Psychophysiology, 43 (2006), 320–328. Blackwell Publishing Inc. Printed in the USA.

DOI: 10.1111/j.1469-8986.2006.00408.x

P50 sensitivity to physical and psychological state influences

PATRICIA M. WHITE AND CINDY M. YEE
Department of Psychology, University of California, Los Angeles, Los Angeles, California, USA

Abstract

Although P50 is described as a largely preattentive process, increasing evidence suggests that the psychological state of a participant may influence P50 and its suppression. A paired-stimulus paradigm was used to examine the contributions of variability in stimulus parameters and state factors, such as expectancy and vigilance, on P50. Results obtained from 34 healthy subjects indicate that stimulus intensity and background stimulus intensity influenced P50 amplitude whereas stimulus duration had no significant impact. Importantly, P50 suppression varied with fluctuations in P50 amplitude to the first stimulus, and both P50 and its suppression reflected possible declines in attention or vigilance over the course of the session. Findings from this study suggest that P50 is not entirely preattentional and may reflect the psychological state of a participant. Implications of these results for research with schizophrenia patients are discussed.

Descriptors: P50, Sensory gating, Stimulus parameters, Attention, Schizophrenia

Patients with schizophrenia have been characterized as experiencing difficulty with filtering sensory information, suggesting a deficit in inhibitory mechanisms (e.g., Braff, 1993; Freedman et al., 1987, 1996). Normal filtering involves a reduced response to certain stimuli, allowing individuals to regulate attention by ignoring or inhibiting responses to irrelevant stimuli and attending to pertinent information. In studies with nonpsychiatric subjects, it has been widely demonstrated that the auditory P50 component of the event-related potential (ERP) is reduced in response to a second stimulus (Stimulus 2) relative to the response elicited by the first stimulus (Stimulus 1) when the two stimuli are delivered 500 ms apart. The initial stimulus is believed to initiate an inhibitory process that then, in turn, suppresses the neural response to the second stimulus (e.g., Eccles, 1969). A metric frequently used to describe the relationship between these two responses is the Stimulus 2/Stimulus 1 suppression ratio, a quantitative index of observed degree of inhibition.

Failure to exhibit P50 suppression is often interpreted as evidence of a loss of normal inhibition (e.g., Freedman et al., 1987). Observations of substantially higher ratios (i.e., less suppression) among schizophrenia patients have been reported by numerous research laboratories (e.g., Adler et al., 1982; Boutros, Zouridakis, & Overall, 1991; Clementz, Geyer, & Braff, 1997; Jin et al., 1997; Judd, McAdams, Budnick, & Braff, 1992; Myles-Worsley, 2002; Thoma et al., 2003; Ward et al., 1996; Yee, Nuechterlein, Morris, & White, 1998), although group differences have not emerged consistently when the intensity of auditory stimuli approaches or falls within the startle-eliciting range (e.g., Arnfred, Chen, Glenthøj & Hemmingsen, 2003; Griffith, Hoffer, Adler, Zerbe, & Freedman, 1995; Jin et al., 1998; Kathmann & Engel, 1990).

In the clinical research literature on schizophrenia, P50 suppression has been generally regarded as a largely preattentive process (e.g., Boutros, Belger, Campbell, D'Souza, & Krystal, 1999; Braff & Light, 2004; Freedman et al., 1987; Jerger, Biggins, & Fein, 1992) and has attracted considerable interest as a putative marker, or endophenotype, for vulnerability to the illness. Meta-analytic studies reveal an effect size of 1.55 when comparing P50 suppression in schizophrenia patients with that of healthy comparison subjects, exceeding all other widely investigated neurobiological and neurocognitive abnormalities (Bramon, Rabe-Hesketh, Sham, Murray, & Frangou, 2004; Heinrichs, 2001). In fact, research with this measure has progressed to reliance upon P50 suppression as a possible endophenotype in genetic linkage analyses (e.g., Freedman et al., 1997) and the recommendation that P50 suppression serve as a target in developing new pharmacological agents for the treatment of schizophrenia (Braff & Light, 2004). If P50 is to be considered a trait marker of schizophrenia or an index of psychopharmacological efficacy, an understanding of not only the moderating

The research was supported in part by an award from the Committee on Research of the Academic Senate of the Los Angeles Division of the University of California, and by a predoctoral fellowship from the National Institute of Mental Health (MH14584). We gratefully acknowledge Maria Nazarin, Halle Jones, and Valerie Gilman for assistance with data collection, and Bill Troyer for technical and software support. Order of authorship is arbitrary, as both authors contributed equally to this study. Patricia M. White is now at the University of Oregon.

Address reprint requests to: Cindy M. Yee-Bradbury, Department of Psychology, University of California, Los Angeles, 405 Hilgard Avenue, Los Angeles, CA 90095-1563, USA. E-mail: yee@psych.ucla.edu.

effects of stimulus parameters but also any influence that the psychological state of research participants may exert on this ERP is essential. As with other sensory or exogenous components, P50 amplitude to paired stimuli is assumed to be controlled primarily by the physical properties of the eliciting stimulus (Donchin, Ritter, & McCallum, 1978). Evidence suggests, however, that some midlatency ERPs may be sensitive to psychological factors such as attention and stress, as reviewed below. The goals of this study were to evaluate the contributions of physical parameters, such as stimulus intensity and duration, along with psychological state factors, such as expectancy and vigilance, on P50 amplitude and to assess the influence of variability in P50 amplitude to Stimulus 1 and Stimulus 2 on the resulting P50 suppression measure.

Physical Properties of the Stimulus

As noted by several researchers (e.g., Griffith et al., 1995; Judd et al., 1992; Naber, Kathmann, & Engel, 1992), considerable variability in stimulus intensity has existed across P50 studies, perhaps accounting for the failure by Kathmann and Engel (1990) to replicate P50 suppression differences between schizophrenia patients and normal comparison subjects. Studies designed to investigate this possibility found a linear increase in P50 amplitude relative to stimulus intensity, but an appreciable impact on the suppression ratio in nonpsychiatric subjects was not seen until the sound intensity approached the startle-eliciting range (Griffith et al., 1995; Lamberti, Schwarzkopf, Crilly, & Martin, 1993; Naber et al., 1992). Additionally, P50 studies have differed in the use of white noise to mask ambient sounds, ranging from no background noise (e.g., Freedman et al., 1987) to the continuous presentation of 60 dB SPL white noise (e.g., Clementz et al., 1997). As the impact of background noise on P50 appears to be relatively unexplored in the literature, the potential influence of white noise remains an empirical question.

In addition to a louder stimulus, Kathmann and Engel (1990) relied on a somewhat longer stimulus duration of 1.5 ms. Most other studies have used a stimulus generated by amplifying a 0.04-ms square wave pulse (e.g., Freedman et al., 1987; Judd et al., 1992; Smith, Boutros, & Schwarzkopf, 1994). As Kathmann and Engel noted, it is difficult to ascertain the extent to which the duration of their stimuli differed from other studies, as amplification and filtering of the auditory signal can lengthen the duration of the stimulus. Furthermore, transducers can vary dramatically in their temporal compliance with such brief inputs. It remains to be determined whether lengthening the duration of stimuli would alter suppression of the P50 response. A comparison between studies suggests that this is an unlikely possibility, as others have obtained the basic P50 suppression effect with auditory stimuli extending up to 10 ms (Guterman, Josiassen, & Bashore, 1992). Nevertheless, the impact of stimulus duration on P50 has yet to be examined directly.

