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Clinical Correlates and Neural Substrates of P50 Suppression Deficits in Schizophrenia



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# Clinical Correlates and Neural Substrates of P50 Suppression Deficits in Schizophrenia

A dissertation submitted in partial satisfaction of the requirements for the degree Doctor of Philosophy in Psychology

by

Holly Kendall Hamilton

2015

ABSTRACT OF THE DISSERTATION

Clinical Correlates and Neural Substrates of

P50 Suppression Deficits in Schizophrenia

by

Holly Kendall Hamilton

Doctor of Philosophy in Psychology

University of California, Los Angeles, 2015

Professor Cindy M. Yee-Bradbury, Chair

The present dissertation evaluated the P50 component of the event-related brain potential (ERP), an index of sensory gating measured during a paired-stimulus paradigm, as an intermediate phenotype between clinical symptoms and neuronal mechanisms that might also contribute to higher-order cognitive dysfunction in schizophrenia. Despite considerable evidence that schizophrenia patients exhibit impaired suppression of the P50 to the second of two identical stimuli, the clinical significance and neural mechanisms associated with the P50 gating deficit remain poorly understood. A series of three related studies sought to more fully define the clinical and neurobiological correlates of P50 suppression deficits in schizophrenia. In Study 1, comparison of 52 schizophrenia patients and 41 healthy participants confirmed a P50 suppression deficit in patients, replicating prior research. Investigation of the clinical correlates

of the P50 deficit in patients revealed associations between impaired suppression and clinician ratings of attentional difficulties as well as poor working memory performance. In examining the neural substrates of P50 gating with diffusion tensor imaging, Study 2 found associations between P50 deficits and compromised structural integrity of white matter tracts connecting brain regions previously implicated in the generation of P50 suppression in schizophrenia. Study 3 examined whether P50 impairments are amenable to cognitive training and predictive of treatment outcome. Compared to a control intervention without cognitive targets, patients who completed cognitive remediation demonstrated significant improvements in P50 suppression. Baseline P50 ratios were also predictive of improvement as evidenced by post-treatment clinician ratings and performance on an attention task, thereby indicating that patients with stronger P50 suppression are likely to receive the most benefit from cognitive remediation. All relationships observed in the present set of studies were specific to P50 and did not extend to the N100 component of the ERP. By characterizing the relationship of P50 to clinical symptoms and cognitive dysfunction in schizophrenia, isolating biological mechanisms that might be involved in P50 suppression, and evaluating its amenability to cognitive training, the present dissertation provided support for P50 as a viable biomarker for guiding the development of interventions that target cognitive impairments in this chronic and debilitating mental illness.

The dissertation of Holly Kendall Hamilton is approved.

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2015

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# Chapter 1: General Introduction

Individuals diagnosed with schizophrenia are frequently unable to filter out distracting sensory information and experience difficulties discriminating relevant from unimportant stimuli (Freedman et al., 1996), thereby contributing to the challenges of independent living, work productivity, and social functioning. Abnormalities in attentional and perceptual processes have been a primary focus of research, as disordered cognition is theorized to play a central role in schizophrenia and its positive and negative symptom profiles (e.g., Braff & Geyer, 1990; Grillon, Courchesne, Ameli, Geyer, & Braff, 1990). Compromised sensory gating, which refers to the brain's ability to gate or filter irrelevant sensory input so as to minimize inundation and overload, has been proposed to reflect a fundamental neural deficit that may account for attentional abnormalities in schizophrenia (McGhie & Chapman, 1961; Venables, 1964).

The P50 component of the auditory event-related potential (ERP), a positive peak with a modal latency of 50 milliseconds following stimulus onset, is a widely used neurophysiological measure of sensory gating derived from the electroencephalogram (EEG). It is typically elicited by a paired-stimulus paradigm that involves the presentation of two identical auditory stimuli, separated by 500 milliseconds. In healthy individuals, P50 amplitude to the second stimulus (S2) is suppressed relative to the P50 elicited by the first stimulus (S1), with S1 triggering an inhibitory mechanism to minimize interference from S2. Using a ratio score of S2/S1 as a measure of the degree of P50 suppression, patients with schizophrenia generally exhibit significantly higher suppression ratios than healthy individuals, reflecting impaired sensory gating (for reviews, see Freedman et al., 1987; Leonard et al., 1996; Patterson et al., 2008). The observed lack of an inhibitory influence of S1 on the S2 response is widely postulated to reflect schizophrenia patients' difficulties in filtering responses to exogenous sensory perceptual

information as well as internally generated stimuli (Braff, Grillon, & Geyer, 1992), and may contribute to patients' reported sense of being constantly overwhelmed (e.g., Yee, Nuechterlein, Morris, & White, 1998).

*P50 Suppression Deficits in Schizophrenia*

Differences in P50 suppression ratios between schizophrenia patients and healthy individuals have been consistently and reliably reported. Meta-analyses reveal a robust effect size of 1.55 for the P50 deficit, exceeding many other cognitive and neurobiological abnormalities in schizophrenia (Bramon, Rabe-Hesketh, Sham, Murray, & Frangou, 2004; Heinrichs, 2001). In the most recent meta-analysis, Patterson et al. (2008) found that 45 of 46 published group comparisons of schizophrenia patients versus healthy controls demonstrated a significantly larger P50 ratio score in the patient group. Additionally, there is some evidence that P50 amplitude to S1 may be reduced relative to that of healthy control participants (e.g., Adler et al., 1982; Boutros, Zouridakis, & Overall, 1991; Freedman, Adler, Waldo, Pachtman, & Franks, 1983). In their meta-analysis, Patterson et al. rejected the null hypothesis of zero difference in S1 P50 amplitude between schizophrenia patients and healthy controls. However, 25 of the 37 studies included in the analysis overlapped the 0 difference line, suggesting that the P50 suppression ratio may differentiate schizophrenia and healthy comparison participants more effectively than S1 P50 amplitude.

The P50 sensory gating deficit has been observed in both unmedicated schizophrenia patients (e.g., Adler et al., 1982) and those stabilized on traditional antipsychotic medications (e.g., Boutros et al., 1991). In a direct comparison, Freedman et al. (1983) reported that P50 suppression ratios did not significantly differ between medicated and unmedicated patients. It has been suggested, however, that P50 suppression may be improved with atypical antipsychotic

medications (e.g., Light, Geyer, Clementz, Cadenhead, & Braff, 2000). Yee et al. (1998) compared P50 responses recorded from patients who were maintained on risperidone, an atypical antipsychotic medication, to those receiving a traditional antipsychotic medication (i.e., fluphenazine decanoate). Although there were no significant group differences in P50 to S1, patients taking risperidone demonstrated significantly better suppression of P50 to S2, consistent with findings involving clozapine, another atypical antipsychotic medication found to improve P50 suppression (Nagamoto et al., 1996, 1999). Importantly, suppression differences between patients and healthy individuals remained and there was no significant difference in ratio scores between schizophrenia patients who received fluphenazine decanoate and those treated with risperidone. Other studies have found, however, that neither conventional nor second-generation antipsychotic medications improve sensory gating deficits in schizophrenia (Adler et al., 2004; Arango, Summerfelt, & Buchanan, 2003). Furthermore, no differential impact of antipsychotic medications has been found on P50 suppression in several other studies of recent-onset and chronic patients (Hong et al., 2009; Sanchez-Morla et al., 2009; Su, Cai, Wang, & Shi, 2012). Taken together, these findings generally suggest that atypical antipsychotics may have the ability to improve P50 suppression although the impact appears modest, particularly during the chronic phase of illness.

*P50 Suppression as an Intermediate Phenotype in Schizophrenia*

Given that P50 suppression is reliably reduced in schizophrenia, research to date offers support for the P50 deficit as a promising intermediate phenotype between disrupted neuronal mechanisms and clinical presentation that might also contribute to higher-order cognitive dysfunction in the illness. The P50 deficit has been postulated to be a genetically associated trait (Freedman et al., 1997; Siegel, Waldo, Mizner, Adler, & Freedman, 1984), supported by

observations of reduced P50 suppression ratios in asymptomatic first-degree relatives of schizophrenia patients (Clementz, Geyer, & Braff, 1998; Siegel et al., 1984; Waldo et al., 2000), as well as genetically at-risk prodromal individuals who have not developed full-blown psychosis (Brockhaus-Dumke et al., 2008; Myles-Worsley, Ord, Blailes, Ngiralmau, & Freedman, 2004). Indeed, the P50 suppression deficit has been proposed to be a potential phenotype for genetic linkage analyses and a marker of the gene for the alpha7-nicotine receptor (Freedman et al., 1997).

However, despite promising initial findings, there is not yet consistent and definitive evidence that P50 suppression deficits are related to clinical symptoms or to specific cognitive dysfunctions in schizophrenia. According to Luck and colleagues (2011), identification of biological indicators, or biomarkers, which provide sensitive and reliable measures of neural processes related to disrupted cognition, is an important and necessary focus of recent research efforts in order to guide the development of effective intervention strategies for schizophrenia. Therefore, clarification of the associations between P50 suppression deficits and cognitive dysfunction as well as clinical symptoms should help to elucidate whether P50 is a viable biomarker that can be used to guide schizophrenia treatment development. Furthermore, although ERP biomarkers may be particularly useful if they are predictive of individual treatment response (Luck et al., 2011), the existing literature on whether P50 suppression is predictive of intervention outcomes remains quite limited.

## Project Overview

Together, the hypothesized associations of P50 deficits with schizophrenia pathology, the genetic basis of the P50 abnormality, and the capacity to modify P50 suppression pharmacologically provide a solid foundation on which progress can be made toward the

development of new pharmacological agents and behavioral treatments designed to improve sensory gating (Potter, Summerfelt, Gold, & Buchanan, 2006). However, in order to use P50 suppression as a target for guiding intervention development, it is necessary to further define the clinical and neurobiological correlates of this mechanism. Currently, there is a dearth of research investigating the extent to which P50 deficits are associated with clinical symptoms, cognitive impairments, and role functioning (Luck et al., 2011; Potter et al., 2006). As such, despite substantial research evidence that suggests that P50 suppression may be a viable biomarker for schizophrenia, a number of important questions remain regarding the clinical significance and neural substrates of this abnormality. The present dissertation was designed to address these gaps in the literature via a series of three studies that examine six primary questions, as detailed below.

*Project Aims*

Data were collected from individuals who participated in a series of studies within the UCLA Center for Neurocognition and Emotion in Schizophrenia; participant samples for Studies 2 and 3 are subsets of the larger Study 1 sample. Overall, the present investigation was designed to evaluate the P50 suppression deficit as a possible biomarker of schizophrenia in order to gain a better understanding of etiological mechanisms so as to inform the development of interventions designed to improve cognitive, social, and occupational functioning for those affected by this severe and chronic mental illness. Specifically, we addressed the following research questions:

1. How does P50 relate to clinical symptoms and real-world functioning in schizophrenia?

Study 1 examined the association between P50 deficits and clinically-rated positive, negative, and cognitive symptoms of schizophrenia, as well as its relationship to functional outcome, to more definitively demonstrate the clinical relevance of P50 suppression deficits.

2. Are P50 suppression deficits related to other aspects of cognitive dysfunction in schizophrenia?

Study 1 also considered the relationship between P50 and measures of working memory and attention. Study 3 examined this relationship over the course of a cognitive training intervention.

3. Is the P50 suppression deficit associated with disrupted connectivity of neural white matter tracts?

Although important progress has been made in understanding the neural regions associated with sensory gating deficits in schizophrenia, with recent gains implicating a complex and distributed neural network (e.g., Popov et al., 2011b; Williams, Nuechterlein, Subotnik, & Yee, 2011), the contribution of disrupted connectivity between relevant brain regions has yet to be investigated. Adopting a neural network approach may also provide important information that allows for inferences to be made regarding the relationship between sensory gating and other prominent cognitive deficits associated with schizophrenia. Using diffusion tensor imaging (DTI), Study 2 examined the biological basis of the P50 deficit by investigating whether compromised structural integrity of white matter tracts may contribute to inhibitory deficits in schizophrenia.

4. Does cognitive remediation training improve P50 suppression in patients with schizophrenia?

Study 3 examined whether P50 deficits are malleable in response to a 12-month cognitive remediation training intervention compared with a control psychosocial intervention.

5. Is P50 suppression predictive of response to cognitive remediation training?

Study 3 also investigated whether P50 suppression is predictive of enhanced cognitive performance in the domains of working memory and attention following completion of cognitive remediation training compared to a control psychosocial intervention.

6. Are the relationships under investigation specific to P50 gating, or do they extend beyond the sensory gating phase of information processing and apply to other ERP measures elicited during the paired-stimulus paradigm, such as N100?

To examine the specificity of P50 deficits in Studies 1, 2, and 3, secondary analyses were conducted on the N100 component of the ERP. N100 is a negative-going wave that occurs approximately 100 ms following stimulus onset, arises primarily from the auditory cortex, and is hypothesized to reflect a later stage of attentional processing during early auditory selection (e.g., Hillyard, Hink, Schwent, & Picton, 1973).

Reductions in N100 amplitude have been shown to be a robust neurophysiological abnormality in schizophrenia (Brockhaus-Dumke et al., 2008; Laurent et al., 1999; Strik et al., 1992, Turetsky et al., 2008) and may reflect specific features of schizophrenia, distinguishing it from other psychotic disorders (O'Donnell, Vohs, Hetrick, Carroll, & Sheckhar, 2004). Recent research has also demonstrated a reduction in N100 suppression in schizophrenia that may reflect disturbed neural inhibitory processes in schizophrenia in a manner similar to P50 (e.g., Boutros et al., 2009; Boutros, Korzyukov, Jansen, Feingold, & Bell, 2004; Brockhaus-Dumke et al., 2008) although the pattern of findings has been mixed (see Turetsky et al., 2008; Yee et al., 1998).

## Chapter 2: Clinical, cognitive, and functional correlates of P50 suppression deficits (Study 1)

Despite consistent evidence of P50 sensory gating deficits in schizophrenia (e.g., Bramon et al., 2004; Patterson et al., 2008), the clinical and functional significance of such impairments and their relationship to other cognitive disturbances remain poorly understood. Conceptually, symptoms of the illness are hypothesized to result from neuronal dysfunction in response to sensory input, leading to sensory overload and difficulty filtering out irrelevant stimuli in the environment (Adler et al., 1992, 1998; Freedman, Adler, & Waldo, 1987; Freedman, Waldo, Bickford-Wimer, & Nagamoto, 1991). There have been relatively few comprehensive investigations, however, of the manner in which sensory gating deficits are expressed symptomatically, reflected in other cognitive domains, and associated with impaired daily functioning.

Although Venables (1964) hypothesized that sensory gating abnormalities may facilitate the expression of symptoms such as delusions, hallucinations, disorganization, bizarre behavior, and thought disorder, evidence from asymptomatic relatives of schizophrenia patients suggests that P50 gating abnormalities can also occur in the absence of psychotic symptoms (e.g., Adler, Hoffer, Griffith, Waldo, & Freedman, 1992; Clementz et al., 1998; Siegel et al., 1984; see Potter et al., 2006). Furthermore, several studies have failed to find a significant association between global positive symptom ratings using either the *Scale for the Assessment of Positive Symptoms* (SAPS; Andreasen, 1984b) or the *Positive and Negative Syndrome Scale* (PANSS; Kay, Fiszbein, & Opler, 1987) positive symptoms subscale score (Arnfred & Chen, 2004; Erwin, Turetsky, Moberg, Gur, & Gur, 1998; Light et al., 2000; Louchart-de la Chapelle et al., 2005; Ringel et al., 2004; Santos et al., 2010). Therefore, it would appear that P50 deficits might not be necessary to facilitate the positive symptoms of schizophrenia.

The majority of studies to date have also failed to find significant associations between P50 deficits and negative symptoms of schizophrenia, such as anhedonia, avolition, alogia, and affective flattening (see Potter et al., 2006). Specifically, P50 ratios have not been found to correlate with the total score for the *Scale for the Assessment of Negative Symptoms* (SANS; Andreasen, 1984a) or the PANSS negative symptoms subscale score (Adler et al., 1990; Arnfred & Chen, 2004; Erwin et al., 1998; Light et al., 2000; Louchart-de la Chapelle et al., 2005; Santos et al., 2010; Thoma et al., 2005; Yee et al., 1998). Notably, Light, Geyer, Clementz, Cadenhead, & Braff (2000) demonstrated that the SANS total score accounted for only 2% of the variance in P50 suppression ratios in a sample of 26 chronic schizophrenia patients. In contrast, Ringel et al. (2004) found that poorer P50 suppression ratios were significantly associated with higher PANSS negative symptom scores, with patients meeting diagnostic criteria for disorganized schizophrenia exhibiting the greatest P50 abnormalities. They suggested, however, that the findings may have reflected item overlap in the PANSS negative symptom subscale and the DSM-IV definition of disorganized schizophrenia. Given that the overall range of clinical symptoms is likely restricted for patients stabilized on antipsychotic medications, a general absence of correlational findings might also be attributed to insufficient statistical power to detect a relatively small effect.

