPRS score	Mean = 48.4; standard error = 1.9	Mean = 51.3; standard error = 1.7
Inpatient/outpatient	8/8	8/7

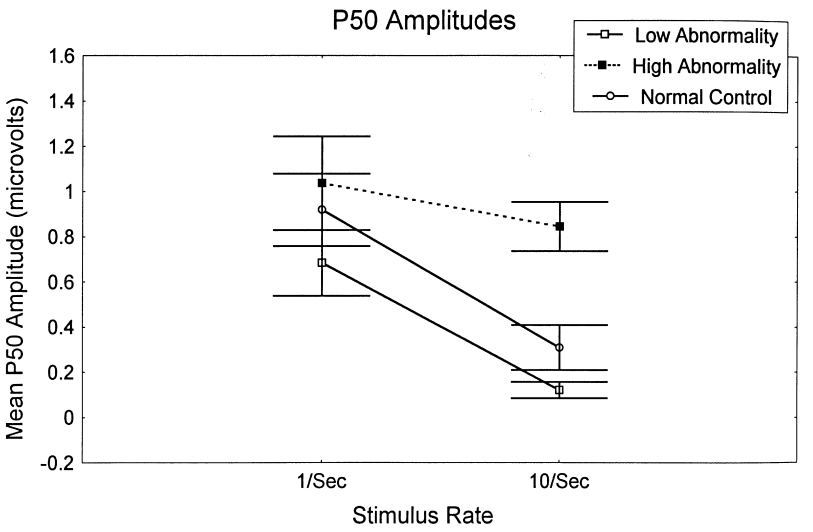

Fig. 1. P50 amplitudes (mean-standard error) for High and Low P50 Abnormality groups at the baseline (1/sec) and recovery (10/sec) stimulus rates. These measures for the normal control group ($n=13$) reported by Erwin et al. (1994) are included for comparison.

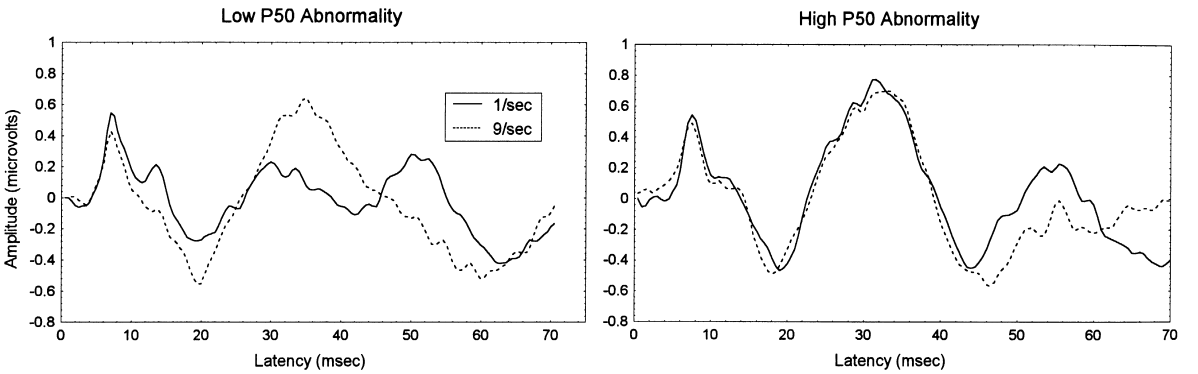

Fig. 2. Grand average waveforms for the High and Low P50 Abnormality groups at the baseline (1/sec) and recovery (10/sec) stimulus rates.

128-ms epoch (28-ms prestimulus). Only vertex recordings (Cz) were examined in this study. Eye movements were monitored using Fp leads and a canthal lead. The reference was linked mandible electrodes. The stimuli used to elicit MAEPs were rarefaction clicks (0.1 ms, 50 dB HL) presented binaurally through TDH headphones. Any single trial MAEP that contained components exceeding 24.5 μV in baseline to peak amplitude was not included in the online average. Six blocks of 250 artifact-free trials were obtained. The first three stimulus blocks consisted of presentation of the click stimuli at three different rates (one rate per 250 trial block): 0.9, 5.1 and 9.9/sec (for clarity, these stimulus rates are referred to as 1, 5 and 10/sec, respectively, in all figures and text). These blocks were presented in a random sequence. The second set of three stimulus blocks consisted of a replication of the first set using a different random sequence of stimulus block presentations. Data obtained across blocks were collapsed, yielding 500 trial averages at each rate.