Psychological State Factors

Reports concerning the influence of psychological state on middle-latency components have been mixed. Using trains of single, auditory stimuli, McCallum, Curry, Cooper, Pocock, and Papakostopoulos (1983) demonstrated that amplitude changes in components occurring as early as 19 ms after stimulus onset are associated with attentional selectivity. Early effects of attention on P20-50 and P50 also have been obtained with dichotic listening (Woldorff & Hillyard, 1991; Woldorff et al., 1993) and oddball tasks (Boutros et al., 1995), respectively. Relying on pairs of stimuli, Guterman et al. (1992) reported that P50 suppression in nonpsychiatric subjects can be reduced with an attentional manipulation that requires participants to maintain a running memory count of a designated stimulus. Other investigators, however, have failed to replicate this effect on P50. Hillyard, Hink, Schwent, and Picton (1973), for example, presented trains of auditory stimuli and found that P50 amplitude was relatively unaltered by attentional changes associated with irregular interstimulus intervals. Using tasks that required subjects to direct voluntary attention to the first or second stimulus in a pair, Jerger et al. (1992) also did not find any influence on P50 amplitude. This finding was subsequently replicated by White and Yee (1997). Thus, definitive evidence concerning whether attentional factors influence P50 has not yet been established.

One relevant factor that has been largely overlooked but that could also influence P50 is expectancy, particularly as it relates to the predictability of the stimulus pairs. In the typical paired-stimulus paradigm, expectancy is controlled by the intertrial interval (ITI), with variable ITIs offering less predictability. Although the P50 suppression effect has been obtained using fixed (e.g., Freedman et al., 1987) as well as variable ITIs (e.g., Jerger et al., 1992), research has focused primarily on identifying the optimum interval between paired stimuli (e.g., Zouridakis & Boutros, 1992). Studies contrasting the use of fixed versus variable ITIs to determine any distinct contribution of expectancy on P50 have yet to be reported. The extent to which P50 might be altered by expectancy was assessed here by comparing data collected with a highly predictable, fixed ITI versus a variable ITI.

Along with attention, other psychological factors have been implicated as influencing P50. Acute psychological stress, for instance, has been shown to disrupt P50 suppression in nonpsychiatric subjects (White & Yee, 1997; Yee & White, 2001). Pain, induced by a cold pressor test, also has led to transient loss of suppression of the P50 response in healthy subjects (Johnson & Adler, 1993). Among schizophrenia patients, an association has been found not only between P50 and clinical ratings of attentional impairment (e.g., Erwin, Turetsky, Moberg, Gur, & Gur, 1998; Yee et al., 1998) but also anxiety (Yee et al., 1998), although other clinical researchers have failed to find a relationship with negative symptoms (e.g., Adler et al., 1990; Thoma et al., 2005; Ward et al., 1996). Taken together, the existing research literature underscores the possibility that, although P50 may be modulated primarily by the physical parameters of a stimulus, it also may reflect to some extent the psychological state of the subject.

Given the duration of P50 test sessions, fatigue, drowsiness, habituation, restlessness, and boredom constitute another set of factors. Clementz et al. (1997) observed that differences in P50 suppression between schizophrenia patients and control subjects were somewhat diminished by the second trial block, based on 30 trials in each block. In nonpsychiatric subjects, Naber et al. (1992) also noted decreases in P50 amplitude across three blocks of 50 trials each. Comparing four blocks of 30 trials each, Lamberti, Schwarzkopf, Boutros, Crilly, and Martin (1993) observed poorer P50 suppression in the second and fourth blocks relative to the first and third blocks among healthy subjects. Schwarzkopf, Lamberti, and Smith (1993), in contrast, did not observe any P50 differences across two trial blocks. Naber et al. employed the longest test period, noting that nearly all subjects reported fatigue by the end of the session; they proposed that P50 decrements might be associated with reductions in vigilance.

Examination of P50 over a substantially longer test period should serve to clarify this possibility.

Experimental conditions that involve minimal task demands, such as the P50 paradigm, may also be susceptible to shifts in psychological set from moment to moment. Subjects, for instance, likely respond with varying degrees of attention or alertness from trial to trial. Visual inspection of P50 recordings often reveals considerable variability within the same individual, although the basis for such fluctuations is unclear. Examining the impact of P50 to Stimulus 1 on the ratio score and the extent to which comparable levels of suppression are obtained across trials may be particularly relevant to evaluating group differences, as schizophrenia patients may exhibit increased variability relative to healthy subjects (Patterson et al., 2000). Variability in P50 could also contribute to poor test–retest reliability of P50 suppression indices (e.g., Lamberti, Schwarzkopf, Boutros, et al., 1993). Additionally, P50 suppression deficits in schizophrenia patients have been attributed to a heightened P50 to Stimulus 2 (e.g., Freedman et al., 1987; Freedman, Adler, Waldo, Pachtman, & Franks, 1983) as well as to an attenuated response to Stimulus 1 (e.g., Clementz & Blumenfeld, 2001; Clementz et al., 1997), highlighting the need to consider the stability of P50 amplitude to the initial stimulus (Smith et al., 1994).

In summary, the present study was designed to examine the relative contributions of (a) specific physical properties of the eliciting stimuli and (b) psychological state factors on P50 amplitude and P50 suppression. If P50 is largely automatic or preattentive, it was expected that only physical qualities of the auditory stimuli would influence the component. Three levels of stimulus duration, stimulus intensity, and background intensity were manipulated in the present study to assess their contributions. In contrast, if P50 is affected not only by physical properties of the stimulus but also by psychological state factors, these variables should have a measurable impact on P50. Specifically, the potential influence of expectancy was assessed by examining stimulus predictability and comparing the impact of a fixed versus variable ITI. The effect of possible declines in attention or vigilance associated with fatigue was evaluated by examining ERP averages computed over successive blocks of trials. The potential for variability in P50 amplitude to contribute to the suppression ratio measure was assessed by constructing ERP averages for each participant on the basis of their largest and smallest P50s to the initial stimulus. To evaluate the relative specificity of any effects on P50, parallel analyses were conducted on N100, as these two components appear to reflect distinct aspects of information processing (e.g., Boutros, Korzyukov, Jansen, Feingold, & Bell, 2004).

Method

Participants

Thirty-four subjects, between 18 and 35 years of age, participated in this study. Cohort 1 consisted of 7 men and 7 women. Two of the participants from Cohort 1 were graduate students; the remaining 12 subjects were undergraduates who received course credit for their participation. Cohort 2 included 10 men and 10 women who were all undergraduates. As described below, the primary distinction between the two cohorts was the number of conditions completed and the number of trials included during each condition. For both cohorts, participants reporting a personal history of drug or alcohol abuse or a personal history of neurological or psychiatric disorders were excluded from analysis. Participants who indicated regular tobacco use also were excluded, as nicotine may have a transient effect on P50 suppression (Adler, Hoffer, Griffith, Waldo, & Freedman, 1992). One White male participant from Cohort 1 was excluded as a measurable P50 response to Stimulus 1 could not be detected in at least one of the eight conditions. Two Asian American women and 3 Asian American men from Cohort 2 were excluded for the same reason. The remaining 13 men and 15 women (15 White, 9 Asian American, 3 African American, and 1 biracial) were included in all reported analyses unless indicated otherwise. The mean age of this sample was 20.8 years ($SD = 3.8$). All participants provided informed consent and received audiometric testing to verify normal hearing.