With regards to associations with cognition, the latency of the P50 suggests an abnormality affecting early stages of information processing (Boutros et al., 2004), and P50 suppression has been considered a preattentional inhibitory filter mechanism that does not involve conscious processing (Freedman et al., 1987, 1991). There is some evidence, however, to suggest a relationship between P50 and more voluntary cognitive processes in the domains of working memory and attention that may be consistent with findings using clinically-rated

measures. For example, in a sample of 14 schizophrenia patients treated with conventional antipsychotics, Cullum and colleagues (1993) examined the association between sensory gating and working memory and found a significant association between P50 ratios and Digit Span performance. The authors also examined Digit Vigilance, a measure of sustained attention, and found poorer P50 suppression ratios to be significantly associated with lower scores. Erwin et al. (1998) reported that unmedicated schizophrenia patients with greater P50 abnormalities had more severe clinically-rated attentional impairments and obtained significantly fewer correct items on the Gordon Continuous Performance Test (CPT) distraction measure, as compared to a subgroup of patients showing less P50 impairment. The high P50 abnormality group also tended to perform more poorly on the vigilance measure of the Gordon CPT.

In contrast to these findings, Sanchez-Morla et al. (2013) reported a failure to find an association between P50 suppression and performance on the Digit Span task as well as another measure of sustained attention, the Degraded Stimulus CPT. Furthermore, there have been no reported associations between P50 and other cognitive domains in schizophrenia patients, such as verbal and visual learning and memory and reasoning and problem solving (Cullum et al., 1993; Erwin et al., 1998; Hsieh et al., 2004; Louchart-de la Chapelle et al., 2005; Sanchez-Morla et al., 2013; see Potter et al., 2006 for a review). In summary, there is some preliminary evidence to suggest a relationship between P50 suppression and cognition, specifically in the domains of working memory and attention, however these associations have been inconsistent and would likely benefit from examination in larger samples of patients.

And while cognitive impairments underlie many of the functional disabilities in schizophrenia, ranging from poor occupational functioning to limited self-care and social relationships (Green, 1996), very few studies have examined the relationship between sensory

gating deficits and functional outcome. Recently, Santos et al. (2010) observed a relationship between functional outcome and P50 suppression, such that DSM-IV *Global Assessment of Functioning Scale* (GAF) scores and community functioning assessed by the *Quality of Life Scale* (Heinrichs, Hanlon, & Carpenter, 1984) were found to correlate negatively with P50 ratio scores in patients with schizophrenia.

Given the mixed findings to date, the present study sought to more definitively demonstrate the clinical relevance of P50 suppression in a relatively large sample of schizophrenia patients by examining its association with clinical symptoms and cognitive dysfunction. Despite strong empirical support for P50 suppression impairments in schizophrenia, strikingly little research has focused on elucidating the relationship between P50 sensory gating deficits and expression of the illness. Therefore, the present study examined within group variability in P50 among schizophrenia patients as a function of clinical symptoms, cognitive impairments, and real-world functional outcome. A group of demographically-matched healthy comparison subjects were included to confirm compromised P50 gating in the present sample of schizophrenia patients.

## Hypotheses

1. It was hypothesized that schizophrenia patients and healthy comparison participants would exhibit sensory gating, with reductions in P50 amplitude to S2 as compared to S1. Replicating prior research, schizophrenia patients were expected to have higher P50 suppression ratios, and therefore poorer gating, compared to healthy individuals.
2. It was expected that P50 suppression ratios would be positively correlated with clinical observations of attentional difficulties in schizophrenia, with higher P50 suppression ratios associated with greater attentional impairment.

3. Poorer P50 suppression was anticipated to predict measures of functional outcome. Given that effective work and social functioning often requires the ability to remain focused and to concentrate on specific tasks while ignoring distractions, it was expected that intact early inhibitory or filtering processes reflected by P50 would predict the ability to work productively, live independently, and engage in interpersonal relationships.
4. As suggested by prior research discussed above, it was hypothesized that P50 suppression would be associated with cognitive performance in the domains of working memory and attention.
5. Findings were predicted to be specific to P50 and not extend to other ERP measures, such as N100.

## Method

### *Participants*

Participants were 54 outpatients with schizophrenia and 45 healthy individuals. Patients were screened using the Structured Clinical Interview for DSM-IV Disorders (SCID; First, Spitzer, Gibbon, & Williams, 1995), and met DSM-IV diagnostic criteria for schizophrenia, schizophreniform disorder, or schizoaffective disorder, depressed type. At the time of participation, patients were clinically stable and receiving antipsychotic medications. Healthy comparison participants were also evaluated using the SCID and had no personal history of a major psychiatric disorder or family history of a psychotic disorder. All participants were screened for mental retardation, history of head trauma, loss of consciousness for greater than 5 minutes, CNS injury or neurological disorder, and significant alcohol or substance use disorder in the past 6 months. All participants had taken part in a series of studies in the Center for Neurocognition and Emotion in Schizophrenia (PI: Keith Nuechterlein, Ph.D.), and provided

written informed consent. In order to avoid anticholinergic effects on the dependent variables, antiparkinsonian medications were discontinued prior to EEG recording, and participants refrained from cigarette smoking at least one hour prior to data acquisition.

Data from 2 schizophrenia patients and 4 comparison participants were excluded from analyses because their P50 data did not meet criteria, as described below. Of the 52 remaining schizophrenia patients, 45 were stabilized on risperidone, whereas 7 patients were stabilized using other antipsychotic agents (i.e., olanzapine, ziprasidone, fluphenazine, haloperidol, clozapine, and aripiprazole). There were no significant differences in any dependent variables between patients taking risperidone and those receiving other medications; unless otherwise noted, all analyses are reported for the entire sample to maximize statistical power.

*Clinical Assessment*

Schizophrenia patients' symptoms were assessed using the clinician-rated *Scale for the Assessment of Positive Symptoms* (SAPS; Andreasen, 1984b) and *Scale for the Assessment of Negative Symptoms* (SANS; Andreasen, 1984a) and two summary scores were derived from these measures. The total global positive symptoms summary score was the sum of the hallucinations, delusions, bizarre behavior, and positive formal thought disorder global subscale scores. The total global negative symptoms summary score was the sum of the affective flattening, alogia, avolition/apathy, anhedonia/asociality, and inattention global subscale scores.

The *Role Functioning Scale* (RFS; Goodman, Sewell, Cooley, & Leavitt, 1993) was administered to assess functioning in the domains of work productivity, independent living and self-care, relationships with family, and relationships with friends. Each domain is evaluated through a semi-structured interview by trained clinical interviewers on a Likert scale, ranging from 1 (severely limited functioning) to 7 (optimal functioning).

The existence and severity of depressive symptoms were assessed by the Beck Depression Inventory (BDI-II; Beck, Steer, & Brown, 1996), a 21-item self-report instrument on which items are rated on a 4-point scale from 0 to 3. Each item corresponds to a specific DSM-IV symptom of depression, and items are summed to provide a composite score. A total score of 0-13 is considered minimal range, 14-19 is mild, 20-28 is moderate, and 29-63 is severe depression.

*Cognitive Assessment*

Cognitive assessments were conducted using the MATRICS Consensus Cognitive Battery (MCCB; Kern et al., 2008; Nuechterlein & Green, 2006; Nuechterlein et al., 2008). This battery assesses seven domains of cognitive functioning: working memory, attention/vigilance, processing speed, verbal learning, visual learning, reasoning and problem solving, and social cognition. Performance in each of the seven MCCB domains is converted to age- and gender-corrected T- scores. With a mean of 50 and a standard deviation of 10, T-scores were calculated based on normative data from 300 community participants aged 20-59 who were stratified by age, gender, and education and drawn from five U.S. cities, as part of the MATRICS PASS and published in the MCCB manual and the MCCB scoring program (Nuechterlein & Green, 2006).

Although performance measures were collected across all MCCB cognitive domains, the present study focused on specific hypotheses related to the domains of working memory and attention. To assess working memory functioning, patients were evaluated using the Wechsler Memory Scale (WMS-III) Spatial Span task (Wechsler, 1997), which measures nonverbal working memory by requiring participants to observe an increasingly long sequence of blocks tapped by the examiner and replicate the tapping pattern (both forward and backward), and the University of Maryland Letter-Number Span (Gold, Carpenter, Randolph, Goldberg, &

Weinberger, 1997), which measures verbal working memory by requiring participants to repeat a series of numbers and letters said aloud by the test administrator after mentally reordering them numerically and alphabetically. A working memory composite T-score was calculated by the MCCB scoring program based on performance on the two tasks (i.e., total sequences correctly tapped for the Spatial Span task and total sequences correctly reordered for the Letter-Number Span task). The Continuous Performance Test – Identical Pairs (CPT-IP; Cornblatt, Risch, Faris, Friedman, & Erlenmeyer-Kimling, 1988) was included as a measure of attention/vigilance; participants are required to monitor numbers as they briefly appear on a computer screen and press a button when two numbers presented sequentially are identical. An attention/vigilance aggregated T-score was calculated across the mean d-prime value for 2-, 3-, and 4- digit conditions.

*Psychophysiological Recording Methods*

EEG recordings were obtained using a SynAmps amplifier system (Neuroscan, Charlotte, NC) with an elastic cap containing 124 Ag/AgCl sintered electrodes (Falk Minow Services, Herrsching, Germany), with an equidistant layout. Electrooculogram (EOG) was recorded by placing electrodes above and below the right eye and near the outer canthi of the eyes. All electrode sites, including the right earlobe, were referenced to the left earlobe during data acquisition and re-referenced offline to averaged earlobes. All impedances were below 10kΩ. The EEG was amplified 2,500 times and EOG signals were amplified 500 times with a resolution of .03μV and .17μV per least significant bit, respectively. Signals were acquired at a sampling rate of 2000 Hz, with filters set from 0.5 to 200 Hz.

Epochs were extracted as 200 ms before stimulus onset to 1,000 ms following stimulus presentation. A time window from -200 ms to stimulus onset (0 ms) was used for baseline

subtraction. After epochs were inspected for gross artifact and removed, blind source separation by independent component analysis (ICA) was conducted using Matlab with the open-source toolbox EEGLAB (Delorme & Makeig, 2004) in order to correct for eye movement and blink artifact as well as electrocardiographic activity. Following artifact correction procedures, trials that contained more than a 100 μV step with 100 ms intervals and a voltage difference of 300 μV through the duration of the trial were rejected. There was not a statistically significant difference in the number of trials retained between schizophrenia patients ($M$ = 78.73, $SD$ = 4.62) and healthy comparison participants ($M$ = 79.88, $SD$ = .33), $p > .05$.

Single EEG trials were digitally filtered with a bandpass of 10-50 Hz for measuring the P50 ERP. P50 was identified as the maximum positivity between 40 and 80 ms after stimulus presentation at the Cz site and was measured relative to the preceding N40. P30 amplitude and latency was identified as the most positive peak between 20 and 40 ms after the stimulus, and the maximum negativity between P30 and P50 was used to score N40 amplitude. Two raters, blind to participant group, independently scored the P50 wave. As noted above, six participants were excluded from analyses as their P50 amplitudes to S1 did not exceed 0.5 μV. N100 was digitally filtered with a bandpass of 1-20 Hz. The N100 component was identified as the most negative peak in the 50-150 ms window and measured relative to a 200 ms prestimulus baseline. As in Nagamoto et al. (1991), P50 ratio values over 2.00 were truncated to 2.00 to prevent outliers from having a disproportionate effect on group means. Therefore, P50 suppression ratios ranged from 0 (maximal gating) to 2.00 (100% or more augmentation of S2).

*Procedure*

After becoming acquainted with the protocol and laboratory equipment, participants completed a variety of self-report measures. They then participated in a series of experimental

tasks as part of a larger protocol examining stress and emotional reactivity in schizophrenia. Recordings of resting P50 and N100 were collected while participants were presented with 80 trials of paired auditory stimuli that were each 3 ms in duration, with a 500 ms interstimulus interval, and a variable intertrial interval of 9-11 sec between pairs of stimuli. Participants were seated comfortably in a sound-attenuated room and auditory stimuli were presented through foam-insert earphones. Symptom ratings were completed during a separate visit and were based on symptoms present over the past three months, which included the day of EEG data collection.

A subset of 39 recent-onset schizophrenia patients, all stabilized on risperidone, completed cognitive testing using the MCCB within one month of EEG collection as part of a separate study. Therefore, analyses involving cognitive variables included only those patients who completed the MCCB.

*Statistical Analysis*

Analyses of variance (ANOVAs) and chi-square tests were used to compare demographic characteristics between schizophrenia and healthy comparison groups. ANOVAs were also used to examine differences in P50 amplitude to each stimulus as well as the P50 ratio, with demographic characteristics included as covariates when indicated. *Partial-eta*$^2$ ($\eta_p^2$) is reported to reflect an ANOVA effect size. Zero-order correlations and hierarchical linear regression analyses were performed to examine relationships between ERP variables and clinical ratings and cognitive performance.

To examine potential confounds related to phase of illness or type and dosage of medication, all analyses were repeated with chlorpromazine (CPZ) equivalent dosages included as a covariate for each schizophrenia participant (using ANCOVAs) and also using a sample constricted to 45 recent-onset patients, all of whom were stabilized on risperidone. To assess for

any potential confounding effect of nicotine, all analyses were repeated with the inclusion of total number of cigarettes smoked in the past week as a covariate. Any deviations in results from the full sample are noted below.

## Results

Demographic and clinical characteristics of the samples are presented in Table 1. Because schizophrenia patients and healthy comparison participants differed significantly in age, $F(1,92) = 7.11$, $p = .009$, it was included as a covariate in all group comparisons of ERP variables. The two groups were matched for highest parental level of education but as might be expected, patients and comparison participants differed in personal years of education, $F(1,92) = 10.66$, $p = .002$, given that an illness such as schizophrenia likely influenced the level achieved. Furthermore, patients and healthy participants differed significantly in severity of depression symptoms as assessed by the BDI-II, $F(1,92) = 19.16$, $p = .000$, although both groups scored in the minimal depression range. For patients, positive and negative symptom levels assessed by the SAPS and SANS were generally mild to moderate.

Table 1. *Demographic and clinical characteristics of schizophrenia and healthy comparison participants.*

| | Schizophrenia Patients ($n$ = 52) | | Healthy Comparison Participants ($n$ = 41) | |
|---|---|---|---|---|
| | *M* | *SD* | *M* | *SD* |
| Age (years)* | 26.10 | 8.17 | 30.22 | 7.06 |
| Education (years)** | 13.43 | 1.94 | 14.71 | 1.96 |
| Parental Education (years) | 14.04 | 3.56 | 15.07 | 2.65 |
| Medication Dosage (mg/day, in Cpz equiv) | 201.83 | 115.79 | - | - |
| SAPS Total Score | 4.17 | 3.55 | - | - |
| SANS Total Score | 8.98 | 4.34 | - | - |
| Age of psychosis onset | 22.49 | 3.96 | - | - |
| BDI-II Total score*** | 8.79 | 7.69 | 3.24 | 3.67 |
| | *n* | | *n* | |
| Gender (Female/Male) | 15/37 | | 6/35 | |
| Ethnicity | | | | |
| African American | 14 | | 4 | |
| Asian American | 8 | | 3 | |
| Caucasian | 11 | | 26 | |
| Latino | 16 | | 7 | |
| Mixed | 3 | | 1 | |

Note. * $p < .05$, ** $p < .01$, *** $p < .001$.

*P50 and N100 Suppression*

Grand-average ERP waveforms are presented in Figure 1, and ERP mean amplitude and suppression ratios by group are shown in Table 2. Consistent with prior reports, P50 suppression ratios were significantly impaired in schizophrenia patients relative to those of healthy comparison participants, $F(1,90) = 6.20$, $p = .02$, $\eta p^2 = .07$. A repeated-measures ANOVA involving group (patient vs. healthy comparison) and stimulus (S1 vs. S2) evaluated the extent to which P50 ratios in each group reflected the response elicited by each stimulus and was used to

provide a difference measure of P50 suppression. A main effect of stimulus, $F(1,90) = 11.51$, $p = .001$, $\eta p^2 = .11$, confirmed suppression and was qualified by a significant group x stimulus interaction, $F(1,90) = 6.23$, $p = .01$, $\eta p^2 = .07$. Post-hoc tests determined that P50 amplitude to S1 tended to be attenuated in patients relative to healthy comparison participants ($p = .05$). Although the magnitude of patients' S2 amplitude response was in the expected direction compared to healthy individuals, the group difference was not statistically significant ($p = .88$). No significant group differences in the P50 latency to S1 or S2 were observed ($p = .12$ and $p = .13$, respectively).