2.1.3. P50 component measurement

The components selected for analyses were peak-to-peak P50-Nb amplitudes. Pa was considered as a relatively broad positivity (approximately 10 ms in duration) and had peak latencies ranging between 26 and 39 ms following stimulus onset. P1 was the next broad positivity, and its peak latency ranged from 46 to 70 ms. Nb was chosen as the negative deflection between Pa and P1. In cases where P1 disappeared completely at the faster rates of stimulation, the amplitude of Nb was measured at the latency of Nb obtained at the slower rates of stimulation for that subject, and the P1-Nb peak-to-peak amplitude was set to zero. All peak selection was conducted blindly with respect to diagnosis and stimulus rate. Percentage recovery measures for P50-Nb were calculated by dividing the component amplitudes obtained at the 5 and 10/sec conditions by the amplitude obtained for the 1/sec condition. Following Nagamoto et al. (1991), percentages greater than 200% were truncated to 200%.

2.2. Procedures

2.2.1. Neuropsychological and clinical assessment

A battery of neuropsychological tests is administered to all patients and controls studied at the Mental Health Clinical Research Center (MHCRC) at the University of Pennsylvania. The domains evaluated included attention–vigilance, abstraction, verbal intelligence, spatial organization, semantic memory, visual memory, verbal learning, language, visual-motor processing and attention, motor, and sensory functions (Saykin et al., 1991, 1994). For clinical measures, the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984), Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1983) and the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham, 1980) were completed with established procedures (Gur et al., 1991). Neuropsychological and clinical data for each subject in the current analysis were collected within 2 weeks of MAEP testing.

2.2.2. Data reduction and variable computation

For neuropsychological measures, a set of neuropsychological function profile scores based on the above described dimensions were derived and were found to be identical to those described in Saykin et al. (1991), with the exception of an additional sensory profile score and the elimination of a separate auditory score. Raw scores for each individual test were regression-adjusted for age, sex and education based on beta weights derived by the MHCRC neuropsychology core from a normative control sample consisting of 120 normal subjects. These adjusted values were then transformed into *z*-scores using the square root of the error variance derived from the normative control sample. The *z*-scores for individual tests within a profile were then averaged to create the profile scores. For clinical measures, global subscores derived from the SAPS and the SANS were examined. For SAPS, these covered the dimensions of Hallucinations, Delusions, Bizarre Behavior and Thought Disorder. For SANS, the dimensions were: Affect, Alogia, Avolition, Anhedonia and Attention.

2.2.3. Statistical analysis

All statistical analyses were conducted using the Statistical Analysis System (SAS Institute, 1985). Multivariate analyses of variance were used to contrast High and Low P50 Abnormality Groups on both neuropsychological profile scores and SAPS and SANS global ratings. These were followed by planned comparisons of those profile scores and global ratings considered to have attentional components. These included the Attention–Vigilance and the Visual Sensory–Motor and Attention neuropsychological profile scores and the SANS attention global score. Additional analyses, *t*-tests, were then performed on the *z*-scores of the individual measures that comprised the two neuropsychological profile scores. A Bonferonni or other experiment-wise correction was not performed as the *t*-tests were planned directional tests and probably not independent, as most of the measures were thought to measure some aspect of attention. The Attention–Vigilance measure was derived from the following measures of the Gordon Diagnostics version (Gordon, 1986) of the continuous performance test (CPT): vigilance total correct, vigilance

total false positives, distraction total correct and distraction false positives. The Gordon CPT uses a custom apparatus for delivering stimuli and recording responses. The Visual Sensory–Motor and Attention measure comprised: (1) Trail Making A and B (Reitan and Wolfson (1985); (2) Digit Symbol (WAIS-R; Wechsler, 1981); and (3) Stroop (Golden, 1978): Word, Color and Color–Word Interference (a paper–pencil version). The Digit Span Arithmetic Measure of the WAIS-R was also examined as a previous study reported a modest relationship between deficits on this measure and P50 recovery abnormalities (Cullum et al., 1993).