Electrophysiological Recording Methods and Apparatus

The electroencephalogram (EEG) was recorded from three midline scalp electrode sites, Fz, Cz, and Pz, and referenced to linked electrodes placed on the ear lobes. Vertical eye movement (EOG) was recorded by placing electrodes above and below the right eye. All of these measures were recorded from Sensormedics miniature Ag-AgCl electrodes and all impedances for recording electrodes were below 5,000 Ω. Signals were collected with a Grass Model 12 Neurodata Acquisition System with analog filters at 0.1 and 1000 Hz. EEG signals were amplified 20,000 times whereas EOG was amplified 5000 times. Data were sampled for 1200 ms at 1000 Hz within each channel, beginning 200 ms prior to stimulus presentation. Stimulus presentation and data collection were controlled with custom software using a Keithley Metrabyte DAS1602 laboratory data acquisition board on a Dell computer.

Auditory Stimulation

Digital auditory stimuli and all background noise were created by amplification of white noise generated by a San Diego Instruments Sound Generator board, amplified further through a Coulbourn Instruments Audio Mixer-Amplifier, and delivered to the subject over Realistic Nova ′28 headphones (Tandy Corporation, TX). Duration and intensity of the digital auditory stimuli were controlled by a DAS 1602 D/A board. In each instance, auditory stimuli resulted in the subjective experience of hearing a click. Sound levels of the stimuli were verified with a Davis Instruments SL-130 sound level meter (A scale) by relying on sustained presentation of white noise over several seconds. Stimulus 1 and Stimulus 2 were separated by a 500-ms interstimulus interval. Unless noted otherwise, the ITI varied between 7 and 10 s.

Procedure

Participants were administered stimuli while awake and seated upright in a sound-attenuated room. They were instructed to sit quietly and listen for the duration of the testing procedure. Within each experimental condition, Stimulus 1 and Stimulus 2 were of the same duration and auditory intensity.

For Cohort 1, four parameters of the paired stimuli were manipulated: (1) stimulus intensity was measured at 80 dB SPL, 90 dB SPL, and 100 dB SPL, all with a 40 dB SPL background noise and a stimulus duration of 3 ms; (2) stimulus duration was measured at 1 ms, 3 ms, and 5 ms, all with a 90 dB SPL and 40 dB SPL background noise; (3) background noise level was measured at 0 dB SPL, 40 dB SPL, and 55 dB SPL, all with 90 dB SPL paired stimuli that were 3 ms in duration; (4) ITI was fixed at 10 s

Table 1. *Experimental Conditions*

Condition	Stimulus parameters			
	Stimulus intensity (dB)	Background intensity (dB)	Stimulus duration (ms)	ITI (s)
1	90	40	3	10
2	90	40	3	7–10
3	80	40	3	7–10
4	100	40	3	7–10
5	90	0	3	7–10
6	90	55	3	7–10
7	90	40	1	7–10
8	90	40	5	7–10

or varied between 7 and 10 s with paired 90 dB SPL stimuli, presented over a 3 ms duration against a 40 dB SPL background.

This series of experimental manipulations generated a total of eight conditions (see Table 1) under which participants from Cohort 1 were tested, with the order of conditions counterbalanced across subjects. Each participant received 80 trials under each condition, and was given a 3-min break between conditions.

Participants in Cohort 2 were administered the same eight conditions delivered to subjects in Cohort 1, with 60 trials included in each condition. A ninth condition, in which auditory stimuli were comprised of a 0.04-ms square wave delivered at 90 dB SPL with 40 dB SPL background noise, was excluded from the present report. Again, condition order was counterbalanced across subjects. So as to include a comparable number of trials for both cohorts, only the first 60 trials of data were included for each condition for Cohort 1.

Waveform and Component Analysis

Single EEG trials were screened with a computer algorithm and excluded from the average if EEG at any electrode site saturated the A/D converter ($>\pm$ 256 μV). Those individual trials remaining after this preliminary screening were corrected for the effect of eye movement using a procedure that removes ocular noise (Gratton, Coles, & Donchin, 1983; Miller, Gratton, & Yee, 1988). Finally, single trials were digitally filtered at 10–50 Hz for measurement of the P30 and P50 components and at 1–20 Hz for measurement of the N100 (e.g., Jerger et al., 1992). A minimum of 54 trials was included in each average.

All ERP components were scored at the Cz site. Using a baseline-to-peak measure, N100 amplitude was identified as the most negative point in the 50–150-ms poststimulus window and P30 was identified at the most positive peak between 20 and 40 ms; both were measured relative to a 200-ms prestimulus baseline. Unless otherwise noted, P50 amplitude was reported as a peak-to-peak measure; it was scored relative to the preceding negativity that was identified as the maximum negativity between the P30 latency and the P50 latency. A baseline-to-peak measure of P50 also was computed by identifying P50 as the maximum positivity between 40 and 70 ms poststimulus, relative to the 200–ms prestimulus baseline.

To examine the effects of the experimental conditions on P50 and N100 amplitude, repeated measures ANOVAS were conducted with two fully crossed within-subject factors: condition (e.g., stimulus intensity, stimulus duration, etc.) and stimulus (i.e., Stimulus 1 and Stimulus 2) to provide a difference score measure of suppression. P50 suppression also was assessed with the Stimulus 2/Stimulus 1 ratio measure. Hypotheses were tested with ANOVA for mixed design (BMDP), and Geisser and Greenhouse (1958) corrected p values were used throughout. Follow-up analyses were performed using the Newman–Keuls statistic at a 95% level of confidence.

Results

Assessment of Stimulus Parameters

Experimental conditions used to examine the impact of stimulus parameters on P50 were three levels of stimulus intensity (80, 90, and 100 dB SPL), three levels of background intensity (0, 40, and 55 dB SPL), and three levels of stimulus duration (1, 3, and 5 ms). To assess the effects of stimulus predictability, experimental conditions were a fixed (10 s) versus variable (7–10 s) ITI. In all instances involving a main effect for stimulus, a significantly larger response was elicited by Stimulus 1 than Stimulus 2; given the consistency of this effect, individual analyses are not described in each instance below. The mean values and standard deviations for P50 amplitude, the P50 suppression ratio, and N100 amplitude for each of the experimental conditions are presented in Table 2.