Figure 1. *Grand average ERP waveforms at the Cz recording site.*

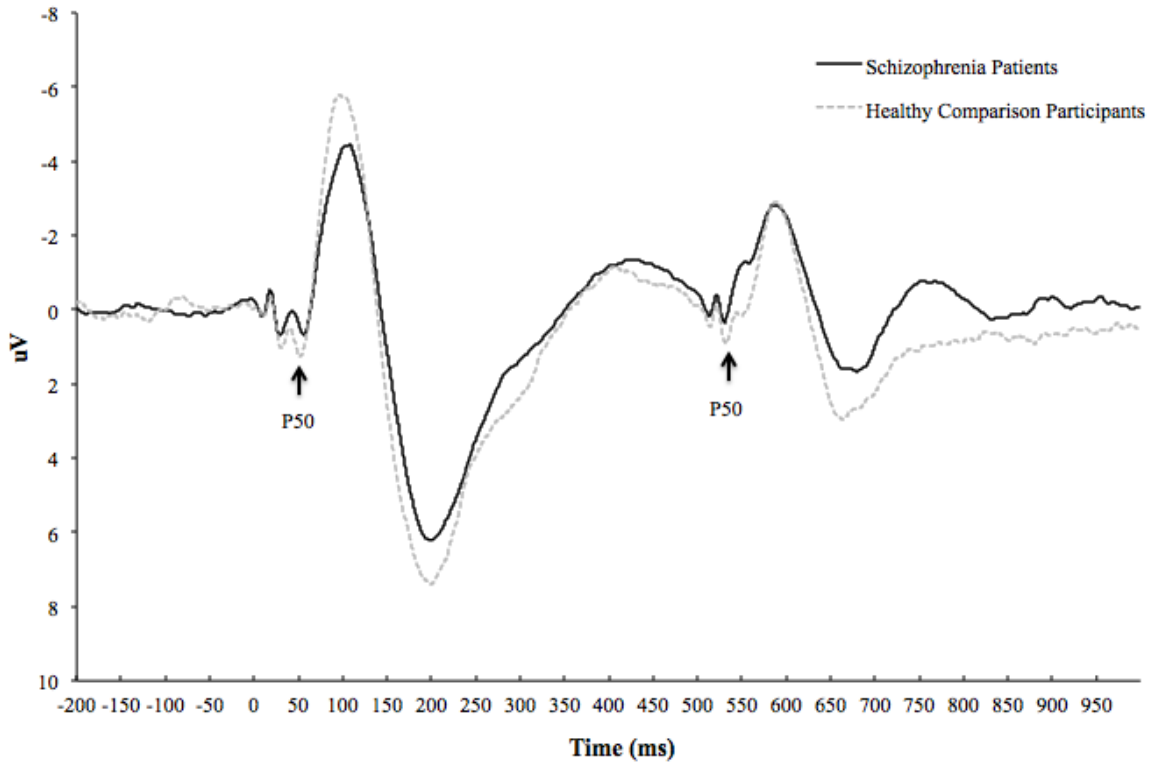


Table 2. *Amplitude and ratio measures of ERPs by participant group.*

| | Schizophrenia Patients ($n$ = 52) | Healthy Participants ($n$ = 41) |
|---|---|---|
| P50 | | |
| S1 amplitude (μV)† | 2.88 (1.65) | 3.50 (1.84) |
| S2 amplitude (μV) | 1.56 (1.01) | 1.44 (1.21) |
| S2/S1 Ratio* | .60 (.41) | .39 (.28) |
| N100 | | |
| S1 amplitude (μV)** | -5.34 (3.60) | -7.69 (3.98) |
| S2 amplitude (μV)* | -2.94 (1.83) | -3.86 (1.87) |
| S2/S1 Ratio | .66 (.42) | .58 (.39) |

Note. † $p < .06$, * $p < .05$, ** $p < .01$.

To assess the relative specificity of the P50 suppression deficit, analyses were conducted to examine N100 measures, which revealed that significant main effects for group, $F(1,90) = 9.10$, $p = .003$, $\eta p^2 = .092$, and stimulus, $F(1,90) = 5.11$, $p = .03$, $\eta p^2 = .04$, were qualified by a significant group x stimulus interaction, $F(1,90) = 3.92$, $p = .05$, $\eta p^2 = .04$. Although both groups demonstrated the expected suppression effect, healthy comparison participants exhibited larger N100 amplitudes than patients to S1, $F(1,90) = 8.08$, $p = .006$, $\eta p^2 = .08$, and, to a lesser extent, S2, $F(1,90) = 5.23$, $p = .03$, $\eta p^2 = .06$. Suppression ratios computed for N100, however, showed no significant differences between schizophrenia patients and comparison participants ($p = .41$). There were no significant group differences in N100 latency to S1 and S2 ($p = .30$ and $p = .32$, respectively).

*P50 and Clinical Presentation*

For schizophrenia patients, a significant positive association was observed between the P50 ratio and SANS summary scores ($r = .315$, $p = .02$) but this relationship did not extend to SAPS summary scores ($p = .76$). To determine the source of the significant effect, correlations

with each SANS subscale measure (see Table 3) confined the association with P50 suppression to the global inattention subscale ($r$ = .408, $p$ = .003). As shown in Figure 2, this effect was driven by the S2 P50 amplitude, such that greater S2 amplitudes were significantly associated with clinical ratings of greater attentional impairment ($r$ = .338, $p$ = .01) whereas P50 amplitude to S1 was found to be unrelated ($p$ = .38). No associations were observed between N100 and either positive or negative symptom summary scores.

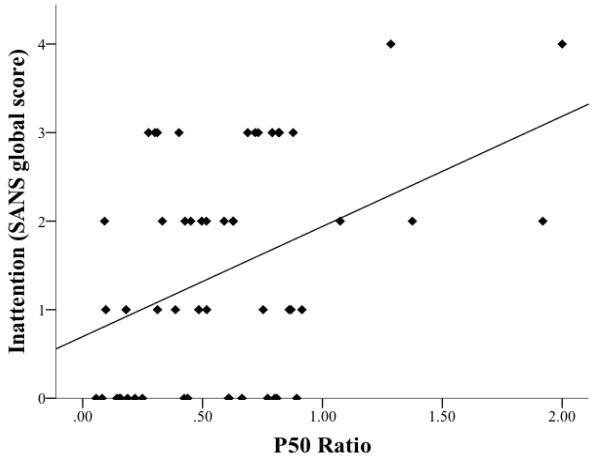
Table 3. *Correlations between P50 measures and negative symptom scores in schizophrenia patients.*

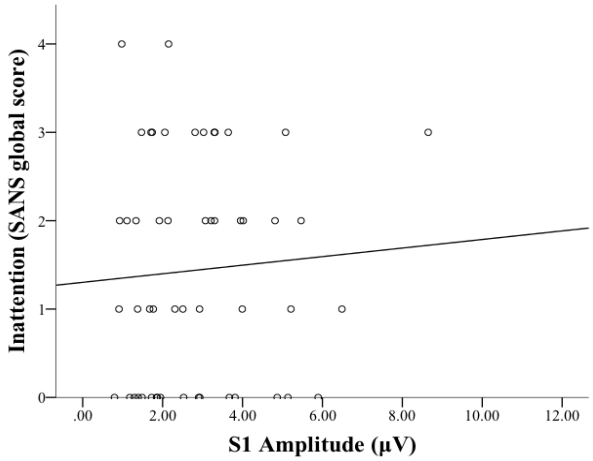
| | P50 | | |
|---|---|---|---|
| Scale Scores | S1 amplitude | S2 amplitude | Ratio |
| SANS summary score | .125 | .276 | **.315*** |
| affective flattening | .146 | .228 | .201 |
| alogia | .077 | .077 | .112 |
| avolition-apathy | .092 | .238 | .248 |
| anhedonia-asociality | .074 | .095 | .143 |
| inattention | .064 | **.338*** | **.408**** |

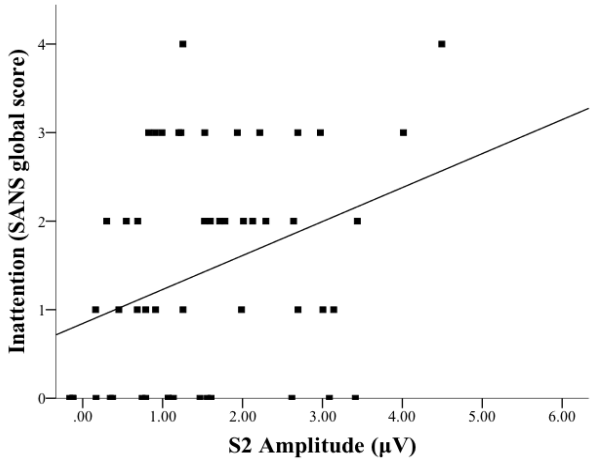
Note. * p < .05; ** p < .005.

To further address the specificity of the association between P50 suppression and clinical ratings of attentional difficulties, a hierarchical linear regression was used to predict P50 ratio from SANS inattention scores while accounting for other negative symptom subscale scores among schizophrenia patients. Results of the corresponding regression analysis are presented in Table 4. This analysis revealed that clinical ratings of attentional impairment uniquely explained 12.8% of the variance in P50 ratio scores, above and beyond 7.2% of the variation accounted for by the other SANS subscale scores (i.e., affective flattening, alogia, avolition/apathy, anhedonia/asociality). Similar results were not obtained when predicting N100 suppression.

Figure 2. *Correlations between inattention scores and P50 ratios (top), S1 P50 amplitudes (middle), and S2 P50 amplitudes (bottom).*



Finally, none of the P50 variables were found to be related to current functioning in the domains of work productivity, independent living/self-care, relationships with family, and relationships with friends (all *ps* > .05). Correlation coefficients are shown in Table 5.

Table 4. *Hierarchical regression model of negative symptoms predicting P50 ratio.*

| | b | SE | β | $R^2$ |
|---|---|---|---|---|
| *Step 1* | | | | .072 |
| affective flattening | .054 | .079 | .154 | |
| alogia | -.028 | .078 | -.073 | |
| avolition/apathy | .064 | .055 | .004 | |
| anhedonia/asociality | .001 | .048 | .004 | |
| *Step 2* | | | | .200 |
| inattention | .129 | .048 | .394** | |

Note. ** $p = .009$.

Table 5. *Correlation coefficients for P50 measures and Role Functioning Scale (RFS) domains.*

| | P50 | | |
|---|---|---|---|
| | S1 amplitude | S2 amplitude | Ratio |
| Work productivity | .085 | .083 | .020 |
| Independent living/self-care | .095 | .036 | -.086 |
| Relationships with family | -.023 | .060 | .055 |
| Relationships with friends | -.080 | -.060 | -.071 |

*P50 and Cognitive Measures of Working Memory/Attention*

Zero-order correlations between ERP measures and aggregated cognitive variables of working memory and attention are presented in Table 6 for the subsample of 39 recent-onset schizophrenia patients who participated in cognitive testing. As predicted, impairments in P50 suppression were significantly associated with poorer working memory performance. Specifically, impaired P50 suppression was associated with poorer performance on both Spatial Span ($r = -.381$, $p = .02$) and Letter-Number Sequencing ($r = -.330$, $p = .04$) tasks. As shown in

the table, this relationship was driven by a significant association with P50 amplitude to S2, as there were no associations between S1 P50 amplitude and working memory performance ($p$ = .33). Correlation plots are presented in Figure 3. None of these findings extended to measures involving N100, and neither P50 or N100 amplitudes nor their gating were associated with attention/vigilance performance (all $p$s > .05). Furthermore, none of the observed relationships with working memory performance could be accounted for by severity of schizophrenia symptoms, as results remained significant when controlling statistically for SAPS and SANS global summary scores ($p$s > .05).

Table 6. *Correlations between P50 measures and cognitive performance.*

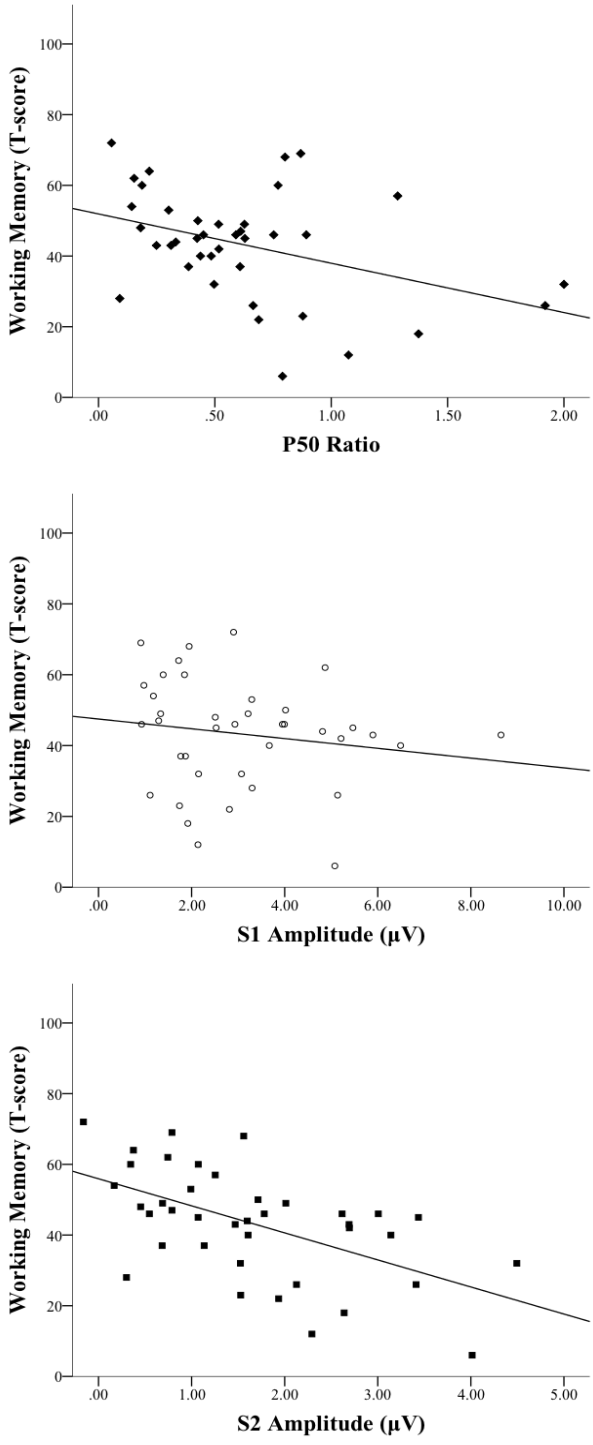
| | P50 | | |
|---|---|---|---|
| | S1 amplitude | S2 amplitude | Ratio |
| Working Memory T-score | -.160 | -.557*** | -.398* |
| Attention/vigilance T-score | -.037 | -.236 | -.104 |

Note. * $p$ < .05, *** $p$ = .000.

*Effects of Medication, Smoking, and Symptom Severity*

When analyses were repeated covarying for CPZ equivalent dosages of antipsychotic medications and number of cigarettes smoked in the past week, all reported findings remained consistent. Similarly, all reported symptom relationships remained significant when the sample was restricted to 45 recent-onset patients who were all stabilized on risperidone.

Figure 3. *Correlations between working memory performance and P50 ratios (top), S1 P50 amplitudes (middle), and S2 P50 amplitudes (bottom).*



## Discussion

Given uncertainty about the clinical significance of P50 suppression deficits in schizophrenia patients, the present study sought to evaluate relationships between P50 suppression measures and clinically-observed symptoms, cognitive performance impairments, and real-world functional outcome. The present findings replicate numerous reports of P50 suppression deficits in schizophrenia, and confirm the hypothesis that P50 gating abnormalities are associated with core clinical characteristics of schizophrenia, including clinician-rated attentional impairments and cognitive deficits in performance on tasks of working memory. The findings also support the specificity of the association between impaired P50 gating and clinically-rated symptoms of inattention in schizophrenia as the observed relationships did not extend to other negative symptom domains, including affective flattening, alogia, anergia, avolition/apathy, and anhedonia/asociality.

Analogous results involving attentional impairment measured by the SANS have been described in smaller samples that relied on dichotomizing participants into subgroups. In a sample of 22 recent-onset schizophrenia patients, Yee et al. (1998) compared patients exhibiting no versus mild to severe attentional impairment and found a significant difference in P50 suppression such that P50 ratios were poorer in the impaired group. Erwin et al. (1998) divided a sample of 31 schizophrenia patients into high and low P50 abnormality groups based on a median split, and group comparisons revealed a significant difference in the attentional impairment subscale. The present study extends these preliminary reports to a larger schizophrenia patient sample and employs a more powerful statistical approach by retaining the continuous range of information offered by the SANS and P50 ratio scores (Maxwell & Delaney, 1993).

