Psychophysiology, 38 (2001), 531–539. Cambridge University Press. Printed in the USA.

Experimental modification of P50 suppression

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

Abstract

White and Yee (1997) found that normal suppression of the P50 component of the event-related potential was disrupted during a paired-click paradigm when nonpsychiatric subjects performed mental arithmetic (MA) problems aloud, concurrently with the presentation of auditory stimuli. In fact, the degree of disruption reflected in the P50 suppression ratio fell within the range that is typically observed in schizophrenia patients. The present study was conducted to clarify the processes that might underlie the apparent disruption of P50 suppression during performance of an oral MA task. Participants completed a series of tasks designed to examine the impact of competing cognitive activity, competing auditory stimulation, muscle activity, and acute psychological stress on P50 amplitude and P50 suppression. Results suggested that psychological stress and heightened facial muscle activity may exert modulatory effects on P50 suppression.

Descriptors: P50, Sensory gating, Psychological stressor, Mental arithmetic task, Schizophrenia

Studies conducted on the P50 component of the auditory event-related potential (ERP) have generated considerable research interest, as there is some evidence that P50 suppression may be a viable psychophysiological marker of vulnerability for schizophrenia (e.g., Freedman et al., 1997). Schizophrenia patients and their biological relatives typically fail to exhibit a reduced response to a second auditory click ("Click 2") when presentation of this stimulus is preceded by a first click ("Click 1") at an interclick interval of 500 ms. In contrast, nonpsychiatric subjects who are assumed to have intact filtering or gating processes generally exhibit a suppressed P50 to Click 2 (e.g., Adler et al., 1982; Judd, McAdams, Budnick, & Braff, 1992; Yee, Nuechterlein, Morris, & White, 1998). Theorists have argued that the first auditory stimulus activates an inhibitory mechanism that protects processing of this initial stimulus from the potentially disruptive effects associated with the occurrence of subsequent, rapidly succeeding stimuli (see discussions by Freedman et al., 1987, 1994; Leonard et al., 1996).

Although inhibitory effects on P50 were initially hypothesized to be largely automatic or preattentive and to primarily reflect neuronal rather than psychological phenomena (e.g., Freedman et al., 1987), experimental manipulations have been found to influence P50 and its suppression. Research by Guterman, Josiassen, and Bashore (1992), for instance, suggests that inhibitory effects on P50 suppression in nonpsychiatric subjects may be altered transiently by manipulating voluntary attention. Utilizing a different set of paradigms, however, other researchers have not observed this effect (Jerger, Biggins, & Fein, 1992; White & Yee, 1997). A potential explanation for this discrepancy is that different aspects or degrees of attention may have been engaged across studies.

Laboratory stressors also have been found to influence inhibitory effects on P50. Johnson and Adler (1993) demonstrated that a cold pressor manipulation can disrupt P50 suppression in normal control subjects. Relying upon a behavioral manipulation, Waldo and Freedman (1986) instructed nonpsychiatric subjects to perform a silent mental arithmetic (MA) task while listening to paired clicks. Although the MA task did not alter the P50 ratio, there was some suggestion that P50 suppression was reduced in subjects who reported increased anxiety. White and Yee (1997) also directed nonpsychiatric subjects to engage in an MA task, concurrent with the P50 paired click paradigm, but the MA problems were performed aloud rather than silently. In addition, subjects were corrected when an incorrect response was provided and were periodically instructed to increase the speed of their performance. Under these more demanding conditions, the degree of disruption in P50 suppression, as indexed by the P50 ratio score, was of a similar magnitude to that obtained in outpatients diagnosed with schizophrenia (e.g., Ward et al., 1996; Yee et al., 1998).

These data are largely consistent with current models that have been offered to account for the neuronal mechanisms that potentially underlie P50 suppression and its impairment. Freedman and colleagues (Leonard et al., 1996) propose that gating of the P50 wave involves interneuron inhibition of pyramidal cells through GABAergic and other inhibitory synapses. Because interneurons and pyramidal neurons also receive cholinergic input from the septum, blockade of the septal cholinergic input is believed to remove the inhibitory effect of the interneurons and to allow

Portions of this research were presented at the annual meeting of the Society for Psychophysiological Research, Vancouver, Canada, 1996. The research was supported in part by 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 thank Maria Nazarin, Halle Jones, and Valerie Gilman for assistance with data collection, and Bill Troyer for technical and software support.