P50. For stimulus intensity and background intensity conditions, main effects for condition (intensity: $F[2,54] = 24.14$,

Table 2. *Mean P50 and N100 Amplitude in Microvolts (SD) and P50 Ratio Score for the Experimental Conditions*

	P50 amplitude			N100 amplitude	
	Stimulus 1	Stimulus 2	P50 ratio	Stimulus 1	Stimulus 2
Stimulus intensity					
100 dB SPL	6.0 (2.8)	2.5 (1.5)	.42 (.27)	– 15.8 (5.4)	– 5.4 (2.7)
90 dB SPL	4.6 (2.3)	1.7 (1.2)	.38 (.29)	– 9.7 (3.8)	– 4.0 (2.0)
80 dB SPL	4.1 (2.0)	1.5 (1.1)	.38 (.35)	– 7.9 (3.2)	– 3.3 (2.0)
Background intensity					
0 dB SPL	4.8 (2.2)	1.7 (1.4)	.35 (.29)	– 10.2 (4.8)	– 3.7 (2.3)
40 dB SPL	4.6 (2.3)	1.7 (1.2)	.38 (.29)	– 9.7 (3.8)	– 4.0 (2.0)
55 dB SPL	3.6 (1.7)	1.8 (1.3)	.51 (.36)	– 8.8 (3.7)	– 3.5 (2.0)
Stimulus duration					
1 ms	4.2 (2.2)	1.6 (1.1)	.39 (.24)	– 9.0 (4.5)	– 3.6 (2.4)
3 ms	4.6 (2.3)	1.7 (1.2)	.38 (.29)	– 9.7 (3.8)	– 4.0 (2.0)
5 ms	4.8 (2.0)	1.7 (1.3)	.35 (.24)	– 11.4 (5.9)	– 4.2 (2.3)
Intertrial interval					
Fixed	5.1 (2.3)	2.2 (1.5)	.43 (.28)	– 10.8 (5.0)	– 4.1 (2.9)
Variable	4.6 (2.3)	1.7 (1.2)	.38 (.29)	– 9.7 (3.8)	– 4.0 (2.0)

$p < .001$; background intensity: $F[2,54] = 6.72$, $p < .01$) and stimulus (intensity: $F[1,27] = 89.39$, $p < .001$; background intensity: $F[1,27] = 97.16$, $p < .001$) were qualified by significant Condition × Stimulus interactions (intensity: $F[2,54] = 4.11$, $p < .05$; background intensity: $F[2,54] = 6.55$, $p < .01$). This pattern of effects for stimulus intensity is shown in Figure 1. Follow-up comparisons revealed that P50 amplitude to Stimulus 1 was significantly larger to 100 dB SPL than to 90 or 80 dB SPL stimuli whereas P50 to Stimulus 2 did not differ across conditions. Follow-up analyses of background intensity demonstrated that P50 to Stimulus 1 was significantly reduced in the presence of a 55-dB SPL background relative to either a 0-dB SPL or 40-dB SPL background intensity. A significant main effect for stimulus also was obtained across stimulus duration conditions, $F(1,27) = 112.25$, $p < .001$. Stimulus duration, however, was not found to exert a significant impact on P50 amplitude, $F(2,54) = 0.45$, n.s.

P50 suppression ratio. P50 ratio did not differ significantly as a function of stimulus intensity, background intensity, or stimulus duration.

N100. For the stimulus intensity and stimulus duration conditions, examination of N100 amplitude yielded main effects for condition (intensity: $F[2,54] = 69.47$, $p < .001$; duration: $F[2,54] = 4.29$, $p < .05$) as well as for stimulus (intensity: $F[1,27] = 136.23$, $p < .001$; duration: $F[1,27] = 85.48$, $p < .001$). The main effects were qualified by significant Intensity × Stimulus, $F(2,54) = 37.96$, $p < .05$, and Duration × Stimulus, $F(2,54) = 3.93$, $p < .05$, interactions. Follow-up comparisons revealed that for Stimulus 1, N100 was significantly larger to more intense stimuli whereas for Stimulus 2, a significant difference was only obtained between the 80- and 100-dB SPL stimuli (see Figure 1). For stimulus duration, the 5-ms duration stimulus elicited a larger N100 to Stimulus 1 as compared with the 1-ms stimulus, whereas N100 to the 3-ms stimulus was not significantly different from either of the other two stimulus durations. N100 to Stimulus 2 was found to be comparable across conditions. Analysis of N100 across varying background intensities revealed only a main effect for stimulus, $F(1,27) = 110.11$, $p < .001$.

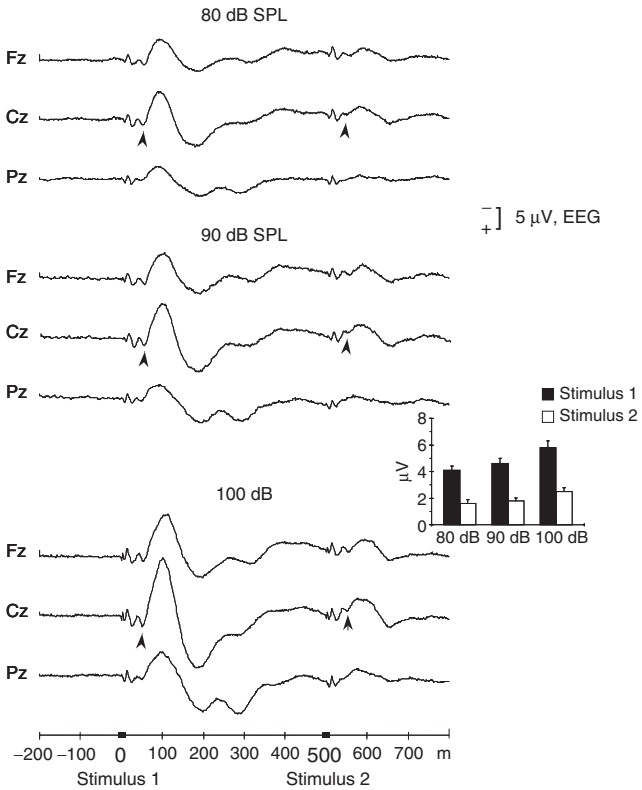

Figure 1. Grand average ERP waveforms, at three midline recording sites, at each stimulus intensity. Arrowheads indicate the P50 component at the Cz site. Inset: P50 amplitude to Stimulus 1 and Stimulus 2, recorded at the Cz site to each stimulus intensity.

Assessment of Stimulus Predictability

P50. Examination of stimulus predictability revealed a significant main effect for stimulus, $F(1,27) = 85.33$, $p < .001$, and a statistical trend for condition, $F(1,27) = 3.59$, $p < .07$, with the fixed ITI eliciting a somewhat larger P50 than the varied ITI. Because potential differences between the two ITI conditions may have been obscured by the inclusion of different ITIs in the variable presentation condition, a separate analysis was undertaken to compare the effects of a 10-s fixed versus a 10-s variable ITI. A composite average was computed for trials that followed a 10-s ITI during the variable interval condition; each average was based upon 44 trials that were drawn from the 1- and 3-ms 90 dB SPL stimulus duration conditions given the absence of effects on P50. Due to technical difficulties in recording the ITI for each trial, data from 3 subjects were not available for this analysis. Comparison of the same time intervals (10 ms) revealed only a main effect for stimulus, $F(1,27) = 82.75$, $p < .001$, as the main effect for condition did not reach statistical significance, $F(1,27) = 3.57$, n.s.

P50 suppression ratio. Comparisons involving the fixed and variable ITI conditions revealed no significant differences for the P50 ratio measure.

N100. A main effect was obtained for stimulus, $F(1,27) = 91.89$, $p < .001$, that was qualified by a significant Condition × Stimulus interaction, $F(1,27) = 4.62$, $p < .05$. On the basis of follow-up comparisons, N100 to Stimulus 1 was found to be larger than to Stimulus 2 in the fixed and varied presentation conditions, although the magnitude of the difference between stimuli was somewhat less in the varied ITI condition. As with P50 data, the effects of a 10-s fixed ITI versus a 10-s variable ITI were examined, yielding a main effect for stimulus, $F(1,24) = 55.31$, $p < .001$, and a trend for N100 amplitude to be larger when presentation of stimuli was fixed and predictable rather than relatively unexpected, $F(1,24) = 3.63$, $p < .07$.