Although we found a significant association with negative symptoms overall, the relationship was driven by the global inattention subscore. It is possible that prior studies failing to detect an association between summary score measures of negative symptoms and P50 suppression (e.g., Adler et al., 1990; Arnfred & Chen, 2004; Erwin et al., 1998; Light et al., 2000; Louchart-de la Chapelle et al., 2005; Santos et al., 2010; Thoma et al., 2005; Yee et al., 1998) have been hindered in their approach. Reliance on composite measures that are heavily weighted towards unrelated negative symptom domains, coupled with the examination of smaller samples of schizophrenia patients, may have contributed towards obscuring relationships between P50 suppression and attention difficulties. Furthermore, questions have arisen as to whether attentional problems assessed by the SANS inattention subscale are conceptually related to a negative symptom construct or would more appropriately load on to a cognitive symptom factor (see Blanchard and Cohen, 2006; Peralta et al., 1992).

In addition to linking P50 suppression to a clinically observed core feature of schizophrenia, the present study provides evidence for an association with working memory performance while completing verbal and nonverbal processing tasks. These findings align with previous work demonstrating a relationship between P50 and working memory assessed using the Digit Span task (Cullum et al., 1993). Results from the present study also are consistent with studies implicating a neural network involving prefrontal cortex and the hippocampus as generators of P50 suppression in patients and healthy comparison subjects (e.g., Adler et al., 1998; Tregellas et al., 2007; Williams et al., 2011), as these regions have been associated with working memory dysfunction in schizophrenia (e.g., see Carter et al., 1998; Meyer-Lindenberg et al., 2014). However, our findings contrast with a recent report in which P50 ratio scores were unrelated to Digit Span performance in schizophrenia patients (Sanchez-Morla et al., 2013).

Notably, participants were in the chronic phase of illness and substantially older than the present sample, with a mean age of 44 years. Illness duration and prolonged exposure to antipsychotic medications, therefore, might account for the discrepancy in findings between the two studies.

Given that we did not obtain evidence to support an association with performance on the attention/vigilance task, present results highlight the possibility that P50 may be related more closely to working memory than sustained vigilance as assessed by the CPT-IP. Specifically, P50 suppression may be more critical to tasks that involve encoding, brief maintenance, and manipulation, as opposed to those that require ongoing monitoring and sustained attention. Such a possibility is consistent with findings reported by Sanchez-Morla and colleagues (2013), who did not find a relationship between P50 suppression and performance on the Degraded Stimulus CPT, but fails to account for the divergence from other studies (Cullum et al., 1993; Erwin et al., 1998). However, prior positive results were derived from the use of tasks other than the CPT-IP (i.e., Digit Vigilance and Gordon CPT). Variability in task parameters used to measure the psychological construct of attention is one potential explanation as results may depend on the specific dimensions that the tasks reflect (e.g., selective attention, vigilance, or orienting/shifting) or other task parameters (e.g., provision of feedback, time restrictions).

Another important consideration is the complex, multifaceted relationship between working memory and attention, which have been linked both behaviorally and neurobiologically (e.g., see Awh, Vogel, & Oh, 2006). Consistent with the present findings of an association between working memory and enhanced P50 suppression, it has been suggested that individuals with high working memory capacity are more successful in resisting attentional capture by salient but irrelevant stimuli than those with lower capacity (Fukada & Vogel, 2009). It may also be that optimal performance on working memory tasks utilized in the present investigation relies

on attentional processes that influence maintenance of the material to be remembered (e.g., Smyth & Scholey, 1994). Likewise, tasks measuring attention often include working memory demands to varying degrees (e.g., see Kurtz, Ragland, Bilker, Gur, & Gur, 2001). Regardless, the present results provide evidence for an important link between deficient P50 suppression and cognitive performance deficits.

It is unclear why the present data do not support a relationship between P50 deficits and functional outcome as suggested by the findings of Santos and colleagues (2010), especially given the well substantiated relationships between cognitive functioning and functional outcome in schizophrenia (e.g., Green et al., 1996, 2000; Green, Kern, & Heaton, 2004). One potential explanation is that the present investigation was limited by a truncated range of scores compared to those of Santos and colleagues, who used the Quality of Life Scale and GAF ratings. Differences in the functional domains assessed by each measure might also contribute to discrepant results. Given present results of a strong association between P50 and working memory deficits, future research should continue to investigate how P50 sensory gating interacts with cognitive deficits to contribute to deficient functional outcomes.

It is noteworthy that in addition to the P50 ratio score, primary findings involved relationships between cognitive dysfunction and S2 amplitude but not with the S1 response. This pattern of findings is consistent with a dominant model of P50 sensory gating, suggesting that S1 activates inhibitory neuronal mechanisms that suppress (i.e., gate) the response to the identical S2, resulting in attenuation of P50 to S2 (e.g., Freedman et al., 1987, 1991). Findings regarding the relative importance of a P50 S1 amplitude deficit have been debated in the literature. A meta-analysis on S1 amplitude group differences demonstrated substantial heterogeneity in findings across studies and suggested that the S1 amplitude alone does not differentiate patients and

healthy comparison subjects as reliably as the P50 ratio (Patterson et al., 2008). Present results support the possibility that patients with schizophrenia, and particularly those with greater working memory deficits, have insufficient activation of inhibitory mechanisms to suppress the response following S2.

Finally, results obtained in the present study suggest that the effects are specific to P50 suppression. Although N100 amplitudes in response to both S1 and S2 were reduced as compared to healthy individuals and exhibited the expected pattern of suppression, similar to previous findings, evidence of a gating deficit in schizophrenia patients was limited to P50 (e.g., Turetsky et al., 2008; Yee et al., 1998, 2010). The current results also do not support a clinical relevance of N100 amplitudes or gating, given lack of significant associations found between N100 measures and clinically rated symptoms, attention and working memory performance, and functional outcome. Given its later latency, however, further consideration is warranted for the role of N100 in downstream processes that were not assessed in the present investigation, such as frontal executive functions (Boutros et al., 2009; Lijffijt et al., 2009; Mazhari, Price, Waters, Dragovic, & Jablensky, 2011).

The present research did not include recruitment of medication-free patients, and at the time of participation, all patients were stabilized on antipsychotic medications. There is evidence to support an effect of antipsychotic medications on cognitive functioning (for meta-analyses, see Keefe, Silva, Perkins, & Lieberman, 1999; Woodward, Purdon, Meltzer, & Zald, 2005), although the findings have been mixed (e.g., see Goldberg et al., 2007). With respect to P50, neither conventional antipsychotic medications nor atypical antipsychotic medications, possibly excepting clozapine (e.g., Nagamoto et al., 1996, 1999) and to a lesser extent, risperidone (e.g., Yee et al., 1998), have been shown to improve sensory gating deficits in schizophrenia patients.

Statistically accounting for CPZ equivalent dosages and limiting the sample to recent-onset patients stabilized only on risperidone, however, did not modify the present results. Therefore, systematic impact of antipsychotic medications on study findings was likely minimal.

Taken together, results of the present study relate P50 gating to core phenomenological features of schizophrenia. In addition, findings further substantiate P50 as a promising indicator of early sensory processing abnormalities by confirming the presence of inhibitory P50 deficits in schizophrenia patients, and by differentiating patients by aspects of symptom and cognitive presentation. Results therefore provide evidence that P50 may be a promising biomarker, or biological indicator of underlying pathological mechanisms that can be used for guiding the development of interventions targeting cognitive impairments in schizophrenia (see Luck et al., 2011). Indeed, there is promising evidence to suggest that gating deficits in individuals with schizophrenia are malleable in response to cognitive training (Popov et al., 2011a). Further research will help to clarify whether P50 suppression deficits are amenable to other forms of cognitive interventions while also determining whether such benefits extend to other aspects of cognition.

## Chapter 3: P50 suppression and white matter tract abnormalities (Study 2)

Human and animal research suggests that a neural network involving the hippocampus, thalamus, superior temporal gyrus (STG), and dorsolateral prefrontal cortex (DLPFC) are involved in the generation of P50 and its gating (e.g., Tregellas et al., 2007; Williams et al., 2011). Specifically, animal research has implicated the hippocampal CA3 region as a central site of activation, with alpha7-nicotinic receptors playing an important role (Adler et al., 1998; Bickford-Wimer et al., 1990). Adler et al. (1998) proposed that projections to the CA3 region of the hippocampus stimulate inhibitory neurons via the opening of alpha-7 nicotinic receptors in response to S1, and the interneuron release of GABA then facilitates inhibition of postsynaptic pyramidal cells due to inhibition by $GABA_B$ receptors on postsynaptic cells. Therefore, when excitation from S2 arrives in the CA3 region it may be suppressed by ongoing inhibition from S1. The alpha7-nicotinic receptor is particularly abundant in the hippocampus of the rat (Cullum et al., 1993), and a blockade of this receptor has been shown to result in disrupted S2 response suppression of the animal analogue of the P50 ERP (Luntz-Leybman, Bickford, & Freedman, 1992). In humans, studies using depth electrodes in epilepsy patients have also implicated the hippocampus in sensory gating (e.g., Grunwald et al., 2003; Wilson et al., 1998) although observations made in patients with pathology in the hippocampus may not be representative of abnormal processes in schizophrenia (Williams et al., 2011).

In addition, the nucleus reticularis thalami have considerable alpha7-nicotinic receptors (Freedman et al., 2000) and contribute to the regulation of inhibitory feedback control of thalamic to cortical pathways (Scheibel, 1997). There is evidence to suggest that these receptors may be reduced by 25% in schizophrenia patients as compared to healthy individuals (Court et

al., 1999), and studies in cats also support the role of the thalamus in sensory gating (Hinman & Buchwald, 1983).

Magnetoencephalogram (MEG) studies examining the M50 analogue of P50 in healthy individuals have generally implicated STG in sensory gating (Hanlon et al., 2005; Thoma et al., 2003). Because P50 and M50 suppression ratios have not been shown to correlate reliably in schizophrenia patients, however, it is possible that structures other than STG are implicated in P50 suppression but have not been detected by MEG (Thoma et al., 2003). Indeed, ERP evidence of suppression deficits in individuals with prefrontal cortex lesions also suggests likely involvement of this region (Knight, Scabini, & Woods, 1989). Relying on EEG source analysis in healthy individuals, Weisser et al. (2001) also found support for frontal cortex contributions to P50. Furthermore, in patients with epilepsy, Korzyukov et al. (2007) covered temporal and frontal lobe areas with intracranial microelectrode grids, and observed significant contributions to P50 from both regions in approximately half of their sample.

More recently, Popov et al. (2011b) examined M50 ratios and EEG oscillatory phenomena, and identified reductions in oscillatory activity in frequency bands (i.e., alpha and gamma) that are associated with the development of cortical networks and somatosensory processing in schizophrenia. Moreover, they observed group differences in evoked and induced oscillatory activity between patients and healthy controls in distributed generator structures, including frontocortical and posterior sources. Furthermore, while sources of sensory gating were confined to the STG and were related to broadly distributed sources in centroparietal regions in healthy subjects, this influence was deficient in schizophrenia.

Finally, fMRI studies have begun to elucidate a complex neural network that may underlie generation of P50 and its suppression. In a study by Tregellas et al. (2007) that relied

upon a modified sensory gating task during fMRI scanning, schizophrenia patients demonstrated greater hippocampal, thalamic, and DLPFC activation during the sensory gating task compared to healthy controls. However, there were no group differences in STG activation. Importantly, P50 ratio scores were correlated with hippocampus, thalamic, and DLPFC activation across patients and controls, suggesting that impaired sensory gating in schizophrenia is related to dysfunction in a network of brain regions. These findings were also replicated in larger samples using urban noise stimuli (Tregellas, Ellis, Shatti, Du, & Rojas, 2009). Additional support for a neural network hypothesis of sensory gating is provided by Mayer et al. (2009), who demonstrated involvement of auditory cortices, prefrontal cortex, and the thalamus in healthy individuals.

*EEG Source Localization of the P50 Sensory Gating Impairments in Schizophrenia*

Consistent with results from studies using other brain mapping techniques, Williams and colleagues (2011) demonstrated with EEG source localization that a distributed neural network involving the hippocampus, STG, thalamus, and DLPFC contributes to the generation and suppression of P50 in schizophrenia patients and healthy controls. Specifically, the hippocampal dipole moment ratio, indicating the strength of that neural source, was found to be strongly associated with the P50 ratio score in healthy individuals, consistent with previous research implicating the CA3 hippocampal region. In schizophrenia patients, however, the hippocampal dipole moment ratio did not correlate significantly with P50 suppression and instead, the DLPFC dipole moment ratio was more strongly associated with the P50 ratio. As such, results suggest that schizophrenia patients and healthy subjects differ in the relative contributions made by neural sources in P50 suppression. Williams and colleagues interpreted the lack of a relationship between the P50 suppression ratio and the ratio computed from hippocampal dipole moments in

the patient group as consistent with hippocampal dysfunction in schizophrenia. Indeed, reductions in hippocampal volume have been well documented in schizophrenia patients (e.g., Narr et al., 2004; Szeszko et al., 2003; Thoma et al., 2008; Velakoulis et al., 1999). Furthermore, the hippocampus has been shown to likely provide inputs to and from DLPFC (Goldman-Rakic, Selemon, & Schwartz, 1984), and schizophrenia patients demonstrate disruptions in the neural connections between these regions (Friston, 1998). Given compromised P50 suppression in schizophrenia, impaired connectivity between the hippocampus and DLPFC may be another important mechanism contributing to the sensory gating deficit (Williams et al., 2011).

*Neural Connectivity in Schizophrenia*

Rather than isolated regions of brain dysfunction, there is considerable evidence to suggest that disrupted neural connectivity in schizophrenia may be fundamental to the development and expression of symptoms (e.g., Bullmore, Frangou, & Murray, 1997; Catani et al., 2011; Cui et al., 2011; Fitzsimmons, Kubicki, & Shenton, 2013; Friston, 1999; Friston & Frith, 1995; Kubicki et al., 2007; Kunimatsu et al., 2012; Nakamura et al., 2012; van den Heuvel & Fornito, 2014) and cognitive impairments (e.g., Choi et al., 2011; Epstein et al., 2014; Karlsgodt et al., 2008; Levitt et al., 2012; Liu et al., 2013; Meyer-Lindenberg et al., 2014; Perez-Iglesias et al., 2010; Roalf et al., 2013; Rosenberger et al., 2012; Voineskos et al., 2012). Diffusion tensor imaging (DTI) facilitates examination of neural connectivity by assessing the coherence and integrity of white matter tracts. In particular, fractional anisotropy (FA) is a measure that estimates tissue coherence by determining the extent to which water diffusion is directionally restricted within each voxel, with a higher value indicating enhanced organization. Variations in FA have been linked to cognitive processes in healthy populations and in psychosis (e.g., Hanlon et al., 2012; Lim et al., 2006; Szeszko et al., 2008). In patients with schizophrenia,

there is substantial evidence for decreased FA within the prefrontal and temporal lobes, as well as in fiber bundles between these regions (e.g., uncinate fasciculus, cingulum bundle, and arcuate fasciculus; for reviews, see Dwork, Mancevski, & Rosoklija, 2007; Kubicki et al., 2007).

*P50 Suppression and Neural Connectivity in Schizophrenia*

Although results of human and animal research implicate the hippocampus, thalamus, STG, and DLPFC in P50 suppression (e.g., Adler et al., 1998; Tregellas et al., 2007), we are unaware of any research examining the relationship between P50 suppression deficits and disrupted structural connectivity in schizophrenia. This is all the more striking as the previously described research by Williams et al. (2011) is suggestive of altered connectivity between regions involved in P50 suppression. The present study, therefore, examined the hypothesis that P50 suppression deficits in schizophrenia reflect compromised structural integrity of white matter tracts, particularly those disrupting connections between prefrontal and temporal areas. Utilizing DTI methodology to identify potential neural pathways or mechanisms that may contribute to P50 suppression deficits, six major white matter tracts presumed to link the areas previously implicated in P50 generation were investigated.

*Arcuate Fasciculus*

The arcuate fasciculus (AF; or the temporal component of the superior longitudinal fasciculus) connects STG with DLPFC (Makris et al., 2005; Petrides & Pandya, 1988). By connecting frontal and temporal regions, the AF is thought to facilitate transmission of auditory information to the prefrontal cortex (Leinonen et al., 1980; Petrides, 2002). Fronto-temporal processing disruptions in schizophrenia have been reported (see Andreasen, 2000; Frith et al., 1995), with DTI studies demonstrating reduced FA in the left AF in adult and adolescent-onset

schizophrenia patients (Burns et al., 2003; Douaud et al., 2007; Kubicki et al., 2005; Phillips et al., 2009).