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.

pyramidal cells to fire in response to a second auditory click. Nicotine, an agonist, has been found to improve gating in individuals who exhibit the P50 deficit whereas antagonists of the α7-nicotinic receptor block P50 inhibition (see review by Leonard et al., 1996). It also is the case that P50 inhibition may be blocked by selectively directing attention towards other sensory stimuli in the environment (Freedman et al., 1994).

In addition to the cholinergic system, the dopaminergic and noradrenergic neurotransmitter systems are also involved in the modulation of P50 amplitude and its suppression. Studies examining the impact of antipsychotic medications on P50 have shown that typical neuroleptic agents, such as haloperidol, can normalize P50 amplitude to Click 1 in schizophrenia patients who otherwise show a diminished P50 response when in an unmedicated state (Adler et al., 1990; Freedman et al., 1983). The authors interpret these data to suggest that the dopaminergic system may be involved in the modulation of P50 to Click 1. Research focusing on Click 2 activity indicates that P50 suppression is also likely to be moderated by noradrenergic influences. As noted earlier, the cold pressor task, which is associated with an increase in noradrenergic neuronal transmission, was shown to transiently disrupt P50 suppression in nonpsychiatric subjects (Johnson & Adler, 1993). Converging evidence for a noradrenergic contribution to P50 suppression is offered from studies involving the administration of yohimbine to humans and animals. The introduction of yohimbine, a presynaptic α-2 antagonist that primarily increases central noradrenergic neuronal transmission, has been found to lead to a transient impairment in P50 suppression (e.g., Adler et al., 1994; Stevens, Meltzer, & Rose, 1993).

Research investigations involving psychiatric patients further highlight the likely influence of noradrenergic activity on P50 suppression. Patients diagnosed with bipolar disorder have been shown to exhibit decreased P50 suppression when in a manic episode and to return to normal levels of suppression during euthymic periods (Franks, Adler, Waldo, Alpert, & Freedman, 1983). Adler and colleagues (1990) subsequently determined that in bipolar patients, the P50 inhibitory deficit is positively correlated with elevations in noradrenergic metabolism during manic episodes. Consistent with the possibility of a noradrenergic contribution to P50 suppression, greater P50 impairment also has been found to correlate with clinical ratings of heightened anxiety in patients diagnosed with schizophrenia (Yee et al., 1998).

Taken together, these data demonstrate that P50 suppression can be modified, and they suggest mechanisms that may be implicated in the P50 suppression deficits observed in patients with schizophrenia and other psychiatric disorders. The purpose of the present research was to extend these findings by clarifying the manner in which P50 suppression can be disrupted in nonpsychiatric subjects when a behavioral manipulation is introduced. Specifically, the present study was designed to specify the factors associated with the disruption of P50 suppression when an oral MA task is performed concurrently. Results of this study will help to further clarify some of the factors that may exert a modulatory influence on P50, and thereby contribute to our growing understanding of the basis for P50 abnormalities.

In the study by White and Yee (1997), concurrent performance of an oral MA task was found to alter the P50 suppression ratio, possibly as the result of attenuating the P50 amplitude response to Click 1. Schizophrenia patients have been observed to exhibit a similar amplitude deficit as well as a reduced P50 suppression ratio (e.g., Adler et al., 1982; Boutros, Zouridakis, & Overall, 1991). The basis for the apparent disruption of P50 suppression in nonpsychiatric subjects when performing an oral MA task is unclear, however, as several possibilities exist.

One possibility is that the oral MA task draws attention away from the auditory clicks as subjects focus on subtracting numbers. P50 disruption, therefore, may be due to *competing cognitive activity*. Another potential explanation is that P50 to the click stimuli is disrupted by the *competing auditory stimulation* of subjects hearing their own voice as they provide responses during the oral MA task at a near continuous rate. Alternatively, the *muscle activity* involved in generating speech may disrupt P50 or its measurement. It also is possible that *acute psychological stress* and anxiety are heightened when subjects engage in the oral MA task and that these factors contribute to alterations in P50. Finally, the observed changes in P50 may represent the combined effects of several of these factors.