3. Results

Multivariate analysis of variance of the 11 neuropsychological function profile scores showed a significant group × profile score interaction (Hotelling t, $F=3.97$, $p<0.005$). Subsequent planned contrasts revealed that the high abnormality group had significantly greater deficits for the attention ($t=1.98$, $df=29$, $p<0.05$) measure, and a similar trend was observed for the visual sensory motor measure ($t=1.6$, $df=29$, $p=0.055$). These findings are presented in Fig. 3.

The vigilance and distractibility measures of the Gordon Diagnostic Systems version of the continuous performance test (CPT) that comprised the Attention–Vigilance profile score were then examined using t-tests. The high abnormality group had significantly greater deficits for the distraction number correct measure ($t=3.25$, $df=29$, $p<0.01$), and there was a similar trend for the vigilance number correct measure ($t=1.62$, $df=29$, $p=0.06$) (Fig. 4). No differences were found for the false positive measures. Of the measures included in the Visual Sensory–Motor and Attention subscale, significant differences were found only for Trails B (visually connecting ascending numbers and letters in an alternating fashion) of the Trail-making test ($t=1.71$, $df=29$, $p<0.05$), with the high abnormality group again performing worse. A similar trend was observed for the digit symbol test ($t=1.66$, $df=29$, $p=0.06$). These findings are presented in Fig. 5. The trend effects are probably due to a lack of statistical power given the relatively small sample sizes rather

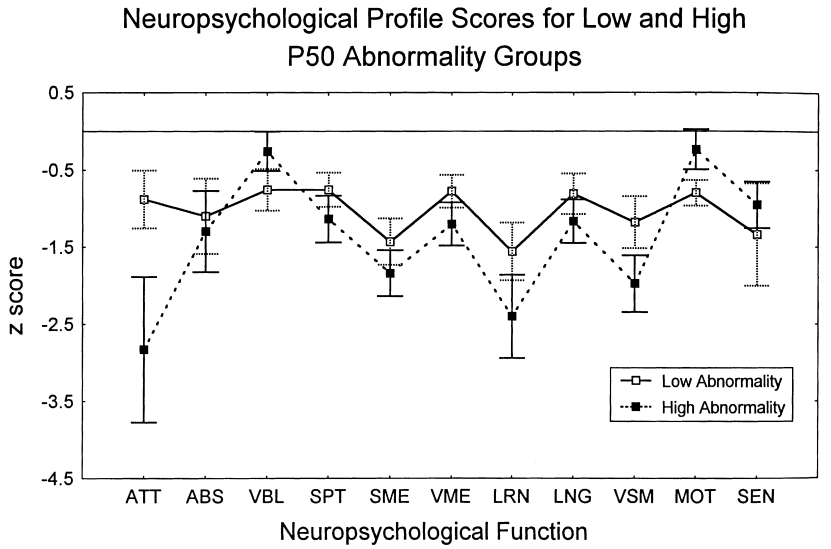

Fig. 3. Neuropsychological profile z-scores (mean-standard error) for High and Low P50 Abnormality groups. The profile function scores were: attention–vigilance (ATT), abstraction (ABS), verbal intelligence (VBL), spatial organization (SPT), semantic memory (SME), visual memory (VME), verbal learning (LRN), language (LNG), visual-motor processing and attention (VSM), motor (MOT), and sensory (SEN).