*Anterior Thalamic Radiation*

The anterior thalamic radiation (ATR) is the medial portion of the anterior limb of the internal capsule and links nerve fibers between the thalamus and prefrontal cortex. Reduced anisotropy of the ATR has been shown in schizophrenia (e.g., Buchsbaum et al., 2006; Mamah et al., 2010; McIntosh et al., 2008), and has been found to correlate with impaired executive functioning and working memory performance in patients (Mamah et al., 2010).

*Fornix*

The fornix is a compact bundle of white matter fibers projecting from the hippocampus to the thalamus and hypothalamus, and is involved in functions such as spatial and verbal memory and memory retrieval (e.g., Calabrese, Markowitsch, Harders, Scholz, & Gehlen, 1995; McMackin, Cockburn, Anslow, & Gaffan, 1995; Parker & Gaffan 1997), which are all processes observed to be impaired in schizophrenia (e.g., Callicott et al., 2000; Carter et al., 1998; Park & Holzman, 1992; Perlstein, Carter, Noll, & Cohen, 2001). Indeed, white matter integrity disturbances of the fornix have been observed in schizophrenia (e.g., Abdul-Rahman, Qui, & Sim, 2011; Fitzsimmons et al., 2009, 2014; Kendi et al., 2008; Kuroki et al., 2006; Luck, Malla, Joober, & Lepage, 2010; Nestor et al., 2007; Takei et al., 2008).

*Cingulum*

The cingulum bundle (CGC) connects the cingulate cortex with the prefrontal cortex (e.g., DLPFC), premotor regions, cortical association areas in the parietal and occipital lobes, parahippocampal cortex, and the thalamus (e.g., Goldman-Rakic et al., 1984; Pandya & Seltzer, 1982; Mori et al., 2008). A number of studies have demonstrated reduced integrity of the CGC in

schizophrenia (e.g., Abdul-Rahman et al., 2011; Fujiwara et al., 2007; Hoptman et al., 2008; Sun et al., 2003; Takei et al., 2009; Wang et al., 2004; Whitford et al., 2015) although there have been exceptions (e.g., Muñoz Maniega et al., 2008). The CGC has been shown to be associated with core cognitive processes that are disrupted in schizophrenia, such as attention, emotion, and memory (e.g., Fletcher, McKenna, Friston, Frith, & Dolan, 1999; Kubicki et al., 2005; Nestor et al., 2004; Nestor et al., 2008).

*Uncinate Fasciculus*

The uncinate fasciculus (UF) connects the temporal lobe with ventral, medial, and orbital frontal cortices (Ebeling & von Cramon, 1992; Schmahmann et al., 2007) and plays a major role in the formation and retrieval of memories (Nestor et al., 2004; Squire & Zola-Morgan, 1991). Although some studies have observed reduced UF FA in schizophrenia (McIntosh et al., 2008; Nestor et al., 2008), findings have been mixed (Jones et al., 2006; Phillips et al., 2009).

*Inferior Fronto-occipital Fasciculus*

The inferior fronto-occipital fasciculus (IFOF) links the frontal lobe to the temporal lobe and is involved in higher-order cognitive functions (e.g., Catani, Howard, Pajevic, & Jones et al., 2002). It has been implicated in schizophrenia, with frequent demonstrations of reduced FA (e.g., Ashtari et al., 2007; Federspiel et al., 2006; Phillips et al., 2009; Szeszko et al., 2008). Reduced FA of IFOF has been shown to correlate with positive and negative symptoms as well as executive functioning deficits in schizophrenia (Lee et al., 2013).

Based on the literature to date suggesting links between P50 suppression and altered connectivity in schizophrenia, the present study examined the hypotheses described below.

## Hypotheses

1. This study addressed the hypothesis that P50 deficits in schizophrenia patients would be associated with poorer white matter tract integrity for neural structures associated with P50 suppression. Specifically, poorer P50 suppression ratio scores were expected to correlate with FA values of tracts connecting the hippocampus, thalamus, STG, and DLPFC, including ATR, AF, fornix, UF, CGC, and IFOF.
2. In contrast, fiber tracts that are disrupted in schizophrenia but are unlikely to be associated with P50 suppression (i.e., corpus callosum, inferior longitudinal fasciculus) were expected to be less strongly associated with P50 ratio scores.

Findings of structural abnormalities of the corpus callosum (CC) have been well documented in schizophrenia (for a meta-analysis, see Woodruff, McManus, & David, 1995). Previous studies using DTI report that schizophrenia patients exhibit reduced white matter integrity in the splenium (CC major), which connects the occipital lobes (Agartz et al., 2001; Ardekani et al., 2003; Foong et al., 2000; Price et al., 2007) and in the genu (CC minor), which connects the medial and lateral surfaces of the frontal lobes (Kanaan et al., 2006; Price et al., 2007), although not all others have documented decreased FA in these tracts in schizophrenia (Kubicki et al., 2005; Kumra et al., 2004; Price, Bagary, Cercignani, Altmann, & Ron, 2005).

The inferior longitudinal fasciculus (ILF) provides an important associative connection between the anterior temporal and occipital lobe, playing a major role in visual memory (Bauer & Trobe, 1984; Shinoura et al., 2007). Reduced FA for ILF has been reported in schizophrenia (Ashtari et al., 2007; Phillips et al., 2009). Despite the potential relevance of the integrity of ILF and CC in schizophrenia, it is expected that FA values of these tracts will be less strongly related to P50 due to their lack of primary connections with regions associated with P50 generation.

## Method

### *Participants and Procedure*

Participants were a subsample from the previous study and included 9 schizophrenia patients for whom imaging data had been obtained as part of the UCLA Family Study (P.I. Katherine Narr, Ph.D.). The 8 male and 1 female participants were stabilized on antipsychotic medications (8 risperidone, 1 olanzapine; CPZ equivalent dosage *M* = 284.44, *SD* = 98.53, range 175-450 mg/day) and had a mean age of 28.56 years (*SD* = 11.48, range 18-51 years). Symptoms of schizophrenia were generally mild to moderate, (SAPS *M* = 3.00, *SD* = 3.16; SANS *M* = 9.00, *SD* = 5.00). DTI data were collected on a separate day from the EEG session. P50 and N100 ERPs as well as symptom ratings (i.e., using the SANS and SAPS) were obtained as previously described in Chapter 2.

### *Diffusion Tensor Imaging (DTI) Acquisition and Analysis*

DTI data were acquired using single-shot spin-echo/echo-planar imaging sequences with 30 non-collinear diffusion encoding directions, 5 b0's, and a 2 mm isotropic voxel size covering 50 brain slices oriented obliquely to the anterior/posterior commissure (AC–PC) line (TR = 7000 ms, TE = 93 ms, b = 0, 1000 s/mm$^2$, FOV: 190 × 190 mm, matrix: 96 × 96, averages: 2, scan time: 7.75 min). DTI data preprocessing was executed within the LONI Pipeline environment (Rex, Ma, & Toga, 2003). After image reconstruction, the diffusion gradient table was corrected for slice prescription and images were corrected for eddy current distortions and motion artifacts using a combined transformation file to minimize interpolation that includes a nonlinear 2D registration (Jezzard, Barnett, & Pierpaoli, 1998) and a 3D rigid body registration (Woods, Grafton, Holmes, Cherry, & Mazziotta, 1998; Woods, Grafton, Watson, Sicotte, & Mazziotta, 1998). The non-diffusion-weighted images were skull stripped by taking advantage of the

manually corrected scalp-edited T1-weighted data, transformed into DTI space, and used to subsequently mask all diffusion-weighted images. The diffusion tensor was estimated at each voxel using a linear least squares algorithm applied to the log-transformed signal intensities to provide measures of the three principal diffusion constants (eigenvalues) and diffusion directions (eigenvectors) and to obtain FA and other scalar diffusion metrics (Pierpaoli & Basser, 1996).

DTIstudio was used to perform 3D tract reconstruction using the Fiber Assignment by Continuous Tracking (FACT) algorithm (Jiang, van Zijl, Kim, Pearlson, & Mori, 2006). A FA threshold of 0.2 and a turning angle threshold of 41° were used for each tract to restrict the algorithm (Phillips et al., 2009; Wakana et al., 2007). Regions of interest were identified on the FA-weighted color maps for each subject using validated protocols (Phillips et al., 2009; Wakana et al., 2007). DTI measures were assessed for each fiber tract within subjects and included FA, mean diffusivity (MD) and tract volume. For the present investigation, FA was used as the dependent measure for statistical analysis.

*Statistical Analysis*

Pearson correlations were conducted to investigate the relationship between P50 suppression ratios and FA values of major projection and association pathways, which were averaged across hemispheres for lateralized tracts to reduce the number of hypotheses tested. Post-hoc exploratory analyses, with Bonferroni corrections applied, examined relationships by hemisphere and the specific associations with S1 and S2 P50 amplitudes. Furthermore, partial correlations were utilized to repeat all analyses while separately controlling for any effects of age, medication dosage, and severity of positive and negative symptoms (i.e., SAPS and SANS total summary scores) on P50 and FA relationships. To evaluate the specificity of findings, analyses were conducted to examine associations between N100 measures and mean FA values.

## Results

Pearson zero-order correlations between major association and projection pathways and P50 variables are provided in Table 7, which includes associations between mean FA averaged across hemispheres and P50 ratios, as well as specific relationships between tracts (by hemisphere) and P50 S1 and S2 amplitudes. As predicted, significant relationships were observed between the P50 suppression ratio and ATR (averaged across hemispheres), ATR (left), AF (left), and fornix, and these associations remained after applying a Bonferroni correction to control for the number of comparisons (all *p*s < .05). Figure 4 shows mean FA by hemisphere plotted against P50 ratios for all tracts with statistically significant associations.

Although P50 ratios and FA of white matter tracts were not significantly correlated with age, medication dosage (CPZ equivalent), or SAPS or SANS total symptoms (all *p*s > .05), with the exception of ILF (right) FA which correlated with CPZ dosage equivalent ($r$ = -.869, $p$ = .002), partial correlations were used to control for any effects of age and severity of symptoms on the relationships between P50 ratios and FA of white matter tracts. Almost all relationships remained significant (all *p*s < .05). The one exception was the association between P50 ratio and CGC (left), which reduced to trend significance (partial correlation controlling for age $p$ = .08, controlling for SAPS and SANS total scores $p$ = .06). In addition, partial correlations controlling for effects of CPZ equivalent dosage demonstrated that all relationships remained significant, except for the association between P50 ratio and FA for UF averaged bilaterally which reduced to trend significance ($p$ = .08). No significant relationships were found between mean FA values and any measures of N100 (i.e., S1 amplitude, S2 amplitude, or suppression ratio).

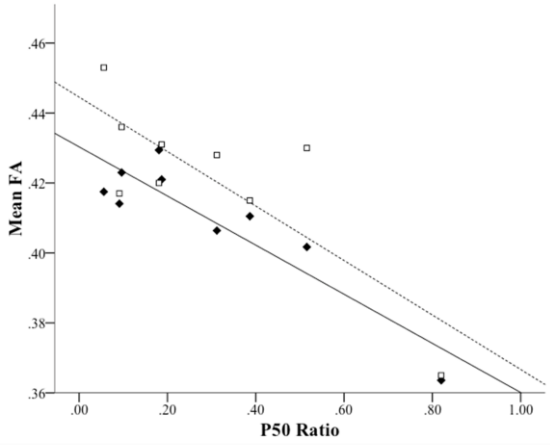
Table 7. *Correlations among P50 measures and white matter tracts.*

| | P50 | | |
|---|---|---|---|
| | S1 amplitude | S2 amplitude | Ratio |
| Arcuate Fasciculus (AF) | -.072 | -.603 | -.615 |
| Left | .479 | -.763* | **-.911*****|
| Right | -.431 | -.350 | -.265 |
| Anterior Thalamic Radiation (ATR) | .377 | -.819** | **-.893*****|
| Left | .387 | -.763* | **-.907*****|
| Right | .337 | -.792* | -.803** |
| Cingulum (CGC) | .400 | -.665* | -.827** |
| Left | .329 | -.608 | -.751* |
| Right | .467 | -.711* | -.884** |
| Inferior Fronto-occipital Fasciculus (IFOF) | .144 | -.671* | -.656 |
| Left | .211 | -.690* | -.739* |
| Right | .012 | -.498 | -.389 |
| Inferior Longitudinal Fasciculus (ILF) | .461 | -.700* | -.650 |
| Left | .513 | -.541 | -.523 |
| Right | .303 | -.727* | -.653 |
| Uncinate Fasciculus (UF) | .285 | -.635 | -.747* |
| Left | .088 | -.687* | -.599 |
| Right | .319 | -.460 | -.647 |
| Fornix | .574 | -.714* | **-.920***** |
| Corpus Callosum (CC) | | | |
| Major | -.524 | -.436 | -.117 |
| Minor | -.396 | -.002 | .211 |

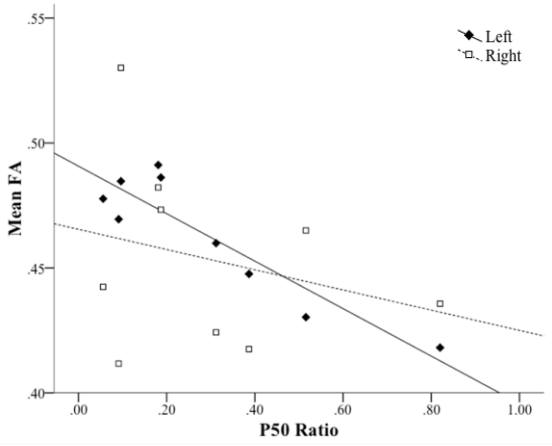
Note. * $p < .05$, ** $p < .01$, *** $p < .005$ (uncorrected p-value). Bold denotes significance ($p < .05$) following Bonferroni correction for number of comparisons.

Figure 4. *Relationships among mean FA and P50 ratio by white matter tract*.

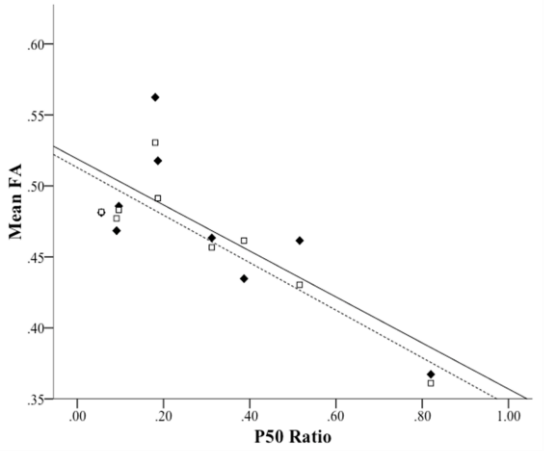
(a) Anterior Thalamic Radiation (ATR)



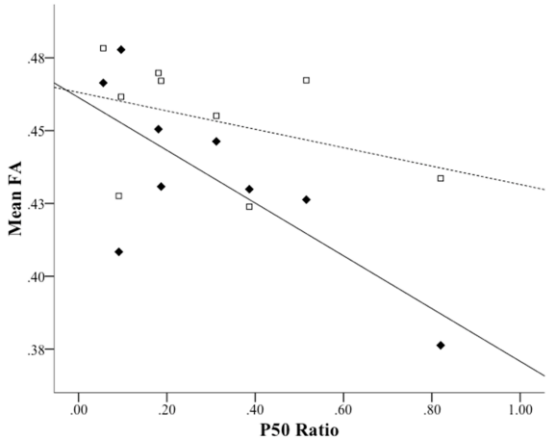

(b) Arcuate Fasciculus (AF)



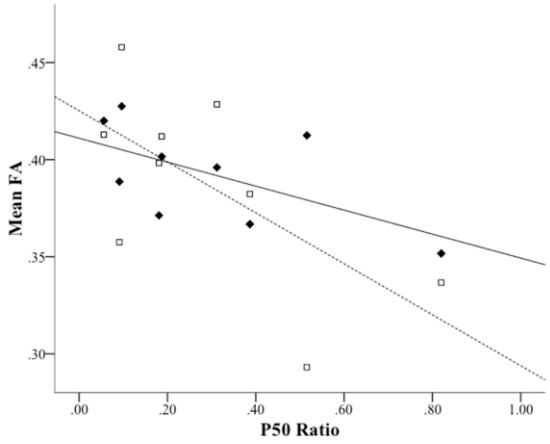

(c) Cingulum (CGC)



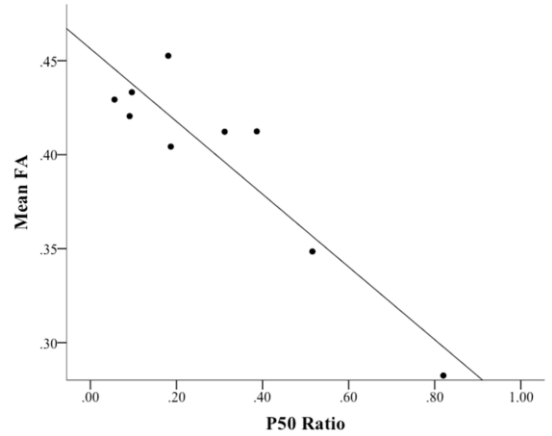

(d) Inferior Fronto-occipital Fasciculus (IFOF)




(e) Uncinate Fasciculus (UF)




(f) Fornix



## Discussion

Although sensory gating dysfunction has been well established in patients with schizophrenia, this is the first study to investigate whether disrupted structural connectivity may be contributing to P50 suppression deficits. Results obtained from a small sample of schizophrenia patients suggest significant associations between P50 ratios and white matter tracts connecting neural regions presumed to be involved in the generation of P50 suppression. Specifically, relationships were observed between P50 ratio scores and mean FA of the ATR (collapsed bilaterally and of the left hemisphere), left AF, and fornix, such that individuals with compromised white matter integrity of these major fiber tracts exhibited poorer P50 suppression. Visual inspection of the relationships between FA values and P50 amplitude measures suggest that these white matter tracts may be of considerable relevance to sensory gating and the magnitude of suppression reflected by P50 to S2, relative to a complete absence of associations with P50 amplitude to S1. Also consistent with study hypotheses, associations were found between P50 ratio scores and mean FA of the CGC (collapsed bilaterally and both left and right hemispheres), right IFOF, and UF (collapsed bilaterally) but these relationships fell to non-significance after correcting for multiple comparisons. None of the observed relationships were attributable to patient age, positive or negative symptom severity, or antipsychotic medication dosage. Importantly, we did not find evidence of associations between P50 and tracts implicated in the pathophysiology of schizophrenia but that connect regions not suspected to be involved in P50, including the CC major/minor and ILF. Furthermore, associations were specific to P50 and did not extend to measures of N100.