In the current study, various aspects of the oral MA task were manipulated to distinguish among the mechanisms described above. In addition to clarifying the relative influence of each of these factors on P50, the present research was undertaken to replicate the finding of reduced P50 suppression during the oral MA task compared with responses elicited during a passive baseline task. Each of the factors cited has received some attention, albeit indirect, in some cases, in the P50 research literature. Results of these prior studies, reviewed below, were used to guide the formulation of the proposed hypotheses. It is unclear from prior research, however, how these factors might interact with each other within the context of an oral MA task.

Research Question I: Competing Cognitive Activity

It was predicted that P50 suppression would not be altered from passive, baseline levels during performance of a cognitive task. Jerger et al. (1992) and White and Yee (1997) both found that, whereas N100 was profoundly influenced by voluntary attentional manipulations, neither P50 amplitude nor its suppression were affected in nonpsychiatric subjects. Therefore, concurrent performance of a cognitive task that might affect attention was not expected to influence P50 amplitude or the P50 inhibitory effect.

Research Question II: Competing Auditory Stimulation

We anticipated that reductions in P50 amplitude would result from competing auditory activity compared with levels observed during a passive, baseline task. Stimulus intensity has been found to alter the magnitude of the P50 such that more intense stimuli elicit larger responses (Griffith et al., 1995). This effect has been obtained regardless of whether the intensity of the click or the background noise were varied; in both instances, P50 amplitude was heightened when click stimuli were more easily discriminated (White & Yee, 2001). The P50 suppression ratio, however, was unaffected. Thus, competing auditory stimulation was expected to attenuate P50 amplitude but to have no impact on P50 suppression.

Research Question III: Muscle Activity

Although there have been suggestions in the literature that P50 recordings may be influenced by muscle artifact from the neck (e.g., Bickford, Jacobson, Thane, & Cody, 1964; Freedman et al., 1996), we expected that the muscle activity involved in sitting and holding the head erect would not have a differential impact on P50 amplitude or its suppression as compared with the reduced muscle activity associated with maintaining a supine position. This hypothesis was based upon the similarity in P50 data when recordings have been obtained from schizophrenia patients and normal control subjects either in a seated position (e.g., Clementz, Geyer,

& Braff, 1997; Jerger et al., 1992) or a reclined position (e.g., Adler et al., 1982; Boutros et al., 1991; Ward et al., 1996). In contrast, conspicuous activity from the face and jaw muscles (in the absence of competing auditory activity or stress) was expected to influence P50, possibly by introducing electrical noise and compromising the measurement of this component.

Research Question IV: Psychological Stress

Finally, we predicted that psychological stress would reduce P50 suppression, but not P50 amplitude, after accounting for any influence of competing sound or overt muscle activity. This prediction is consistent with research described earlier on the influence of various laboratory stressor manipulations on P50 and with noradrenergic modulation of P50 suppression (e.g., Adler et al., 1994).

In summary, this study was designed to identify the locus for disruptions to P50 during concurrent performance of an oral MA task. We examined the possibility that any one of the four variables outlined above, or some combination of them, might serve to alter P50 responding. Identification of such factors provides an opportunity to clarify not only normal modulatory influences on P50 but mechanisms that might underlie P50 abnormalities in schizophrenia patients. Because the precise relationship between P50 responses to Click 1 and Click 2 has yet to be specified (see Smith, Boutros, & Schwarzkopf, 1994), the influence of each task condition was examined for absolute P50 amplitude to each click and for a standard, ratio measure of P50 suppression (Click 2/Click 1).

Method

Participants

Twenty subjects (11 men and 9 women), between 18 and 33 years of age, participated in this study. All were students who received course credit for their participation. To qualify for participation, potential subjects were required to complete individual screening interviews to determine any history of psychiatric illness, neurological disorders, drug abuse, or alcohol abuse. Subjects reporting a personal history of any of these conditions were excluded. Subjects who smoked regularly or during the 48 hr prior to testing also were excluded, as nicotine has been shown to have a transient effect on P50 suppression (e.g., Adler, Hoffer, Griffith, Waldo, & Freedman, 1992). Prior to testing, all subjects provided informed consent and received audiometric testing to verify normal hearing.