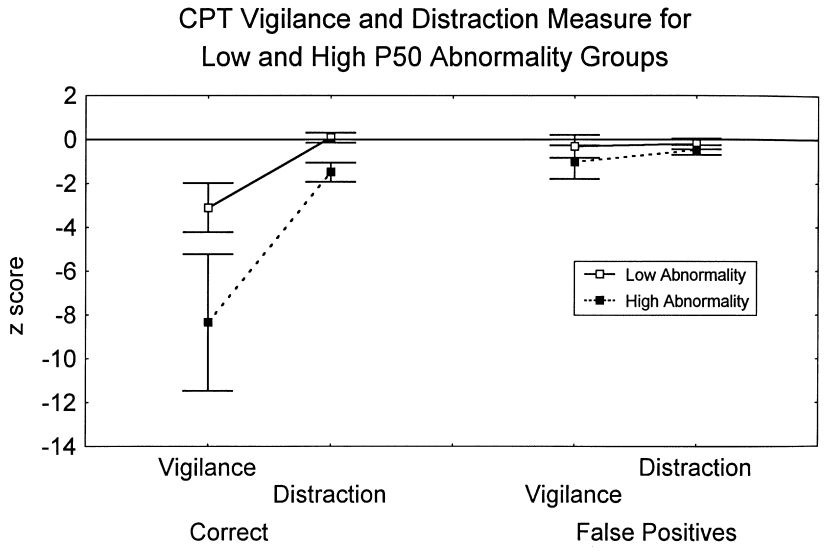

Fig. 4. Individual item *z*-scores (mean-standard error) of the attention/vigilance profile score for High and Low P50 Abnormality groups. These scores, derived from the Gordon Diagnostics Continuous Performance (CPT) task, included: vigilance correct, distraction correct, vigilance false positives and distraction false positives.

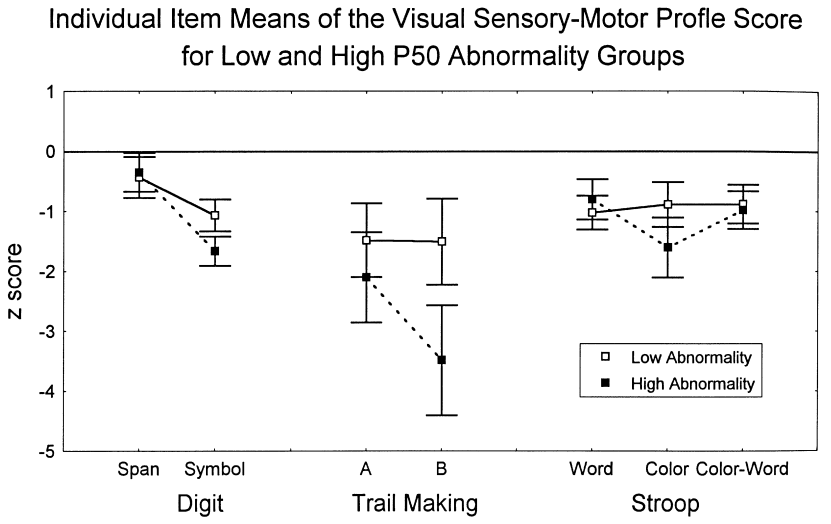

Fig. 5. Individual item *z*-scores (mean-standard error) of the Visual Sensory–Motor and Attention (VSM) profile score for High and Low P50 Abnormality groups. These items included: Digit Symbol from the WAIS-R, Trail Making A and B, and Stroop Word, Color and Color–Word Interference. Digit Span from the WAIS-R is also included although not part of the VSM profile score.

than negative findings. A power analysis in which a moderate effect size of 0.5 is assumed yielded a power of 0.4, which is somewhat low.

A multivariate analysis of global subscores for SAPS and SANS clinical measures did not reveal any significant group main effect or any group by global score interaction. A planned comparison did show a significant difference across groups for the SANS attention subscale ($t=1.85$, $df=29$, $p<0.05$). The High Abnormality Group was rated

as having a greater severity on the attention global measure (Fig. 6).