The present results are consistent with reports that specifically implicate prefrontal cortex (i.e., DLPFC), STG, thalamus, and hippocampus in P50 generation (Adler et al., 1998; Tregellas

et al., 2007; Williams et al., 2011) and extend these findings by suggesting that pathways that link areas related to P50 generation, and not merely the neural regions, may be of considerable relevance to P50 suppression deficits. Disruptions to cortico-subcortical pathways as well as networks interconnecting fronto-temporal regions in both neural hemispheres appear most germane to deficiencies in P50 suppression and this association could have important implications for understanding cognitive dysfunction in individuals with schizophrenia. For example, there is evidence to suggest that disrupted frontal-temporal connections involving UF may be correlated with measures of verbal memory while reduced integrity of CGC has been associated with errors in executive function related to performance monitoring in patients with schizophrenia (Kubicki et al., 2002a,b; 2003). It has been suggested that normal age-related loss of white matter integrity, particularly in tracts of the temporal and frontal lobes and thalamus, is associated with working memory decline (Charlton et al., 2006, 2008). Taken together, these findings imply that the associations between P50 suppression deficits and relevant white matter tracts may have substantial significance for cognitive functioning in schizophrenia patients and should be further investigated with larger samples.

In the present study, relationships between P50 suppression and white matter abnormalities generally appeared to be stronger in left hemisphere regions (i.e., ATR, AF, and IFOF). The predominance of left hemisphere associations may be related to failures of left hemisphere dominance in schizophrenia, which have been hypothesized to play a role in the pathophysiology of the illness (Crow, 1995; Highley et al., 1998). Indeed, there is DTI evidence of abnormal anisotropic diffusion in left hemisphere white matter of schizophrenia patients (Burns et al., 2003; Kubicki et al., 2002; Szeszko et al., 2008). In addition, it may be the case that P50 is generated primarily by the left hemisphere. An investigation of the M50 MEG analogue of

P50 found that left, but not right, hemisphere M50 gating correlated with P50 suppression and differentiated schizophrenia patients from healthy comparison subjects, suggesting that the functional pathology in the processing of S1 and the subsequent failure of S2 inhibition may be localized primarily in the left hemisphere (Thoma et al., 2003). Given that measures of P50 are assessed with EEG scalp recordings and do not allow for differential assessment of left and right hemisphere contributions, the capacity to make conclusions about possible hemispheric asymmetry in the generation of P50 is limited.

The present study was limited by its small sample size, cross-sectional and correlational design, and lack of a healthy comparison group that would allow for investigation of the specificity of the reported associations to a schizophrenia diagnosis. In addition, although two-thirds of patients in the present sample were recent-onset patients with relatively short medication histories, patients were nevertheless not medication-naïve. There are reports of an association between FA and antipsychotic dosage (Minami et al., 2003; Kuroki et al., 2006) and length of treatment (Szescko et al., 2008). Although the present study did not find an association between white matter tracts and medication dosage, future research with medication-free samples will clarify whether antipsychotic medications impact the relationship between P50 and white matter connectivity. Furthermore, patients in the present sample had a wide age range. Although we controlled for the effects of age in the correlational analyses, it is unclear to what extent age-related changes in white matter FA may have contributed to present findings as age effects have been reported in healthy populations (Bonekamp et al., 2007) and schizophrenia patients (Jones et al., 2006; Rosenberger et al., 2008).

In summary, results of this preliminary study suggest that associations exist between impaired P50 suppression and compromised white matter integrity of major fiber tracts

connecting neural structures that have been largely implicated in sensory gating in schizophrenia. By linking sensory gating deficits to white matter disconnectivity, these initial findings extend current knowledge regarding the neural pathways that might account for inhibitory deficits in schizophrenia and suggest important directions for future research.

## Chapter 4: P50 suppression and improvements following cognitive remediation (Study 3)

Cognitive dysfunction is a core characteristic of schizophrenia that is evident during early stages of illness, with nearly all patients demonstrating deficits relative to their own premorbid cognitive abilities (e.g., Gold, 2008; Medalia & Choi, 2009; Wilk et al., 2004). Given considerable evidence demonstrating the detrimental impact of cognitive impairment on functional outcome over the course of schizophrenia (e.g., Green et al., 2004, 2006), behavioral interventions have sought to target cognitive remediation for these individuals. Aiming to improve various aspects of cognition with the further goal of enhancing psychosocial functioning, cognitive remediation interventions developed for individuals with schizophrenia appear successful, as a large body of research has yielded moderate to large effect sizes on cognitive functioning, functional outcomes, and to a lesser extent, symptoms of the illness (see Krabbendam & Aleman, 2003; Kurtz et al., 2001; McGurk, Twamley, Sitzer, McHugo, and Mueser, 2007; Suslow et al., 2001; Twamley et al., 2003, 2007; Wykes, Huddy, Cellard, McGurk, & Czobor, 2011). To date, however, there remains a lack of consensus regarding the optimal techniques and targets for cognitive remediation, although heterogeneity of cognitive deficits in schizophrenia suggests that a broad approach pursuing multiple domains (i.e., attention, memory, executive functioning, metacognition) may offer the most benefit for patients (Wykes & Huddy, 2009).

In addition to improvements in cognitive and functional domains, there is mounting evidence for training-induced plasticity of associated neural systems as a consequence of cognitive remediation training for schizophrenia (see Vinogradov, Fisher, & Nagarajan, 2013). For example, increased activation in prefrontal networks associated with attention and working memory processes, including DLPFC, cingulate, frontopolar cortex, and inferior frontal gyrus,

have been demonstrated following cognitive remediation (e.g., Bor et al., 2011; Haut, Lim, & MacDonald, 2010; Wexler et al., 2000; Wykes et al., 2002). Additionally, cognitive remediation intervention has been associated with greater preservation of grey matter volume over a two-year period in the left hippocampus, parahippocampal gyrus, and fusiform gyrus, as well as grey matter increases in the left amygdala (Eack et al., 2010). Penades et al. (2013) also found that in schizophrenia patients, patterns of activation in the central executive and default mode networks normalized and white matter integrity of the genu of the corpus callosum improved following cognitive intervention. These findings suggest that cognitive remediation promotes robust effects on fundamental cognitive processes and their associated neural mechanisms, particularly when patients are clinically stable and cognitive remediation is provided in conjunction with psychiatric rehabilitation (for a meta-analysis, see Wykes et al., 2011), such as supported employment (e.g., McGurk, Mueser, Feldman, Wolfe, & Pascaris, 2007). Despite such promising findings, relatively little is known regarding the impact of cognitive training on many of the neural mechanisms associated with dysfunction in schizophrenia.

One such mechanism is the sensory gating deficit that is associated with impaired P50 suppression in schizophrenia. P50 suppression abnormalities appear to have important cognitive and functional consequences for individuals with schizophrenia, as evidenced by associations between poor P50 suppression and cognitive impairments, particularly in working memory and attention (for a review, see Potter et al., 2006; see also Chapter 2). These two cognitive domains of intricately linked processes (e.g., Awh et al., 2006) have been shown to benefit from cognitive remediation training, particularly for individuals in the early phase of illness (e.g., see McGurk et al., 2007). Therefore, cognitive remediation procedures that engage both cognitive processes may also have the capacity to improve P50 suppression deficits.

The potential malleability of P50 abnormalities is supported by two lines of research. Yee and colleagues (2010) reported that manipulation of early attentional control can have a modulatory influence on P50 and transiently normalizes the P50 suppression deficit in schizophrenia patients. Using MEG, Popov and colleagues determined that cognitive training aimed specifically at improving auditory/verbal discrimination and working memory also normalizes schizophrenia patients' inhibitory gating deficits (i.e., M50 gating ratio and associated oscillatory activity; Popov et al., 2011b; Popov, Rockstroh, Weisz, Elbert, & Miller, 2012). Whether cognitive remediation interventions can impact P50 dysfunction and contribute to associated clinical benefits has yet to be determined.

Thus, one purpose of the present study was to examine whether the P50 suppression deficit is malleable in response to cognitive remediation training provided to schizophrenia patients with a recent onset of illness. Determining whether P50 deficits are responsive to intervention would provide further support for learning-induced neural plasticity in the early course of the illness. The current investigation also sought to examine whether any changes associated with this neurobiological mechanism might extend to behavioral and cognitive manifestations of sensory gating deficits, including clinical symptoms of inattentiveness.

In addition to being a strong candidate for cognitive remediation, P50 suppresion might also predict improvements over the course of treatment. Research to date is limited but some individual difference factors have been identified with researchers capitalizing on within-cohort variations to gain additional information regarding specific targets of remediation (Wykes & Huddy, 2009). For example, McGurk & Mueser (2008) found that schizophrenia patients over 40 years of age were less likely to benefit from cognitive remediation, possibly related to reductions in neural plasticity with increased age. Additionally, Bell, Zito, Greig, and Wexler (2008)

showed that schizophrenia patients with poor functioning prior to treatment demonstrated increased rates of employment following cognitive remediation training, whereas individuals with higher levels of functioning achieved similar rates of employment regardless of participation in cognitive training. Given the relevance of P50 suppression to cognitive functioning, measurement of P50 prior to treatment engagement may be a useful indicator of outcome by identifying which schizophrenia patients will benefit most from cognitive remediation training. Therefore, another aim of the present research was to examine whether baseline P50 suppression deficits predict capacity for improvement in the relevant cognitive domains of working memory and attention, as well as the expression of sensory gating deficits reflected in clinican ratings of inattention post-treatment. Accordingly, P50 may hold significant promise as a biological indicator, or biomarker, of neural events associated with cognitive deficits in schizophrenia that can be used to inform treatment development (Luck et al., 2011) should it prove to be amenable to cognitive intervention and predictive of indivdual differences in treatment outcome.

## Hypotheses

1. Given findings by Popov and colleagues (2011a) that M50 gating can be normalized in schizophrenia patients following cognitive remediation training, it was hypothesized that P50 suppression ratios would similarly exhibit improvement from baseline to post-treatment following cognitive remediation training as compared with no change following a psychosocial treatment that served as a control condition. In addition, it was anticipated that improvements in P50 over the course of treatment would be evident clinically and reflected in symptom ratings of inattention.

2. It was further hypothesized that P50 suppression ratios prior to cognitive training would predict improvements in cognition following the intervention, expressed in both performance-based and clinician-rated measures. Specifically, schizophrenia patients with less impaired suppression at baseline were expected to benefit most from cognitive remediation training. In contrast, baseline P50 was not expected to be predictive of subsequent cognitive performance in patients who were assigned to the control condition involving a psychosocial intervention.
3. It was anticipated that treatment effects and predictive capacity would be specific to P50 and not extend to the N100 component of the ERP.

## Method

### *Participants*

Participants were drawn from the Study 1 sample (described in Chapter 2) and included 36 recent-onset schizophrenia patients who also participated in the UCLA Developmental Processes in Schizophrenic Disorders project (P.I. Keith Nuechterlein, Ph.D.). Patients were randomized to 12 months of either cognitive remediation training ($n$ = 22) or healthy behavior training ($n$ = 14), which served as a control condition. For medication treatment, participants were randomly assigned to oral versus long-acting injectable risperidone (i.e., Consta), with the exception of three patients who were maintained on aripiprazole. All patients were clinically stabilized at the time of EEG data collection and initiation of the intervention protocols.

Data from one cognitive training participant were excluded from analyses because baseline P50 data did not meet criteria (i.e., P50 amplitude to S1 did not exceed 0.5 μV). Two additional patients were excluded from the analyses (one from each treatment group) as they

dropped out of the treatment program. Therefore, the final sample included 20 patients in the cognitive remediation condition and 13 patients in the healthy behaviors condition.

*Procedure*

Prior to treatment randomization but after stabilization on study medication, cognitive and symptom assessments were conducted using the MATRICS Consensus Cognitive Battery (MCCB; Kern et al., 2008; Nuechterlein & Green, 2006; Nuechterlein et al., 2008) and the clinician-rated *Scale for the Assessment of Positive Symptoms* (SAPS; Andreasen, 1984b) and *Scale for the Assessment of Negative Symptoms* (SANS; Andreasen, 1984a). Because hypotheses were specifically related to cognitive domains of attention and working memory, aggregated performance T-scores were calculated for attention/vigilance (i.e., performance on the CPT-IP; Cornblatt et al., 1988) and working memory (i.e., performance on the WMS-III Spatial Span and University of Maryland Letter-Number Span tasks; Gold et al., 1997; Wechsler, 1977).

All patients received an intensive behavioral intervention (i.e., cognitive remediation training or healthy behavior training) for 6 months, followed by less intensive treatment of the same type for an additional 6 months. To encourage return to schooling or competitive work, all participants received supported education or employment following the Individual Placement and Support model (Becker & Drake, 2003).

Patients randomized to cognitive remediation training completed a total of 2 hours per week of a computer-assisted cognitive training program and participated in a weekly "bridging" group session to encourage transfer of learning to school and work activities for a total of 6 months, followed by less intensive training (i.e., 1 hour per week) for another 6 months. Cognitive training exercises, which increased in difficulty level, integrated bottom-up and top-down approaches using computerized training programs with a diverse range of sensory stimuli

and emphasized cognitive processes often compromised in schizophrenia (e.g., attention, memory, processing speed, executive functioning). Specific exercises were drawn from those used in Neurocognitive Enhancement Therapy (NET; Bell, Bryson, Greig, Fiszdon, & Wexler, 2005) and the Neuropsychological Educational Approach to Remediation program (NEAR; Medalia & Freilich, 2008), which included exercises that involved more complex, life-like situations (e.g., higher-order memory and problem solving; see Appendix for specific cognitive targets and exercises used in the present program). As a whole, training emphasized educational and cognitive aspects of remediation, such that patients were encouraged to reflect on unique learning styles while playing active roles in their own training programs. The intervention also fostered intrinsic motivation and enjoyment.

Patients who were randomized to healthy behavior training were instructed in behavioral components of a healthy lifestyle, including relaxation training, education in nutrition and healthy eating, and light exercise practice. These domains were chosen because they have been found to be beneficial for psychiatric patients, but do not rehabilitate cognitive impairments (Starkey, Deleone, & Flannery, 1995). Patients participated in equivalent amounts of instruction per week to that of cognitive training for 6 months followed by less intensive participation (i.e., 1 hour per week) over the next 6 months.

Cognitive assessments were conducted again following 6 and 12 months of treatment to assess improvements in response to intervention. The specific effects of cognitive remediation training versus healthy behavior training on cognitive performance in the present sample are reported by Nuechterlein et al. (2014). Symptoms were also re-evaluated throughout the interventions, including post-treatment at 12 months.