Psychophysiological Recording Methods and Apparatus

The electroencephalogram (EEG) was recorded from Sensormedics miniature Ag-AgCl electrodes, located at the Fz, Cz, and Pz midline electrode sites and referenced to linked electrodes placed on the participant's ear lobes. The electrooculogram (EOG) was recorded by placing electrodes above and below the right eye. All impedances were below 5,000 Ω. EEG and EOG signals were amplified 20,000 and 5,000 times, respectively, with a Grass Model 12 Neurodata Acquisition System; half-amplitude frequency cutoffs were set at 0.1 and 1000 Hz. Data were sampled at 1000 Hz within each channel, beginning 200 ms prior to the first stimulus in each trial and continuing for 1,000 ms. All data collection and stimulus presentation were controlled with a personal computer.

Auditory Stimulation

Click stimuli and background noise were created by amplification of white noise generated by a San Diego Instruments Sound Generator board. Further amplification was accomplished with a Coulbourn Instruments Audio Mixer-Amplifier. The 90 dB SPL auditory clicks were presented against a 40 dB SPL white-noise background and delivered to the subject over Realistic Nova '28 headphones (Tandy Corporation, Houston, TX). Sound levels of the stimuli were verified by a Davis Instruments SL-130 sound level meter (A scale). All auditory clicks were 3 ms in duration and were separated by an interclick interval of 500 ms. The intertrial interval (ITI) varied between 8 and 10 s.

Procedure

Participants were instructed to perform 10 tasks that were presented in counterbalanced order across subjects. Tasks were performed with participants seated upright (unless otherwise noted) in a sound-attenuated room. After each task, participants provided ratings on seven-point scales to assess self-reported level of stress, interest, anxiety, effort, and task difficulty. The experimental tasks each involved the presentation of 60 trials of paired auditory clicks and were as follows:

Passive baseline. Subjects sat and listened to click presentation.

Oral counting. Subjects counted aloud at a rate of approximately once per second during click presentation.

Silent counting. During click presentation, subjects counted at a rate of approximately once per second without producing any sound or observable facial movements.

Passive listening. Subjects were presented with an audio recording of a female voice counting at the rate of approximately once per second during click presentation.

Oral mental arithmetic (oral MA). Subjects performed six series of serial subtraction problems aloud. Each subtraction series lasted 1.5 min and varied in difficulty (i.e., Subtraction 1: 3,605 by 3s, Subtraction 2: 5,428 by 7s, Subtraction 3: 6,507 by 13s, Subtraction 4: 8,203 by 8s, Subtraction 5: 7,417 by 14s, Subtraction 6: 9,545 by 19s). This task was performed concurrently during click presentation. Subjects were informed immediately of any errors, in which case, the experimenter provided the correct response. To further induce stress, subjects were prompted to hurry on trials 8, 12, 34, and 46.

Silent mental arithmetic (silent MA). During click presentation, subjects performed the same type of problems included in the oral MA task (i.e., Subtraction 1: 2,907 by 3s, Subtraction 2: 6,828 by 7s, Subtraction 3: 9,561 by 13s, Subtraction 4: 5,113 by 8s, Subtraction 5: 8,318 by 14s, Subtraction 6: 8,442 by 19s) but were instructed to refrain from speaking aloud or making any facial movements. On trials 8, 12, 34, and 46 and after the final trial, subjects were asked to provide their current response as an estimate of performance accuracy; if an error was detected, it was corrected. Subjects also were encouraged to speed up their performance at these times.

Silent social stressor. During click presentation, subjects were asked to recall and rehearse silently for 3 min each an embarrassing situation, a current stressor, and their greatest personal fault for later discussion. Participants were asked to avoid making any facial movement. This task always immediately preceded the oral social stressor task.

Oral social stressor. Using an intercom, subjects were asked to describe to the experimenter for 3 min each an embarrassing situation, a current stressor, and their largest personal fault while clicks were being presented.

Reclined posture. During click presentation, subjects reclined on a cot.

Facial movement. While clicks were presented, subjects made exaggerated facial movements, such as pursing their lips, yawning, or baring their teeth, while remaining silent and otherwise immobile and relaxed. Prior to data collection, subjects were provided with examples of various exaggerated facial movements but were informed that they were not limited to these movements.