Comparison of ERP Averages over the Testing Session

Change over the course of the test session was assessed by comparing P50 responses across the eight study conditions. As order of presentation was counterbalanced, any impact of specific conditions should effectively be removed. Trend analyses were used to test the goodness-of-fit of linear, quadratic, and cubic models for each dependent measure over the course of the testing session.

P50. P50 amplitude to Stimulus 1 showed a linear decrease over the test session, $F(1,27) = 11.86$, $p < .01$. P50 to Stimulus 2 tended to follow a similar pattern although the regression equation did not reach statistical significance, $F(1,27) = 2.48$, n.s.

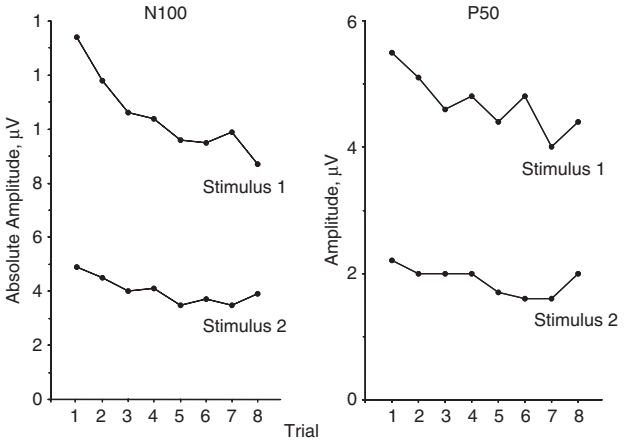

Figure 2. Mean N100 and P50 amplitude to Stimulus 1 and Stimulus 2 over the course of the test session.

These effects are shown in the right panel of Figure 2. Because it was not possible to include a within-subject variable in this analysis with the BMDP statistical software, a subtraction measure (Stimulus 1 – Stimulus 2) was used to enter this factor into the procedure. Results of the regression analysis indicated that P50 suppression deteriorated in a linear fashion over time, as reflected in a decline in the magnitude of the difference score, $F(1,27) = 4.26$, $p < .05$.

P50 suppression ratio. The ratio measure of P50 suppression appeared to remain constant over time as a linear trend was not obtained for these data, $F(1,27) = 0.41$, n.s.

N100. As with P50, the decline in N100 amplitude to Stimulus 1 and Stimulus 2 over the course of the test session was best described with a linear model, $F(1,27) = 37.24$, $p < .001$ and $F(1,27) = 12.48$, $p < .01$, respectively. As shown in the left panel of Figure 2, there appears to have been a gradual decrement in N100 to both stimuli over time.

Comparison of ERP Averages Based on Larger versus Smaller P50 Amplitudes

To assess the influence of P50 amplitude to Stimulus 1 on the P50 ratio measure, ERP averages of relatively "large" versus "small" P50 amplitude trials were generated using the following procedure. For each participant, 40 trials with the largest P50 to Stimulus 1 and 40 trials with the smallest P50 to Stimulus 1 were drawn from the 1- and 3-ms stimulus duration conditions when 90 dB SPL stimuli were presented against a 40-dB SPL background. Data were selected from these two stimulus durations, as comparisons between the conditions did not reveal any significant effects for N100, P50, or the P50 suppression ratio. Moreover, equal numbers of trials (i.e., 20 each) were drawn from each of the two stimulus duration condition for each participant. ERP components were scored in the same manner applied to the traditional averages. Not unexpectedly, this selection procedure resulted in averages yielding very small P50s to Stimulus 1 (i.e., < 0.5 μV) for 8 participants. Data from these subjects were excluded, as it can be difficult to discriminate such small signals from noise in the data; the following reports, therefore, are based on data obtained from the remaining 20 participants.

P50. In addition to the expected main effects for size, $F(1,19) = 155.09$, $p < .001$, and stimulus, $F(1,19) = 93.96$, $p < .001$, peak-to-peak measurement of P50 yielded a significant Size × Stimulus interaction, $F(1,19) = 65.67$, $p < .001$. Follow-up comparisons revealed a distinct pattern of P50 suppression on averages computed from large P50 responses (Stimulus 1: $M = 10.49$, $SD = 3.93$; Stimulus 2: $M = 2.01$, $SD = 1.36$) but a failure to suppress on averages derived from relatively small responses (Stimulus 1: $M = 1.73$, $SD = 0.79$; Stimulus 2: $M = 1.60$, $SD = 1.35$). As shown in Figure 3, it is possible that peak-to-peak measurement of P50 may reflect the magnitude of the preceding N40 to some degree; that is, a smaller P50 may appear to be relatively diminished to the extent that a large negativity precedes it. To address this issue, baseline-to-peak measures of P50 were computed, yielding the same pattern of effects. Again, significant effects were obtained for size, $F(1,19) = 100.78$, $p < .001$, stimulus, $F(1,19) = 108.67$, $p < .001$, and the Size × Stimulus interaction, $F(1,19) = 76.66$, $p < .001$. Follow-up comparisons once more revealed a clear pattern of suppression on large P50 averages (Stimulus 1: $M = 7.11$, $SD = 2.48$; Stimulus 2: $M = 1.21$, $SD = 0.88$) as compared with averages computed when only a small P50 was present (Stimulus 1: $M = 1.70$, $SD = 1.03$; Stimulus 2: $M = 0.76$, $SD = 0.94$). Although the P50 to Stimulus 2 was somewhat minimized when averages were computed from small P50 trials, it is unlikely that the magnitude of this response results from a floor effect, as complete P50 suppression is possible.

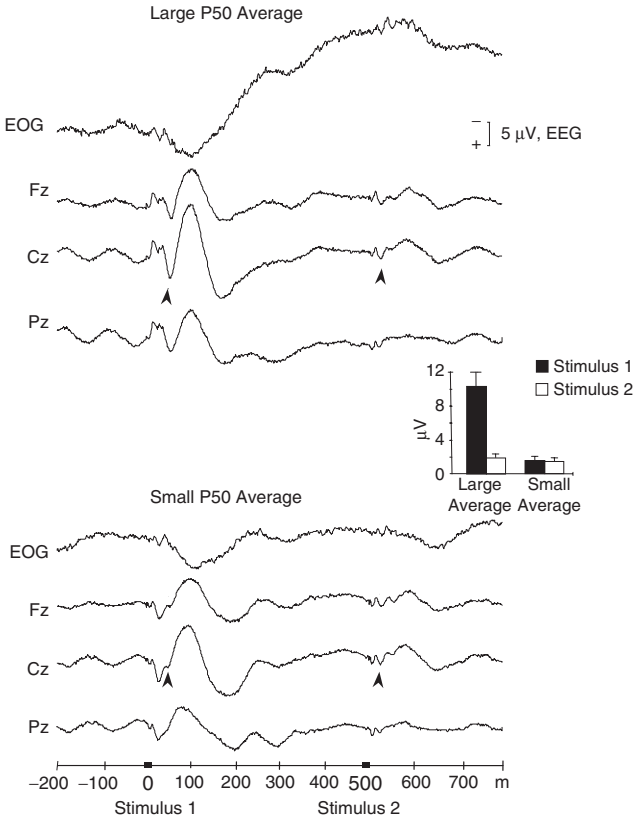

Figure 3. Grand average ERP waveforms, at three midline recording sites after correcting for ocular artifact, constructed from relatively large and relatively small P50 amplitude trials. Arrowheads indicate the P50 component at the Cz site. EOG tracings are included for illustrative purposes only. Inset: P50 amplitude to Stimulus 1 and Stimulus 2, recorded at the Cz site and derived from large and small P50 trials.