Exploratory analyses using Spearman rank order correlations were conducted to examine the relationship between neuropsychological and clinical measures of attention. The SANS global attention score was correlated with the z-transformed neuropsychological tests scores for CPT vigilance, CPT distraction, Digit Symbol and Trails B both across High and Low Abnormality Groups and within each group. The only neuropsychological measure that was significantly correlated with the SANS global attention score in overall analyses was Trails B ($r=-0.44$, $p<0.05$). A greater severity of attention as assessed by the SANS was negatively related to Trails B performance. When the correlations were performed for each group separately, this relationship was only observed in the High Abnormality Group ($r=-0.58$, $p<0.05$). Again, no other significant correlations were obtained.

4. Discussion

These convergent findings across phenomenological and neuropsychological measures suggest that abnormalities in P50 recovery may be linked to deficits in attention processes in schizophrenia. Patients with greater lack of supression at a 10/sec stimulus rate showed greater deficits in attention as assessed by both phenomenological and neuropsychological indices. Neuropsychological deficits were greatest for vigilance as assessed by the Gordon Diagnostics version of the CPT and for attention switching as measured by Trails B.

The present findings are consistent with the findings of Cullum et al. (1993) in that P50 recovery abnormalities were associated with greater deficits on neuropsychological measures of attention and not learning and memory. However, it is unclear why P50 recovery deficits were not linked to poorer digit span performance as suggested by the findings of Cullum et al. (1993). Differences in protocol used [stimulus train in the present study, paired stimuli in Cullum et al. (1993)], interstimulus interval [100 ms in this study, 500 ms in Cullum et al. (1993)] or subject composition may have accounted for these somewhat divergent findings. Also, no linkage between P50 abnormalities and attention was obtained when using the recovery measure commonly employed in P50 studies such as that of Cullum et al. (1993). One possibility is that the baseline P50 measure (1/sec rate) used in the present study did not allow the full P50 amplitude to be expressed (Zouridakis

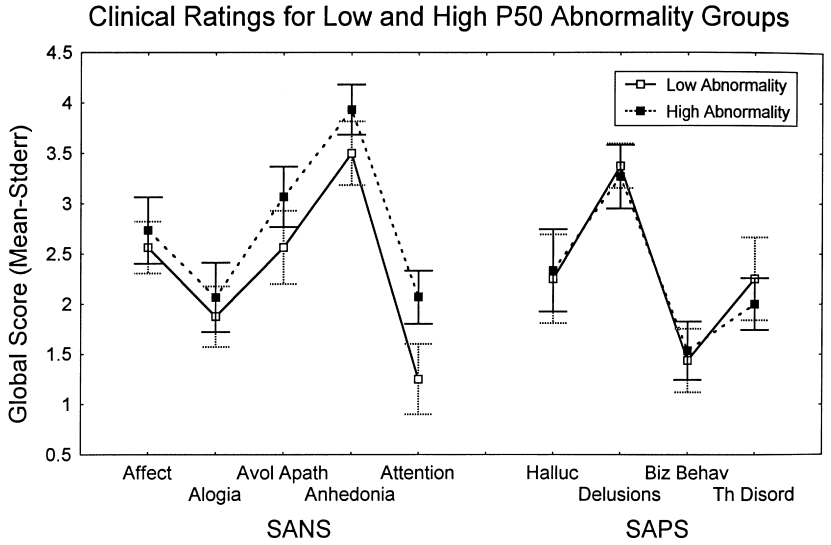

Fig. 6. Global ratings (mean-standard error) for the SANS and SAPS subscales for High and Low P50 Abnormality groups.

and Boutros, 1992) and may have obscured findings. Alternately, the present findings were based primarily on neuropsychological measures of attention in the visual modality, and it may be that auditory attention measures would show stronger effects and perhaps be associated with recovery ratio measures. Another possibility is that the short interstimulus interval and perhaps the stimulus protocol (stimulus train) used in the present study may engage different underlying neuronal mechanisms from the paired stimulus protocol with a longer interstimulus interval. Nagamoto et al. (1991) suggest that deficits in recovery observed at short interstimulus intervals may reflect a dysfunction in noradrenergic and gabaergic mechanisms rather than the cholinergic mechanisms that are associated with trait-like recovery deficits in schizophrenia when longer interstimulus intervals are used. However, pharmacological studies in both the human and the animal model with both the stimulus protocol and short interstimulus interval used in the present study are needed before any definitive statements regarding separate neuronal mechanisms and possible deficits can be made.