Waveform and Component Analysis

EEG data were converted to microvolts and deviated from a 200 ms prestimulus baseline. After correcting for the effect of eye movement with a procedure that removes ocular noise (Gratton, Coles, & Donchin, 1983; Miller, Gratton, & Yee, 1988), single EEG trials were digitally filtered to pass 10–50 Hz for measurement of the P30 and P50 components before ERP averages were computed. P50 amplitude and latency were measured at the Cz site and scored relative to the preceding negativity. P50 latency was identified as the most positive point occurring 40 to 70 ms after the stimulus. For purposes of identifying the maximum negativity preceding P50, P30 was scored as the most positive point occurring 20–40 ms after the stimulus. The maximum negativity between the P30 and P50 latencies was then used for measuring P50 amplitude. If P50 amplitude to Click 1 was less than or equal to 0.5 μV during any of the tasks, the subject's data were excluded from any analyses involving that task, as it is difficult to discriminate such small signals from noise in the data. This procedure never eliminated data from more than two subjects in any given statistical analysis. A minimum of 56 trials was included in each of the ERP averages.

Data Analysis

A series of planned comparisons, implemented as repeated measures analyses of variance (ANOVAs), were conducted on P50 amplitude using two within-subject, fully crossed factors: task (e.g., Passive baseline versus a comparison task), and click (Click 1 versus Click 2), yielding a measure of relative suppression. In addition, the P50 suppression ratio (Click 2/Click 1) was subjected to ANOVA with one within-subject factor, task (e.g., Passive baseline versus a comparison task). In all instances, the task factor involved two levels.

Results

The planned comparisons presented were designed to isolate, as best possible, each of the factors identified by the four research questions. When appropriate, an initial comparison to the passive baseline condition was conducted to determine if an experimental condition had any impact on P50. Once an effect was established, additional comparisons were performed with the goal of identifying the specific factor(s) that contributed to an observed effect.

Replication of Prior Findings

P50 measures obtained during the oral MA and passive baseline tasks were compared to determine whether the pattern of results obtained was similar to those reported by White and Yee (1997).

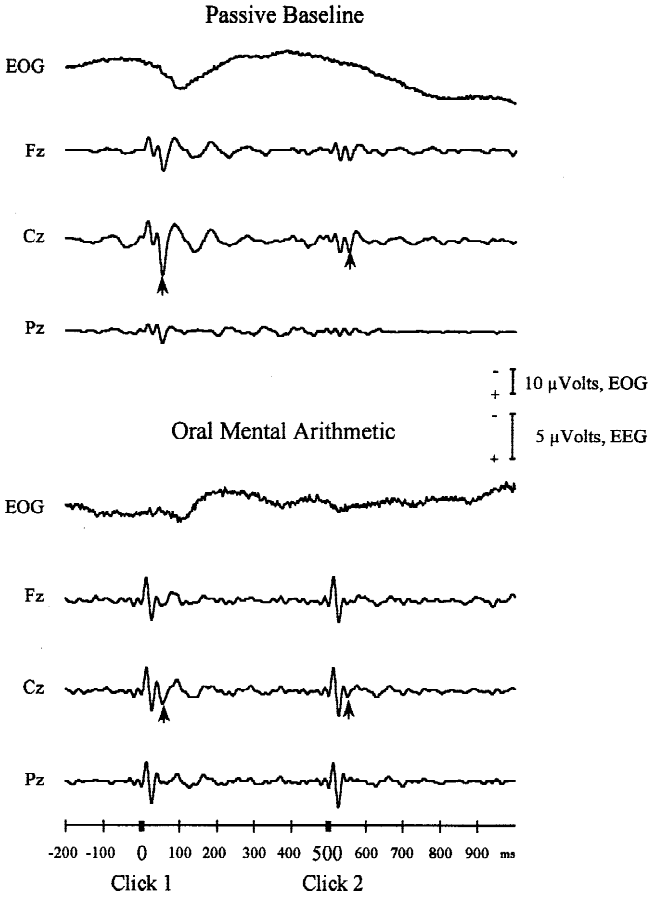

Figure 1. Grand average event-related potential (ERP) waveforms, at the three midline recording sites, for the passive baseline and oral mental arithmetic tasks. Waveforms were smoothed with a three-point moving average. The P50 component is indicated with arrowheads at the Cz lead.