P50 suppression ratio. As might be expected on the basis of the amplitude data, P50 ratio varied significantly between the large and small P50 component averages, $F(1,19) = 20.98$, $p < .001$, with a mean ratio of .21 ($SD = .15$) for the large P50 averages and a mean ratio of .96 ($SD = .68$) for the small P50 averages.

N100. Significant main effects were obtained for size, $F(1,19) = 47.14$, $p < .001$, and stimulus, $F(1,19) = 101.84$, $p < .001$, which were accompanied by a significant Size × Stimulus interaction, $F(1,19) = 18.41$, $p < .01$. Follow-up analyses revealed that although N100 was significantly greater to Stimulus 1 than Stimulus 2 in both types of averages, N100 to Stimulus 1 was substantially larger when averages were derived from relatively large P50 responses as compared with those averages based on smaller P50 responses (see Figure 3). To examine whether large components tend to be generated on the same trials, large and small ERP averages were computed on the basis of N100 amplitude to Stimulus 1, following the same procedure used for deriving large and small P50 averages. In contrast to effects obtained from P50-based averages, P50 amplitude to Stimulus 1 and Stimulus 2 was significantly *larger* on averages derived from the smallest N100 responses as compared with the large N100 component averages, $F(1,19) = 6.29$, $p < .05$. These data suggest that P50 amplitude is independent of N100 magnitude and, instead, has its own sources of variance.

Discussion

Prior conceptualizations of P50 have been based on the assumption that P50 suppression is largely a preattentive process that is influenced primarily by physical properties of the eliciting stimulus. Results of the present study lend support to this view by demonstrating the influence of physical characteristics of the initial stimulus on P50 amplitude. The data also suggest, however, that P50 suppression is not an invariant response mechanism and the psychological state of a participant may influence P50 amplitude and its suppression.

Consistent with prior research (e.g., Griffith et al., 1995), P50 amplitude to both paired stimuli was found to vary with stimulus intensity, increasing from 80 and 90 to 100 dB SPL, although the difference between the lower intensity stimuli was not statistically significant. Background stimulus intensity also was found to influence P50 to the first stimulus, as the P50 response was smaller when louder background white noise (i.e., 55 dB SPL) was present. Although the impact of stimulus and background intensity was apparent on P50 amplitude to the initial stimulus, P50 suppression as quantified by the ratio measure was unaffected. In contrast to P50 amplitude, the N100 reflected changes in stimulus intensity but not in background intensity.

P50 and N100 amplitude also differed in response to changes in stimulus duration, as only N100 amplitude to the initial stimulus yielded an appreciable change when each stimulus was presented for 5 ms. Although it is possible that the limited range of stimulus durations included in the present study was insufficient to elicit significant P50 effects, the current data suggest that variations in the production, amplification, and presentation of auditory stimuli across research studies are unlikely to account for disparities in the reported data when the resulting difference in stimulus duration is on the order of a few milliseconds.

The present study also revealed an intriguing pattern of effects that implicate the role of various psychological state factors. Evidence for an association between P50 and psychological state is offered by the observed decline in P50 amplitude and its suppression over the course of the session. This effect is most consistent with data reported by Naber et al. (1992), in which decrements in P50 amplitude also were found, even across three successive trial blocks. As noted earlier, Naber and colleagues attributed these declines to reductions in vigilance or attention due to most subjects reporting fatigue by the end of the testing session. The P50 ratio score, however, did not reflect any significant change over time in either of the two studies. In the present study, P50 suppression did deteriorate when quantified as the difference between Stimulus 1 and Stimulus 2 amplitude. Naber and colleagues, therefore, may not have observed this effect because they relied only on a ratio measure of P50 suppression. The present study also included eight trial blocks and more than three times as many total trials as Naber et al., contributing further to differences between the two studies. In sum, further investigation is needed to specify the time course of this effect and the specific contribution of factors, such as drowsiness, fatigue, and declines in vigilance to changes in P50 (e.g., Cardenas, Gill, & Fein, 1997) while also evaluating the different indices for quantifying P50 suppression.

In addition to changes over time, considerable trial-to-trial variability exists in P50 amplitude in the absence of any experimental manipulations, such as altering the intensity of stimuli. Although the basis for fluctuations in P50 amplitude in a given individual has yet to be established, shifts in attention or alertness may be possible contributing factors. In the present study, the impact of P50 amplitude to the initial stimulus on the P50 suppression score was examined by constructing ERP averages for each participant on the basis of their largest and smallest P50s to the initial stimulus. The magnitude of the initial P50 was found to exert an appreciable impact on the suppression ratio, with the smaller component demonstrating less or weaker suppression. Therefore, even in healthy individuals who generally exhibit strong P50 suppression, a subset of their responses may reflect poor suppression, arguing for the need to obtain stable estimates of P50 activity. Analyses conducted with data parsed on the basis of N100 magnitude revealed that differential P50 suppression for small and large P50 trials cannot be attributed merely to a tendency for large components to aggregate separately from small components. It is possible that the bandpass filter of 10–50 Hz, applied to the data before scoring P50, may have allowed a certain amount of low-frequency activity to remain in the data, which, in turn, could have a disproportionate impact on the small P50 components and obscured their measurement. This possibility seems unlikely given that the smaller P50 amplitude to Stimulus 2 did not differ substantially between the large and small P50 averages. Thus, these data support the view that P50 suppression covaries to some extent with normal fluctuations in P50 amplitude to the initial stimulus, which, in turn, may be associated with shifts or changes in psychological state.

Data obtained in the present study also suggest the possibility that P50 amplitude increases when eliciting stimuli are expected rather than when they are less predictable. As this effect only approached statistical significance, it is unclear to what extent expectancy serves as a moderating influence on P50 and its suppression. Given that divergent results have been obtained between studies concerning P50 suppression, variations involving this parameter will need to be considered in future research.

The suggestion that P50 suppression may be associated with variations in psychological state is not a novel idea. In fact, a central tenet in schizophrenia research is that poor P50 suppression may reflect basic attentional difficulties (e.g., Braff & Geyer, 1990; Freedman et al., 1987). Such a proposition is consistent with the available research. Yee and colleagues (1998), for instance, obtained data suggesting that the P50 suppression deficit in schizophrenia may be related to the degree of attentional impairment observed in patients. What is most striking is that the finding of an attentional influence on P50 stands in contrast to several research reports examining the relationship between P50 and attention in nonpsychiatric subjects. As noted earlier, the evidence suggesting that P50 suppression may be influenced by attentional manipulations in nonpsychiatric subjects is limited (Guterman et al., 1992), with the majority of research reports failing to confirm this finding (e.g., Hillyard et al., 1973; Jerger et al., 1992; White & Yee, 1997). One possible explanation is that the modulatory influences of attention on P50 may vary depending on which aspect of attention is invoked. This study, for instance, relied on naturally occurring fluctuations in attention and vigilance rather than the active manipulation of voluntary attention associated with experimental task demands.