Whereas a strong relationship between clinical and neuropsychological measures of attention was not obtained, a modest relationship was found with Trails B for the High Abnormality group. Individual variability within groups and differences in scaling across measures probably contributed to the overall findings. Also, the neuropsychological measures were corrected for several demographic characteristics based on a normative sample. The present findings are also somewhat inconsistent with Adler et al. (1990b), who reported that Trails B measures distinguished negative symptom patients from positive symptom patients (greater deficits for negative symptom patients), whereas P50 measures were consistently abnormal. However, Adler et al. used the paired stimuli protocol and a longer interstimulus interval than the present study. The P50 recovery measures in the present study appear to be more state-like and sensitive to the presence of attentional deficits. This is consistent with the notion of different neuronal mechanisms responsible for recovery being engaged at shorter interstimulus intervals.

It is possible that the state-like deficits in P50 suppression observed in this study may be nonspecific as state deficits in P50 abnormalities have been reported for other clinical conditions such as depression (Adler et al., 1990a). It is important to note, however, that state deficits do not equate to lack of specificity, and P50 abnormalities may not be associated with attentional dysfunction in other clinical populations.

The linkage between P50 suppression and attention does not necessarily mean that P50 suppression as assessed by this protocol directly reflects attentional processes. In this study, attentional deficits were associated with an increase in amplitude of a potential. This is typically the opposite of what is reported in the evoked and event-related potential literature [i.e. decreases in attention are associated with decreases in evoked potential component amplitudes; e.g. Woldorff and Hillyard (1991)]. It may be that P50 suppression reflects pre-attentive processes that adversely impact attentional processes when dysfunctional. However, this possibility does not negate evidence that manipulating attention by changing stimulus saliency modifies P50 amplitudes (Guterman et al., 1992).

Specific delineation of the mechanisms that underlie the psychological construct of attention is problematic. Numerous taxonomies have been proposed (e.g. Posner and Boies, 1971; Mirsky, 1987; Posner and Petersen, 1990) and have included processes such as alerting/vigilance, selective attention, processing capacity and orienting/attention shifting. While the rationale for some dimensions are based on observed linkages between specific aspects of attention and neuroanatomic and neurophysiologic measures [see Posner and Petersen (1990) for a review], it remains unclear as to whether these are general divisions that cut across all forms of psychological processes or reflect mechanisms applicable only to specific neurobehavioral operations. Equally difficult is the development of tasks that measure unitary dimensions of attention and are not confounded by mediating operations such as memory and the derivation of meaning. The attentional tasks used in this study are relatively gross neuropsychological measures of attention, and measures such as Trails B may involve other psychological

processes (e.g. working memory or executive processes) for which evidence also suggests deficits in patients with schizophrenia (e.g. Weinberger et al., 1986; Park and Holzman, 1992).

Overall, our findings suggest that abnormalities in the gating of sensory information may be related to, and possibly account for, attentional deficits in schizophrenia. However, further investigation is needed to clarify the relationships among these measures, to address the issue of specificity of abnormalities to schizophrenia, to identify underlying neuronal mechanisms and to develop and employ purer, more precisely defined measures of attention that can be examined in relation to psychophysiological measures such as P50. We plan to develop attentional tasks, as well as employ existing tasks (e.g. Cornblatt et al., 1989), that will allow us to obtain more precise quantitative measures of attention and to adapt these tasks in evoked/event related potential protocols in conjunction with P50 protocols. This will allow us to examine potential multistage neural dysfunction in schizophrenia and possible causal relationships among abnormalities. Such studies may provide a greater understanding of the underlying core deficits in brain dysfunction and consequent behavioral abnormalities in schizophrenia.

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