Grand average ERP waveforms, comparing the oral MA task to the passive baseline task, are shown in Figure 1. Significant effects were obtained for task, $F(1,18) = 6.73$, $p < .05$, click, $F(1,18) = 30.35$, $p < .001$, and Task $\times$ Click, $F(1,18) = 14.01$, $p < .01$. Replicating our prior research, results of post hoc comparisons showed a significant reduction in P50 amplitude to Click 2 ($M = 2.26$, $SD = 1.38$) relative to the response elicited by Click 1 ($M = 5.61$, $SD = 2.94$) during the passive baseline task, whereas P50 magnitude to Click 1 ($M = 3.83$, $SD = 1.94$) and Click 2 ($M = 2.23$, $SD = 1.77$) during the oral MA task was not statistically different. The ratio measure of P50 suppression also showed a main effect for task, $F(1,18) = 4.58$, $p < .05$, with the stressor task ($M = 0.65$, $SD = 0.48$) significantly disrupting the P50 ratio score as compared with the traditional passive task ($M = 0.47$, $SD = 0.34$).

Research Question I: Competing Cognitive Activity

To examine the impact of competing cognitive activity while attempting to control for the potential influence of muscle movement or stress, P50 elicited during the silent counting task was compared with responses evoked by the passive baseline task. Grand average ERP waveforms obtained from each of the task

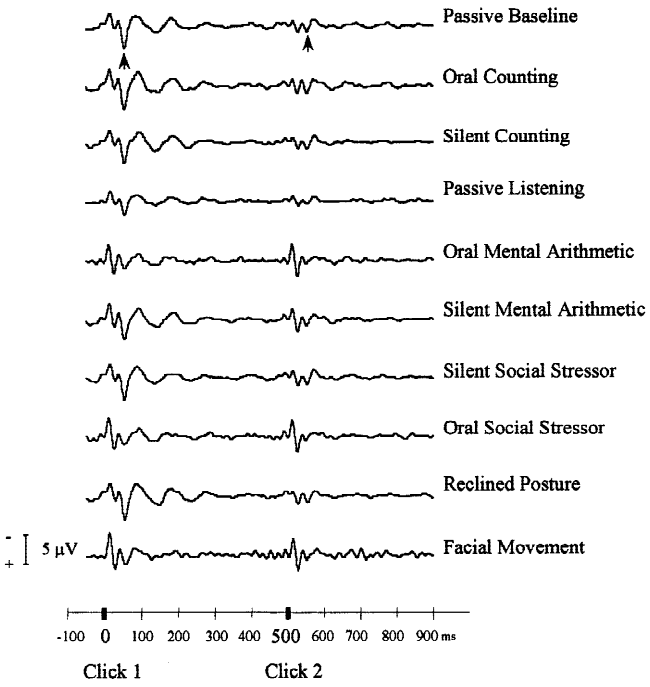

Figure 2. Grand average event-related potential (ERP) waveforms at the Cz site for each of the experimental tasks. Waveforms were smoothed with a three-point moving average and the P50 component is indicated with arrowheads.

conditions included in the present study are shown in Figure 2.[1] Across P50 measures, results were consistent with the hypothesis that P50 suppression is uninfluenced by the effects of directing attention towards another task. During the silent counting task, neither P50 amplitude to Click 1 ($M = 5.55$, $SD = 3.32$) or Click 2 ($M = 2.01$, $SD = 1.64$) were significantly affected by the cognitive activity associated with counting silently to oneself, relative to P50 activity observed during the passive baseline task (Click 1: $M = 5.65$, $SD = 2.89$; Click 2: $M = 2.21$, $SD = 1.38$), $F(1,18) = 0.31$, n.s. Similarly, neither task was found to exert a differential impact on the P50 ratio score (passive baseline: $M = 0.43$, $SD = 0.25$; silent counting: $M = 0.35$, $SD = 0.23$), $F(1,18) = 1.25$, n.s.