Taken together, the present findings suggest that P50 may be influenced not only by physical properties of the eliciting stimuli but also by psychological state factors, such as declines in attention or vigilance, fatigue, and drowsiness. Monitoring the impact of these variables on P50 suppression and determining their contribution to observed differences between psychiatric and healthy populations will be critical in future studies. Deficits in sustained attention have been well documented in schizophrenia patients in both psychotic and clinically remitted states (e.g., Nuechterlein et al., 1992). And there already is some indication that the magnitude of P50 responses may diverge between schizophrenia patients and normal comparison subjects even over two successive trial blocks (Clementz et al., 1997). Given the passive nature of the typical P50 paired-stimulus paradigm and length of testing sessions, groups also may differ in level of distractibility and focus from trial to trial. It is recommended that P50 averages contain a sufficient number of trials to reduce susceptibility to trial-to-trial variations and the study design should provide participants with frequent breaks during testing to minimize fatigue and drowsiness.

Results of this study also underscore the importance of examining fluctuations in P50 amplitude to the initial stimulus within an individual and evaluating the contribution of component variability to the P50 suppression measure (Jin et al., 1998). A related issue concerns the choice of measure for quantifying P50 suppression. With the exception of comparing ERP averages generated from relatively large or small P50 amplitude trials, none of the other conditions in this study were found to influence the P50 suppression ratio. It has been suggested that the suppression ratio may be more robust to variance in P50 amplitude to the initial stimulus (Light & Braff, 1998;see also Freedman, Adler, Nagamoto, & Waldo, 1998) and more highly correlated with genetic heritability (Freedman et al., 1997). The P50 suppression ratio, therefore, may have been immune to almost all of the factors examined in the present study. Alternatively, there is evidence to indicate that the ratio score may be unstable and less than ideal as a measure of P50 suppression given the correlation that exists between P50 amplitude to the paired stimuli and differences in the reliability of the two responses (Smith et al., 1994). Rather than providing a more robust measure, it is possible that the suppression ratio was largely insensitive, demonstrating no systematic effects despite significant effects on the initial P50 amplitude and the difference score.

With continued methodological and theoretical advancement, further identification of the processes and conditions affecting P50 and its suppression will become possible. This study represents an initial attempt to determine whether the psychological state of a participant might influence P50 and its suppression. Additional research is needed to clarify the range of psychological states that might be involved, determine their relative impact on each of the P50 indices, and establish their contribution toward our evolving conceptualization of P50 suppression as a preattentive process.

REFERENCES

Adler, L. E., Hoffer, L. J., Griffith, J., Waldo, M. C., & Freedman, R. (1992). Normalization by nicotine of deficient auditory sensory gating in the relatives of schizophrenics. *Biological Psychiatry*, *32*, 607–616.

Adler, L. E., Pachtman, E., Franks, R. D., Pecevich, M., Waldo, M. C., & Freedman, R. (1982). Neurophysiological evidence for a defect in neuronal mechanisms involved in sensory gating in schizophrenia. *Biological Psychiatry*, *17*, 638–654.

Adler, L. E., Waldo, M. C., Tatcher, A., Cawthra, E., Baker, N., & Freedman, R. (1990). Lack of relationship of auditory gating defects to negative symptoms in schizophrenia. *Schizophrenia Research*, *3*, 131–138.

Arnfred, S. M., Chen, A. C. N., Glenthøj, B.Y, & Hemmingsen, R. P. (2003). Normal P50 gating in unmedicated schizophrenia outpatients. *Psychiatry Research*, *160*, 2236–2238.

Boutros, N. N., Belger, A., Campbell, D., D'Souza, C., & Krystal, J. (1999). Comparison of four components of sensory gating in schizophrenia and normal subjects: A preliminary report. *Psychiatry Research*, *88*, 119–130.

Boutros, N. N., Korzyukov, O., Jansen, B., Feingold, A., & Bell, M. (2004). Sensory gating deficits during the mid-latency phase of information processing in medicated schizophrenia patients. *Psychiatry Research*, *126*, 203–215.

Boutros, N. N., Torello, M. W., Barker, B. A., Tueting, P. A., Wu, S-C., & Nasrallah, H. A. (1995). The P50 evoked potential component and mismatch detection in normal volunteers: Implications for the study of sensory gating. *Psychiatry Research*, *57*, 83–88.

Boutros, N. N., Zouridakis, G., & Overall, J. (1991). Replication and extension of P50 findings in schizophrenia. *Clinical Electroencephalography*, *22*, 40–45.

Braff, D. L. (1993). Information processing and attention dysfunctions in schizophrenia. *Schizophrenia Bulletin*, *19*, 233–259.

Braff, D. L., & Geyer, M. A. (1990). Sensorimotor gating and schizophrenia: Human and animal model studies. *Archives of General Psychiatry*, *47*, 181–188.

Braff, D. L., & Light, G. A. (2004). Preattentional and attentional cognitive deficits as targets for treating schizophrenia. *Psychopharmacology*, *174*, 75–85.

Bramon, E., Rabe-Hesketh, S., Sham, P., Murray, R. M., & Frangou, S. (2004). Meta-analysis of the P300 and P50 waveforms in schizophrenia. *Schizophrenia Research*, *70*, 315–329.

Cardenas, V. A., Gill, P., & Fein, G. (1997). Human P50 suppression is not affected by variations in wakeful alertness. *Biological Psychiatry*, *41*, 891–901.

Clementz, B. A., & Blumenfeld, L. D. (2001). Multichannel electroencephalographic assessment of auditory evoked response