*ERP measurement*

Baseline P50 and N100 ERPs were measured as previously described (see Chapter 2) following medication stabilization but prior to participation in any intervention sessions. ERP data were also collected following 12 months of intervention in a limited sample of patients who agreed to return for EEG recording (i.e., 14 cognitive training participants and 8 healthy behavior participants). Post-treatment P50 data were excluded from analyses for 2 cognitive training participants and 1 healthy behavior participant due to P50 not meeting criteria (i.e., P50 amplitude to S1 did not exceed 0.5 μV).

*Statistical Analyses*

Independent-samples t-tests and chi-square tests were used to compare demographic and clinical characteristics between treatment groups, as well as baseline ERP and cognitive performance measures. To examine whether suppression ratios and associated clinically-rated inattention improved following intervention, a repeated-measures ANOVA was utilized, with time point (i.e., baseline and 12 months) as the within-groups factor and treatment group (cognitive remediation vs. healthy behavior) as the between-groups factor. Post-hoc repeated-measures ANOVAs were used to isolate effects within each treatment group. *Partial-eta*$^2$ ($\eta_p^2$) is reported for ANOVA effect sizes. To determine whether changes in P50 depended on the amount of intervention received, gain scores were calculated for P50 ratios and amplitudes, and Pearson correlations examined the relationship between the magnitude of P50 change and the total number of cognitive training sessions completed by each participant.

Linear regression analyses, covarying for baseline performance, were used to determine whether baseline P50 measures predicted cognitive performance following 6 and 12 months of treatment within each intervention group in a larger sample of patients with baseline P50 data. Furthermore, linear regression analyses accounting for baseline SANS inattention ratings were

used to examine whether baseline P50 measures predicted clinician-rated attentional impairments post-treatment at 12 months in each intervention group.

To examine potential confounds related to medication adherence and type, all analyses were repeated using a subsample of participants restricted to those who were medication adherent on risperidone for the duration of the 12-month protocol (i.e., excluding 3 patients stabilized on aripiprazole and 8 who discontinued risperidone but continued participation in the cognitive or psychosocial intervention). All results reported reflect the larger sample of participants in order to maximize statistical power, and any deviations in results obtained in the reduced sample are noted.

## Results

Demographic and clinical characteristics of all patients assigned to cognitive remediation and healthy behavior training are presented in Table 8. Upon treatment assignment, groups did not differ in gender, age, level of education, or positive and negative symptom severity. In addition, there were no group differences in baseline P50 and N100 measures, baseline performance on tasks of working memory and attention, and SANS inattention global scores. Furthermore, treatment groups did not differ with respect to medication adherence over the course of the 12-month treatment protocol, nor did they differ in the distribution of assigned antipsychotic medications ($\chi^2 = .25$, $p = .88$).

### *Treatment Effects on P50 Suppression and Clinical Ratings of Inattention*

In the sample constrained to patients with both pre- and post- treatment P50 data, P50 ratios decreased as a function of treatment group participation as evidenced by a significant Treatment x Time interaction effect [$F(1,17) = 4.59$, $p = .047$, $\eta p^2 = .21$; Treatment and Time main effect $F$s < 1]. Upon post-hoc examination of hypotheses of improvements in P50

suppression following cognitive remediation training, support for reductions in P50 ratio scores from pre- to post- intervention was obtained for the cognitive remediation training group [Time $F(1,11) = 9.01$, $p = .01$, $\eta p^2 = .45$] but not for patients participating in healthy behavior training [Time $F < 1$]. Although P50 amplitude to S1 did not vary across time with either type of intervention [both Time $F$s < 1], S2 P50 amplitude decreased following cognitive training [Time $F(1,11) = 9.19$, $p = .01$, $\eta p^2 = .46$] but not after healthy behavior training [Time $F < 1$]. Similar improvements in N100 amplitude and ratio scores as a function of intervention were not obtained (all $p$s > .05). P50 measures pre- and post- training are shown in Table 9 and P50 measures for patients who completed cognitive training are shown in Figure 5.

Table 8. *Demographic and clinical characteristics, as well as pre-treatment ERP and cognitive measures, in the cognitive remediation and healthy behavior intervention groups.*

| | Cognitive Training ($n$ = 20) | Healthy Behavior ($n$ = 13) |
|---|---|---|
| *Demographic and clinical characteristics* | | |
| Gender (M/F) | 15/5 | 9/4 |
| Age (years) | 22.30 (3.74) | 24.00 (4.62) |
| Education (years) | 13.50 (2.12) | 12.77 (1.69) |
| SANS (total score) | 8.05 (3.72) | 10.31 (5.85) |
| SAPS (total score) | 3.90 (4.30) | 4.77 (3.65) |
| Medication Adherence (days) | 270.60 (151.54) | 263.62 (138.36) |
| *ERP measures* | | |
| P50 S1 amplitude (μV) | 3.14 (1.45) | 3.04 (2.42) |
| P50 S2 amplitude (μV) | 1.68 (1.20) | 1.58 (1.13) |
| P50 Ratio | .65 (.56) | .61 (.29) |
| N100 S1 amplitude (μV) | -5.16 (2.82) | -5.11 (5.82) |
| N100 S2 amplitude (μV) | -2.96 (1.88) | -1.93 (1.62) |
| N100 Ratio | .71 (.63) | .68 (.57) |
| *Cognitive/symptom measures* | | |
| CPT-IP (T-score) | 35.95 (11.38) | 40.38 (14.08) |
| Spatial Span (T-score) | 46.95 (15.69) | 47.62 (12.95) |
| Letter-Number Span (T-score) | 41.75 (14.87) | 42.08 (14.11) |
| Inattention (SANS score) | 1.35 (1.14) | 1.46 (1.51) |

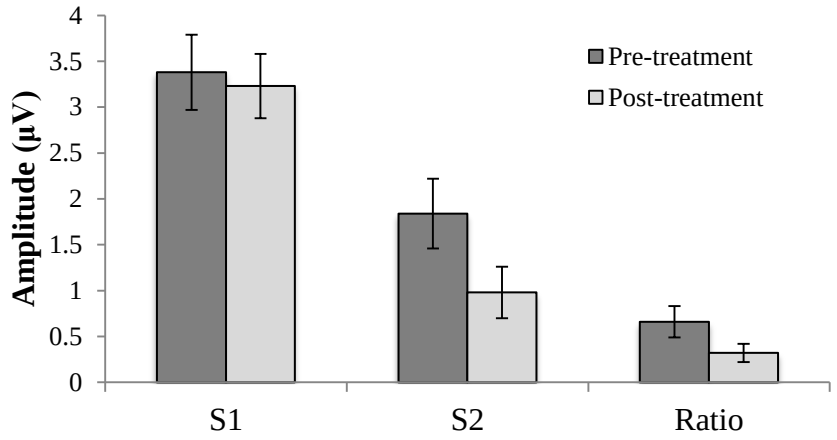
Note. Variables (except for gender) are described by mean and standard deviation. There were no significant differences in any of the above variables between treatment groups.

Table 9. *Means and standard deviations of P50 measures by treatment group, pre- and post-treatment for patients with pre- and post- treatment P50 data.*

| | Cognitive Training | | Healthy Behavior | |
|---|---|---|---|---|
| | Pre-treatment | Post-treatment | Pre-treatment | Post-treatment |
| S1 amplitude (μV) | 3.38 (1.43) | 3.23 (1.22) | 3.09 (1.58) | 2.71 (1.58) |
| S2 amplitude (μV) | 1.84 (1.32) | .98 (.97)* | 1.45 (1.25) | 1.47 (1.25) |
| Ratio | .66 (.58) | .32 (.33)* | .49 (.20) | .67 (.51) |

Note. * $p < .05$ within group.

Figure 5. *P50 measures pre- and post- cognitive remediation training.*




The magnitude of change in P50 over the course of cognitive training was significantly associated with number of sessions completed, such that more frequent participation over the course of the 12-months of intervention was associated with improvements in P50 ratio scores ($r = .586$, $p = .04$) and suppression of S2 amplitudes ($r = .748$, $p = .005$).

Despite significant improvements in P50 as a function of participation in cognitive training, benefits were not reflected in changes in symptom expression. Specifically, no significant treatment effects on SANS inattention ratings were detected as a function of the type

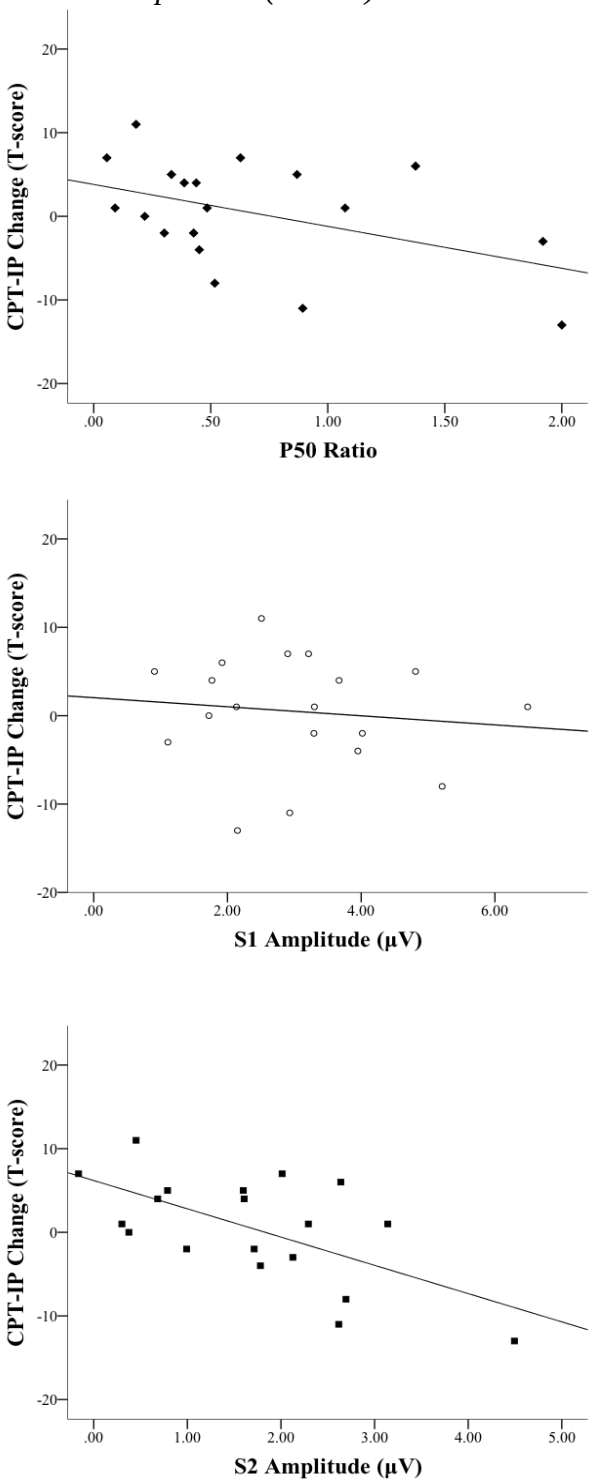
of intervention or time [Treatment x Time $F(1,18) = .04$, $p = .85$, $\eta p^2 = .002$; Treatment $F(1,18) = 3.38$, $p = .08$, $\eta p^2 = .16$; Time $F(1,18) = .04$, $p = .85$, $\eta p^2 = .002$].

*Baseline P50 Suppression as a Predictor of Treatment Response*

As shown in Figure 6, P50 suppression ratios at baseline predicted attention performance following 6 months of cognitive remediation training after accounting for baseline attention performance, such that patients with lower P50 ratios (i.e., better suppression) exhibited greater gains in CPT-IP performance ($ß = -.248$, $p = .04$). This predictive relationship appeared to be driven by an association between S2 P50 amplitude and CPT-IP performance, as individuals with lower S2 amplitudes had higher scores on the CPT-IP following 6 months of cognitive remediation training ($ß = -.336$, $p = .005$), whereas a similar association was not observed between S1 amplitude and CPT-IP performance ($p = .92$). This predictive relationship was not maintained, however, following 6 additional months of less frequent cognitive intervention ($p = .69$). As expected, P50 ratios did not predict improvement following the healthy behavior intervention after 6 months ($p = .80$) or 12 months ($p = .66$).

In contrast to attention/vigilance, P50 suppression did not predict working memory performance following 6 months of cognitive training after accounting for baseline performance (aggregated working memory T-score $p = .89$; Spatial Span $p = .38$; Letter-Number Span $p = .83$) or after 12 months (aggregated working memory T-score $p = .60$; Spatial Span $p = .44$; Letter-Number Span $p = .55$). Similarly, P50 ratio scores did not predict improvements in working memory following 6 months (aggregated working memory T-score $p = .71$; Spatial Span $p = .46$; Letter-Number Span $p = .79$) or 12 months (aggregated working memory T-score $p = .47$; Spatial Span $p = .21$; Letter-Number Span $p = .93$) of healthy behavior training.

Figure 6. *Correlations between changes in attention/vigilance performance following 6 months of cognitive remediation training. CPT-IP T-score change (T-score pre-treatment subtracted from T-score post-treatment) is plotted against P50 ratios (top), S1 P50 amplitudes (middle) and S2 P50 amplitudes (bottom).*



Consistent with the predictive association between P50 and attention performance following cognitive remediation training, P50 ratio scores significantly predicted SANS inattention ratings following cognitive training over and above baseline inattention ratings, such that patients with lower P50 ratios had lower SANS inattention scores following the intervention (*ß* = .578, *p* = .03). This effect was not attributable to either S1 amplitude (*ß* = .029, *p* = .92) or S2 amplitude (*ß* = .457, *p* = .12) alone. In patients who completed the healthy behavior intervention, the magnitude of P50 suppression did not predict SANS inattention scores (*p* = .23).

Furthermore, predictive relationships were specific to P50 as there were no significant findings when N100 measures were used as predictors of cognitive performance or SANS inattention scores (all *p*s > .05).

*Medication Effects*

When the sample was limited to participants who completed the 12-month risperidone medication protocol, findings were consistent with those reported above with two exceptions. Associations between baseline P50 suppression and CPT-IP performance following 6 months of cognitive remediation training, covarying for baseline performance, reduced to trend level significance (i.e., for P50 ratio, *ß* = -.219, *p* = .10). Of note, the predictive capacity of S2 amplitude maintained statistical significance (*ß* = -.312, *p* = .03). In addition, the relationship between P50 ratios and SANS inattention ratings following 12-months of cognitive training fell below statistical significance (*p* = .13). Importantly, all other effects on P50 remained as previously described in this reduced sample.

## Discussion

Despite the robust and growing empirical basis for cognitive remediation (e.g., Krabbendam & Aleman, 2003; Kurtz et al., 2001; McGurk et al., 2007; Suslow et al., 2001; Twamley et al., 2003), we believe this is the first investigation of the malleability of P50 sensory gating deficits following a cognitive remediation training intervention for outpatients with schizophrenia. The present study also expanded the limited research on the extent to which individual differences predict successful response to cognitive intervention by determining that baseline P50 suppression deficits are related to treatment outcome. Taken together, results of the present investigation provide evidence to confirm the utility of P50 suppression as a biomarker for aiding research efforts to uncover targets for the effective treatment of schizophrenia.

### *Treatment Effects on P50 Suppression*

Results of the present study demonstrate that P50 deficits are amenable to cognitive remediation training, with documented improvements in P50 suppression following 6 months of treatment. Similar changes were not found following a psychosocial intervention. These findings replicate and extend recent research by Popov and colleagues (2011a), who observed normalized M50 auditory gating in an inpatient sample of schizophrenia patients, by treating clinically-stable outpatients and employing a longer but less intensive intervention program. Although Popov and colleagues failed to demonstrate treatment effects on M50 when using a standard cognitive training program, the present study found significant cognitive remediation effects with a broader program that targets several cognitive domains. Of note, the treatment methods of Popov and colleagues were matched with respect to total treatment duration (i.e., 4 weeks) but they were less similar in frequency and duration of training sessions and these differences were not assessed (i.e., patients in the more effective treatment condition involving auditory

discrimination received more frequent intervention at 60-minutes per day, while patients in the broader program had three 60-90 minute sessions per week). In fact, the present study found evidence to suggest that the magnitude of improvement in P50 suppression is significantly associated with the number of cognitive training sessions completed over the course of treatment. Therefore, increasing session frequency and/or intervention duration may optimize improvements in sensory gating processes following broad interventions that target several domains of cognitive impairment.