Because the cognitive demands associated with performing the silent counting task may have been insufficient to interfere with P50 suppression, data obtained during the silent MA and silent social stressor tasks were examined. Although these tasks were developed to evaluate the influence of stress on P50, 13 of the participants reported experiencing no stress during the performance of at least one of the two tasks. The P50 data obtained from these 13 subjects, therefore, were contrasted with recordings acquired during the passive baseline task to assess the impact of relatively demanding cognitive activity associated with silently solving mental arithmetic problems or preparing to deliver a brief statement concerning a personal issue. This level of cognitive activity was not found to influence P50 amplitude to Click 1 (passive baseline: $M = 6.17$, $SD = 3.28$; cognitive activity: $M = 6.26$, $SD = 3.38$) or Click 2 (passive baseline: $M = 2.49$, $SD = 1.53$; cognitive activity: $M = 2.27$, $SD = 1.68$), $F(1,12) = 0.06$, n.s. The P50 suppression ratio also was unaffected (passive baseline: $M = 0.45$, $SD = 0.27$; cognitive activity: $M = 0.38$, $SD = .17$), $F(1,12) = 0.45$, n.s.

[1]The waveforms are derived from the total sample participating in the present study. As noted earlier, subject's data were excluded from statistical analysis when the P50 could not be scored reliably. Utilizing this criteria, data from no fewer than 18 participants were included in any of the analyses.

Research Question II: Competing Auditory Stimulation

The influence of competing auditory stimulation was examined by comparing P50 during the passive baseline with responses elicited when an audio recording of a female voice counting was presented concurrently with the auditory clicks. Consistent with predictions, competing auditory activity during the passive listening task significantly reduced P50 amplitude from levels observed during the passive baseline task, $F(1,18) = 18.38$, $p < .001$. Post hoc comparisons revealed that P50 amplitude to Click 1 was significantly reduced when the recording of a female voice was presented concurrently with the click stimuli ($M = 3.60$, $SD = 2.81$) relative to the P50 elicited in the presence of clicks alone ($M = 5.64$, $SD = 2.91$). Although a similar pattern was observed for Click 2, the difference failed to reach statistical significance (passive baseline: $M = 2.25$, $SD = 1.38$; passive listening: $M = 1.68$, $SD = 1.58$). These results are illustrated in Figure 3. P50 suppression also was not affected differentially by the two tasks (passive baseline: $M = 0.46$, $SD = 0.33$; passive listening: $M = 0.53$, $SD = 0.53$), $F(1,18) = 0.27$, n.s.

Research Question III: Muscle Activity

To investigate whether the muscle activity involved in sitting and holding the head erect would have an impact on P50, recordings obtained while subjects maintained a sitting posture were compared with those taken while participants were in a supine position. As expected, the muscle activity associated with maintaining an upright position during the passive baseline task as compared with

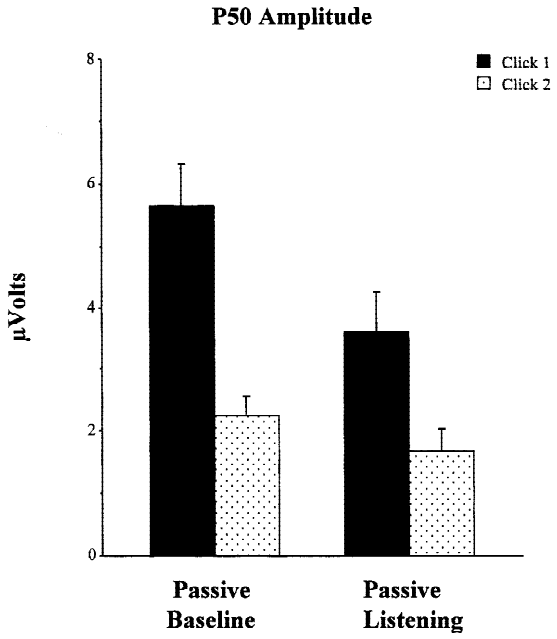

Figure 3. P50 amplitude to Click 1 and Click 2 during competing auditory stimulation.

the minimal muscle activity required by the reclining task did not significantly affect P50 amplitude to either Click 1 (passive baseline: $M = 5.65$, $SD = 2.89$; reclining: $M = 5.71$, $SD = 3.48$) or Click 2 (passive baseline: $M = 2.21$, $SD = 1.38$; reclining: $M = 2.24$, $SD = 1.95$), $F(1,18) = 0.02$, n.s. The P50 suppression ratio also did not reflect a significant effect for posture (passive baseline: $M = 0.43$, $SD = 0.25$; reclining: $M = 0.40$, $SD = 0.28$), $F(1,18) = 0.16$, n.s.