suppression in schizophrenia. *Experimental Brain Research*, *139*, 377–390.
Clementz, B. A., Geyer, M. A., & Braff, D. L. (1997). P50 suppression among schizophrenia and normal comparison subjects: A methodological analysis. *Biological Psychiatry*, *41*, 1035–1044.
Donchin, E., Ritter, W., & McCallum, R. C. (1978). Cognitive psychophysiology: The endogenous components of the ERP. In E. Callaway, P. Tueting, & S. H. Koslow (Eds.), *Event-related brain potentials in man* (pp. 349–411). New York: Academic Press.
Eccles, J. C. (1969). *The inhibitory pathways of the central nervous system*. Springfield, IL: Charles C. Thomas Publisher.
Erwin, R. J., Turetsky, B. I., Moberg, P., Gur, R. C., & Gur, R. E. (1998). P50 abnormalities in schizophrenia: Relationship to clinical and neuropsychological indices of attention. *Schizophrenia Research*, *33*, 157–167.
Freedman, R., Adler, L. E., Gerhardt, G. A., Waldo, M. C., Baker, N., Rose, G. M., et al. (1987). Neurobiological studies of sensory gating in schizophrenia. *Schizophrenia Bulletin*, *13*, 669–678.
Freedman, R., Adler, L. E., Myles-Worsley, M., Nagamoto, H. T., Miller, C., Kisley, M., et al. (1996). Inhibitory gating of an evoked response to repeated auditory stimuli in schizophrenic and normal subjects: Human recordings, computer simulation, and an animal model. *Archives of General Psychiatry*, *53*, 1114–1121.
Freedman, R., Adler, L. E., Nagamoto, H. T., & Waldo, M. C. (1998). Selection of digital filtering parameters and P50 amplitude. *Biological Psychiatry*, *43*, 921–922.
Freedman, R., Adler, L. E., Waldo, M. C., Pachtman, E., & Franks, R. D. (1983). Neurophysiological evidence for a defect in the inhibitory pathways in schizophrenia: Comparison of medicated and drug–free patients. *Biological Psychiatry*, *18*, 537–551.
Freedman, R., Coon, H., Myles-Worsley, M., Orr-Urtreger, A., Olincy, A., Davis, A., et al. (1997). Linkage of a neurophysiological deficit in schizophrenia to a chromosome 15 locus. *Proceedings of the National Academy of Sciences, USA*, *94*, 587–592.
Geisser, S., & Greenhouse, S. W. (1958). An extension of Box's results on the use of the F distribution in multivariate analysis. *Annal of Mathematics and Statistics*, *29*, 886–891.
Gratton, G., Coles, M. G., & Donchin, E. (1983). A new method for off-line removal of ocular artifacts. *Electroencephalography and Clinical Neurophysiology*, *55*, 468–484.
Griffith, J., Hoffer, L. D., Adler, L. E., Zerbe, G. O., & Freedman, R. (1995). Effects of sound intensity on a midlatency evoked response to repeated auditory stimuli in schizophrenic and normal subjects. *Psychophysiology*, *32*, 460–466.
Guterman, Y., Josiassen, R. C., & Bashore, T. R. (1992). Attentional influence on the P50 component of the auditory event–related potential. *International Journal of Psychophysiology*, *12*, 197–209.
Heinrichs, R. W. (2001). *In search of madness: Schizophrenia and neuroscience*. Oxford: Oxford University Press.
Hillyard, S. A., Hink, R. F., Schwent, V. L., & Picton, T. W. (1973). Electrical signs of selective attention in the human brain. *Science*, *182*, 177–179.
Jerger, K., Biggins, C., & Fein, G. (1992). P50 suppression is not affected by attentional manipulations. *Biological Psychiatry*, *31*, 365–377.
Jin, Y., Bunney, W. E. Jr., Sandman, C. A., Patterson, J. V., Fleming, K., & Moenter, J. R. (1998). Is P50 suppression a measure of sensory gating in schizophrenia? *Biological Psychiatry*, *43*, 873–878.
Jin, Y., Potkin, S. G., Paterson, J. V., Sandman, C. A., Hetrick, W. P., & Bunney, W. E. Jr. (1997). Effects of P50 temporal variability on sensory gating in schizophrenia. *Psychiatry Research*, *70*, 71–81.
Johnson, M. R., & Adler, L. E. (1993). Transient impairment in P50 auditory sensory gating induced by a cold–pressor test. *Biological Psychiatry*, *33*, 380–387.
Judd, L. L., McAdams, L. A., Budnick, B., & Braff, D. L. (1992). Sensory gating deficits in schizophrenia: New results. *American Journal of Psychiatry*, *149*, 488–493.
Kathmann, N., & Engel, R. R. (1990). Sensory gating in normals and schizophrenics: A failure to find strong P50 suppression in normals. *Biological Psychiatry*, *27*, 1216–1226.
Lamberti, J. S., Schwarzkopf, S. B., Boutros, N., Crilly, J. F., & Martin, R. (1993). Within-session changes in sensory gating assessed by P50 evoked potentials in normal subjects. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *17*, 781–791.
Lamberti, J. S., Schwarzkopf, S. B., Crilly, J. F., & Martin, R. (1993). Sensory gating assessed by P50 suppression in normal controls: Effects of changing stimulus intensity. *Schizophrenia Research*, *9*, 161.
Light, G. A., & Braff, D. L. (1998). The "incredible shrinking" P50 event-related potential. *Biological Psychiatry*, *43*, 918–920.
McCallum, W. S., Curry, S. H., Cooper, R., Pocock, P. V., & Papakostopoulos, D. (1983). Brain event-related potentials as indicators of early selective processes in auditory target selection. *Psychophysiology*, *20*, 1–17.
Miller, G. A., Gratton, G., & Yee, C. M. (1988). Generalized implementation of an eye movement correction procedure. *Psychophysiology*, *25*, 241–243.
Myles-Worsley, M. (2002). P50 sensory gating in multiplex schizophrenia families from a Pacific Island isolate. *American Journal of Psychiatry*, *159*, 2007–2012.
Naber, G., Kathmann, N., & Engel, R. R. (1992). P50 suppression in normal subjects: Influence of stimulus intensity, test repetition and presentation mode. *Journal of Psychophysiology*, *6*, 47–53.
Nuechterlein, K. H., Dawson, M. E., Gitlin, M., Ventura, J., Goldstein, M. J., Snyder, K. S., et al. (1992). Developmental processes in schizophrenic disorders: Longitudinal studies of vulnerability and stress. *Schizophrenia Bulletin*, *18*, 387–425.
Patterson, J. V., Jin, Y., Gierczak, M., Hetrick, W. P., Potkin, S., Bunney, W. E. Jr., et al. (2000). Effects of temporal variability on P50 and the gating ratio in schizophrenia: A frequency domain adaptive filter single-trial analysis. *Archives of General Psychiatry*, *57*, 57–64.
Schwarzkopf, S. B., Lamberti, J. S., & Smith, D. A. (1993). Concurrent assessment of acoustic startle and auditory P50 evoked potential measures of sensory inhibition. *Biological Psychiatry*, *33*, 815–828.
Smith, D. A., Boutros, N. N., & Schwarzkopf, S. B. (1994). Reliability of P50 auditory evoked potential indices of auditory gating. *Psychophysiology*, *31*, 495–502.
Ward, P. B., Hoffer, L. D., Liebert, B. J., Catts, S. V., O'Donnell, M., & Adler, L. E. (1996). Replication of a P50 auditory gating deficit in Australian patients with schizophrenia. *Psychiatry Research*, *64*, 121–135.
Thoma, R. J., Hanlon, F. M., Moses, S. N., Edgar, J. C., Huang, M., Weisend, M. P., et al. (2003). Lateralization of auditory sensory gating and neuropsychological dysfunction in schizophrenia. *American Journal of Psychiatry*, *160*, 1595–1605.
Thoma, R. J., Hanlon, F. M., Moses, S. N., Ricker, D., Huang, M., Edgar, C., et al. (2005). M50 sensory gating predicts negative symptoms in schizophrenia. *Schizophrenia Research*, *73*, 311–318.
Woldorff, M. G., Gallen, C. C., Hampson, S. A., Hillyard, S. A., Pantev, C., Sobel, D., et al. (1993). Modulation of early sensory processing in human auditory cortex during auditory selective attention. *Proceedings of the National Academy of Sciences, USA*, *90*, 8722–8726.
Woldorff, M. G., & Hillyard, S. A. (1991). Modulation of early auditory processing during selective listening to rapidly presented tones. *Electroencephalography and Clinical Neurophysiology*, *79*, 170–191.
White, P. M., & Yee, C. M. (1997). Effects of attentional and stressor manipulations on the P50 gating response. *Psychophysiology*, *34*, 703–711.
Yee, C. M., Nuechterlein, K. H., Morris, S. E., & White, P. M. (1998). P50 suppression in recent-onset schizophrenia: Clinical correlates and risperidone effects. *Journal of Abnormal Psychology*, *107*, 691–698.
Yee, C. M., & White, P. M. (2001). Experimental modification of P50 suppression. *Psychophysiology*, *38*, 531–539.
Zouridakis, G., & Boutros, N. N. (1992). Stimulus parameter effects on the P50 evoked response. *Biological Psychiatry*, *32*, 839–841.

(Received August 3, 2005; Accepted March 16, 2006)