By examining effects on S1 and S2 P50 amplitudes separately, it was revealed that improvements in P50 ratios were accompanied by significant attenuations in S2 amplitude over the course of cognitive remediation training, whereas no changes were found in S1 amplitudes, again similar to the M50 findings of Popov and colleagues (2011a). These results provide further evidence that the malleability of the P50 ratio potentially reflects improvements in sensory gating processes, with changes in gating of neural activation resulting from inhibition of P50 to S2 rather than changes in stimulus encoding in response to S1. Strikingly, P50 ratio scores and S2 amplitudes following cognitive remediation improved to such an extent that they were similar post-treatment to P50 suppression levels observed in healthy individuals reported previously (see Chapter 2) and elsewhere (e.g., Yee et al., 1998, 2010), suggesting that cognitive training has the capacity to normalize sensory gating in recent-onset schizophrenia.

Despite notable improvements in P50 suppression following intervention, changes were not reflected in SANS inattention ratings over the course of the intervention. Such results are consistent with meta-analyses reporting only a modest effect of cognitive remediation training on symptom improvement and functional outcome (e.g., see Wykes et al., 2011). It is possible that longer or more intensive interventions may be needed before detecting overt symptom changes.

Future longitudinal studies should continue to investigate aspects of symptom remission, and in particular, clinical inattention ratings, at later follow-up intervals post-treatment. Alternatively, the present investigation may have been underpowered to detect relatively small changes within the restricted range of clinical symptoms studied here.

The absence of findings involving N100 amplitude or suppression suggests that cognitive remediation interventions specifically impact the P50 suppression deficit. Future research would benefit from examination of whether P50 changes over the course of cognitive training reflect plasticity of associated neural regions, given prior reports of grey matter changes in DLPFC and hippocampus (Eack et al., 2010; Haut et al., 2010), as well as changes in disrupted white matter connectivity among associated regions (e.g., see Chapter 3). Such explorations would assist in clarifying the neural mechanisms responsible for cognitive improvements following intervention.

Finally, it is noteworthy that improvements in P50 suppression were not attributable to medication effects. Although it has been reported that antipsychotic medications, and risperidone in particular, may have a normalizing effect on P50 (e.g., see Yee et al., 1998; Nagamoto et al., 1996), the absence of a main effect of time across treatment groups, and within the healthy behavior control intervention group, implies that antipsychotic medication did not substantially contribute to improvements in P50. Consistent with this interpretation, others have shown effects of medication on P50 to be limited (e.g., Hong et al., 2009; Sanchez-Morla et al., 2009; Su et al., 2012).

*P50 Suppression as a Predictor of Treatment Response*

Consistent with study hypotheses, P50 suppression was found to be an effective predictor of improvements following cognitive remediation training with regard to both attention performance on the CPT-IP after 6 months and clinically-rated inattention symptoms after 12

months. The relationship for CPT-IP was not maintained, however, after 6 more months of less intensive treatment. As previously noted, improvements associated with cognitive remediation training may be dosage dependent, and it is possible that relationships were not obtained due to the decreased frequency of intervention. Further research is needed to determine if a more intensive version of training is necessary for lasting effects.

Nonetheless, present findings support the promise of P50 suppression as a predictor of outcome following cognitive remediation training by providing important information about which schizophrenia patients in the early stage of illness are most likely to benefit from the intervention. As such, results are consistent with the possibility that more significant impairments in P50 sensory gating may limit a patient's ability to show improvements in response to cognitive training. It may be that individuals who are less able to filter out distracting stimuli in the environment, as reflected by P50 suppression impairments, also have difficulty minimizing distraction during training and engaging in cognitive exercises and thereby preventing them from obtaining optimal benefits from cognitive skills training. Further examination of the neural mechanisms of change over the course of treatment and their associations with P50 would help to elucidate causal contributing factors.

Interestingly, there is some suggestion that genetic factors associated with the P50 deficit may predict an individual's response to cognitive remediation training. Bosia et al. (2007) examined the catechol-O-methyltransferase (COMT) valine (val) methionine (met) polymorphism, and found that schizophrenia patients who carried the met allele benefitted from cognitive remediation to a greater extent than did patients who were homozygous for the val allele. Individuals homozygous for the val allele have been found to exhibit P50 deficits to a greater extent than carriers of the met allele (e.g., Lu et al., 2007). Given that both COMT

polymorphism and P50 suppression deficits predict cognitive performance following cognitive remediation training, research using multiple levels of analysis is needed to determine whether P50 sensory gating may be providing an important intermediate pathway through which genetically-mediated differences in neural activity impact cognitive performance in response to cognitive remediation.

Findings from the present investigation also support the specificity of P50 in its predictive capacity, as baseline N100 measures were unrelated to improvements following cognitive training. These results again highlight the relative importance of the S2 P50 amplitude, as the predictive relationship of P50 suppression and CPT-IP performance appeared to be driven by S2. Similar to our observations involving the malleability of the P50 response to S2, there was further confirmatory evidence to suggest that P50 suppression deficits reflect impairments in inhibitory gating attributed to deficient suppression of the response to S2, rather than an abnormal response to S1. The predictive utility of the S2 P50 as a sole indicator may be limited, however, as only the P50 ratio score predicted clinically-rated inattention following 12 months of intervention and not P50 to S2.

The absence of evidence supporting the hypothesized association between P50 suppression and training effects in the working memory domain raises several possibilities that are not mutually exclusive. As suggested by Nuechterlein and colleagues (2014), it may be that the cognitive remediation procedure used in the present study was more effective at improving attention than working memory. Additionally, patients' mean CPT-IP score at baseline was approximately 1.5 standard deviations below the normative population sample mean, whereas working memory performance was in the normative range at baseline, which possibly limited the amount of improvements patients could make and therefore restricted the range in which

associations could be discovered. Alternatively, baseline P50 gating may interact to a greater extent with the attentional processes captured by the CPT-IP task. As previously noted, working memory and attention are interrelated processes (Awh et al., 2006), such that an individual's working memory capacity may predict the ability to attend selectively (e.g., Giuliano, Karns, Neville, & Hillyard, 2014). For example, Fukada and Vogel (2009) demonstrated that individuals with high working memory capacity were more capable of resisting attentional capture by salient but otherwise irrelevant stimuli than those with low working memory capacity. Consistent with previous findings of an association between P50 suppression and working memory (see Potter et al., 2006 and see Chapter 2), it may be that when P50 suppression is less compromised at baseline it provides patients with an opportunity to capitalize on intact aspects of working memory and to improve in attentional control following cognitive training.

*Limitations and Future Directions*

The present study has several limitations. First, the intervention study did not allow for examination of medication-free patients. However, there were no differences in medications and dosage between the treatment groups, so it is unlikely that a medication confound influenced the results. And as noted above, the P50 effects could not be attributed to medication alone. Second, three patients were stabilized on aripiprazole rather than risperidone although the same pattern of results were reproduced in the sample limited to participants on risperidone only. Lastly, the investigation was limited by a relatively small sample size and would have benefitted from additional follow-up time point assessments to determine any lasting effects of treatment.

Despite these limitations, the present study provides initial evidence for training-induced plasticity of P50 sensory gating deficits in schizophrenia patients by demonstrating improvements in P50 suppression deficits in response to cognitive remediation training.

Furthermore, present findings suggest that P50 suppression is a useful indicator of successful change as a function of cognitive remediation training, providing further support for P50 as a promising biomarker of schizophrenia. Future longitudinal studies will help to establish optimal cognitive training procedures that improve cognitive and functional outcomes and promote further plasticity of compromised neural systems in schizophrenia.

# Chapter 5: General Discussion

The present dissertation examined the P50 ERP component as an intermediate phenotype between clinical symptoms and disrupted neural processes that may contribute to cognitive dysfunction in schizophrenia. Despite consistent evidence that schizophrenia patients exhibit impaired P50 suppression compared to healthy individuals, the clinical significance and neural mechanisms associated with the P50 deficit have remained poorly understood to date. Therefore, the present dissertation sought to more clearly define the clinical and neurobiological correlates of the P50 suppression deficit in schizophrenia by further examining its association with symptoms and cognitive impairments, exploring dysfunction in associated neural networks, and identifying its role in intervention with respect to its malleability and its utility in predicting treatment outcome.

## *Summary of Results*

The results presented in Chapters 2-4 address the questions and objectives stated in the General Introduction, as follows:

1. How does P50 relate to clinical symptoms and real-world functioning in schizophrenia?

Given mixed results regarding the clinical relevance of P50 (e.g., Potter see et al., 2006), Study 1 examined the association between P50 deficits and positive and negative symptom ratings in schizophrenia. Results confirmed the hypothesis that P50 suppression deficits are associated with clinician ratings of attentional impairments, a core clinically-observed characteristic of schizophrenia. In contrast, P50 was not associated with any other negative symptom domains or positive symptom ratings. Although attentional deficits likely impact functional capacity to some extent, P50 was not found to be significantly associated with specific domains of role functioning (i.e., work productivity, independent living/self-care, and

interpersonal relationships with family and friends). Nevertheless, the findings of Study 1 suggest that P50 suppression may be a promising indicator of early sensory processing abnormalities that relates to patients' symptoms of inattentiveness.

2. Are P50 suppression deficits related to other aspects of cognitive dysfunction in schizophrenia?

In addition to linking P50 to a clinically observed feature of schizophrenia, Study 1 also provided evidence for an association with working memory performance on tasks that require maintenance as well as manipulation of briefly stored material. Furthermore, results of Study 3 demonstrated a relationship between P50 suppression and cognition, showing that P50 deficits predicted improvements on an attention/vigilance task as well as improvements in clinically-rated inattention, over the course of a cognitive intervention. Taken together, these results suggest that P50 suppression deficits in schizophrenia are strongly associated with aspects of cognitive dysfunction and its successful treatment.

3. Is the P50 suppression deficit associated with disrupted connectivity of neural white matter tracts?

The results of Study 2 demonstrated associations between P50 suppression and disrupted neural connectivity of regions hypothesized to be involved in the generation of P50. Specifically, relationships were demonstrated between P50 ratios and mean FA of several lateralized or bilateral white matter tracts, including the ATR, AF, fornix, CGC, IFOF, and UF, such that individuals with compromised integrity of these tracts had poorer P50 suppression. In contrast, there were no associations involving tracts implicated in the pathophysiology of schizophrenia but that connect regions not suspected to be involved in P50, such as the CC major/minor and ILF. These findings suggest that in addition to distinct neural regions, disruptions in white matter

networks connecting relevant regions may also account for P50 inhibitory deficits in schizophrenia.

4. Does cognitive remediation training improve P50 deficits in patients with schizophrenia?

Study 3 revealed that P50 suppression deficits are responsive to cognitive intervention. P50 ratios and S2 amplitudes improved significantly over the course of 12 months of a cognitive remediation treatment, whereas P50 suppression did not improve for schizophrenia patients who participated in an intervention that did not target domains of cognitive functioning. Importantly, P50 ratios following cognitive remediation training improved to levels that have been reported for healthy individuals (e.g., as in Study 1), suggesting that cognitive intervention may have the capacity to normalize P50 suppression in schizophrenia.

5. Is P50 suppression predictive of response to cognitive remediation training?

Study 3 confirmed that P50 suppression ratios prior to initiation of cognitive remediation intervention predicted improvements in attention/vigilance following six months of cognitive remediation training. In addition, baseline P50 suppression ratios predicted improvements in clinician-rated levels of inattentiveness. None of these predictive relationships were replicated in patients who completed a control psychosocial intervention. These results suggest that P50 suppression is a promising candidate for predicting outcome following cognitive remediation training, indicating which patients may receive the most benefit from cognitive intervention.

6. Are the relationships under investigation specific to P50 gating, or do they extend beyond the sensory gating phase of information processing and apply to other ERP measures elicited during the paired-stimulus paradigm, such as N100?

Although Study 1 demonstrated the expected reductions in S1 and S2 N100 amplitudes of schizoprenia patients relative to healthy comparison subjects, evidence for a statistically

significant N100 gating deficit was not found. In patients, N100 measures were not associated with clinical or neurobiological phenomena investigated in the present series of studies, suggesting that all results were specific to earlier stages of information processing as reflected by P50.

*Conclusions*

Cognitive dysfunction is pervasive in schizophrenia, with strong evidence supporting its significant impact on functional outcomes (Green et al., 2004, 2006). Identifying biomarkers that provide reliable and sensitive measures of the neurobiological processes associated with cognitive dysfunction has therefore become a major priority for research aiming to aid in the development of therapeutic targets for this chronic and debilitating mental illness (Luck et al., 2011). By evaluating P50 suppression as an intermediate phenotype between clinical presentation and neuronal mechanisms that may contribute to cognitive deficits, the present dissertation provides evidence to suggest that P50 suppression holds promise as one such biomarker of schizophrenia.

As noted by Luck and colleagues (2011), ERPs hold great potential as valuable biomarkers of cognitive dysfunction by providing a direct measure of neural activity that may be used to improve treatment development for schizophrenia. Requisite characteristics of the ERP include indicating clinical state by correlating with symptom status across time and providing opportunities to detect individual differences in treatment response. Together, results of the present series of studies relate compromised neuronal functions associated with P50 dysfunction to specific cognitive and clinical phenomena in schizophrenia that may be treatable with cognitive remediation interventions. Evidence has also been provided to link P50 deficits to neural networks and disease mechanisms that have been previously implicated in cognitive

impairment in schizophrenia. By examining multiple levels of analysis, the present investigation assists in clarifying aspects of the underlying biological processes involved in symptom expression in the illness.

As a state indicator of cognitive dysfunction that varies with severity of specific symptoms, P50 may also be a useful indicator of treatment outcome by marking change over the course of cognitive intervention. In the present research, improvements in cognitive performance following cognitive remediation training were reflected both on a neural level, via training-induced plasticity of P50 deficits, and on a clinical level, with improvements in attentional performance and clinically-rated inattention. Importantly, the demonstrated malleability of P50 suppression implies that P50 may be an immediate measure of the biological effects of candidate intervention targets. In addition, given that P50 suppression is associated with disrupted cognitive processes prior to treatment and predicts treatment response, P50 may be a useful tool for tracking illness severity as newly developing interventions are evaluated. Furthermore, P50 suppression deficits may prove useful in predicting individual differences in treatment response, defining subgroups of patients who are likely to receive the most benefit from cognitive remediation treatments.

*Limitations and Future Directions*

Despite the promising findings, the present investigations were limited in several aspects. First, analyses did not directly examine the relationship between P50 and phase of illness. In order to maximize sample size and statistical power, recent-onset and chronic schizophrenia patient groups were collapsed to form a single schizophrenia patient group for Studies 1 and 2. Although the patient groups did not differ in the extent of P50 deficits, future work would benefit from recruitment of larger samples that would allow for exploration of whether the nature of

relationships between P50 and clinical and cognitive symptoms vary through the prodromal, recent-onset, and chronic phases of illness. Additionally, because patients who participated in these studies were clinically stable and relatively low in rated symptom levels, they may not be entirely representative of the broader schizophrenia population.

Although the current studies confirmed hypothesized P50 relationships from neural pathways to clinical expression, they were largely cross-sectional and correlational in nature, therefore limiting the ability to define causal relationships and identify mediating neural mechanisms, particularly with regards to the association between P50 and improvements in cognitive performance in response to treatment. In addition, the present investigations relied on a wide range of clinical, behavioral, and neuroimaging assessment measures that did not allow for concurrent measurement. Future work would benefit from larger scale longitudinal studies that allow for the study of the neural systems that underlie P50 suppression throughout the course of illness, as well as its associated neural changes in response to intervention.

Despite the noted limitations, the present results provide important information regarding the clinical significance of P50 suppression deficits, and begin to clarify associated disruptions in neural pathways in schizophrenia. Furthermore, the present dissertation offers initial evidence that P50 suppression deficits are amenable to cognitive remediation intervention. By integrating neurophysiological and behavioral assessments, the present results support P50 suppression as a viable biomarker that may ultimately help to inform development of behavioral and pharmacological interventions for cognitive dysfunction in schizophrenia.

Appendix. Cognitive training targets and exercises (Chapter 4).

| Target Skill | Cognitive Exercise |
|---|---|
| *Fundamental Skills* | |
| Attention and Processing Speed | Simple Visual Reaction |
| | Simple Auditory Reaction |
| Attention (Multiple Dimensions) | Simultaneous Multiple Attention |
| Attention (Multiple Objects) | Frogger |
| Memory (simple) | Sequential Recall Digits Auditory |
| | Sequential Recall Words Visual |
| | Spatial Memory |
| | Frippeltration |
| *Intermediate Skills* | |
| Memory (intermediate) | Recognition Recall |
| | Verbal Memory Categorizing |
| | Paired Associates Recall |
| | Phone Message |
| Problem Solving (simple) | Frippeltration |
| | Factory |
| | Stocktopus |
| | Pyramids |
| *Complex Skills* | |
| Problem Solving (complex) | Carmen San Diego |
| | Math for the Real World |
| | Grammar for the Real World |
| | Ice Cream Truck |
| | Mission Think |
| | Mountain Rescue |
| | Logic Quest |

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