To examine whether muscle activity associated with the production of speech had an impact on P50, data obtained from the passive baseline task were contrasted with those from the oral counting task. P50 amplitude showed task, $F(1,19) = 14.64$, $p < .01$, click, $F(1,19) = 35.05$, $p < .001$, and Task × Click, $F(1,19) = 6.60$, $p < .02$, effects. These data are shown in Figure 4. Post hoc analysis revealed a significant reduction in P50 amplitude to Click 1 when subjects counted aloud ($M = 3.69$ $SD = 2.77$) compared to levels observed during the traditional passive task ($M = 5.45$, $SD = 2.95$); distinct influences were not apparent, however, for P50 amplitude to Click 2 (passive baseline: $M = 2.22$, $SD = 1.35$; oral counting: $M = 1.91$, $SD = 1.65$). The difference observed between tasks for the P50 suppression ratio also was not statistically significant, (passive baseline: $M = 0.48$, $SD = 0.34$; oral counting: $M = 0.67$, $SD = 0.59$), $F(1,19) = 1.49$, n.s.

In evaluating the specific contribution of muscle activity to the P50 data, an important consideration is that the oral counting task also involved auditory stimulation. A comparison between P50 amplitude elicited during the passive listening task (Click 1: $M = 3.61$, $SD = 2.82$; Click 2: $M = 1.68$, $SD = 1.58$) and during the oral counting task (Click 1: $M = 3.68$, $SD = 2.85$; Click 2: $M = 1.92$, $SD = 1.69$) suggests considerable similarity in the impact of the experimental conditions. No significant effects were observed for task, $F(1,18) = 0.26$, n.s., or Task × Click, $F(1,18) = 0.13$, n.s. Taken together, these data suggest that the muscle activity involved in speech does not appear to have a discernible impact on P50.

Muscle activity during the facial movement task, in contrast, had relatively dramatic effects on both amplitude and ratio measures of P50. For P50 amplitude, significant effects were obtained for task, $F(1,19) = 5.31$, $p < .04$, click, $F(1,19) = 14.96$, $p < .001$, and Task × Click, $F(1,19) = 26.14$, $p < .001$. Post hoc analyses did not distinguish between P50 amplitude to Click 1 during the facial movement task ($M = 5.22$, $SD = 2.09$) and the passive baseline task ($M = 5.45$, $SD = 2.95$). However, P50 amplitude to the second click during the facial movement task ($M = 4.65$, $SD = 2.09$) was more than twice that during the passive baseline task ($M = 2.23$, $SD = 1.35$). As shown in Figure 5, this pattern is reflected in the mean ratio scores, with significantly greater disruption to P50 suppression during the facial movement task ($M = 1.03$, $SD = 0.65$) than during the passive baseline task ($M = 0.48$, $SD = 0.34$), $F(1,19) = 21.14$, $p < .001$.

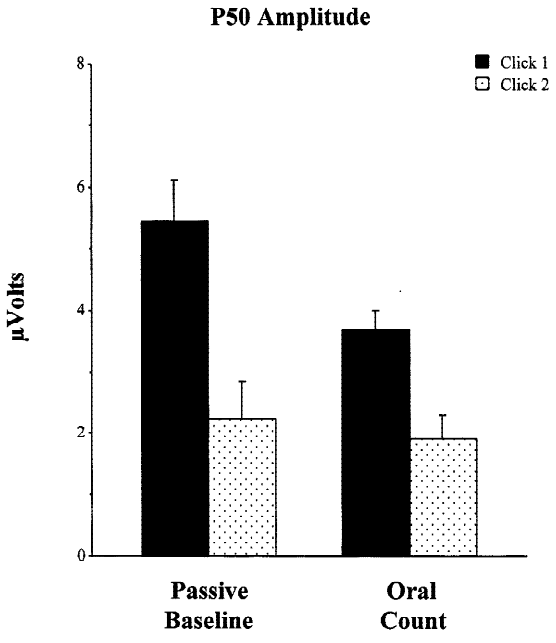

Figure 4. P50 amplitude to Click 1 and Click 2 during speech production.

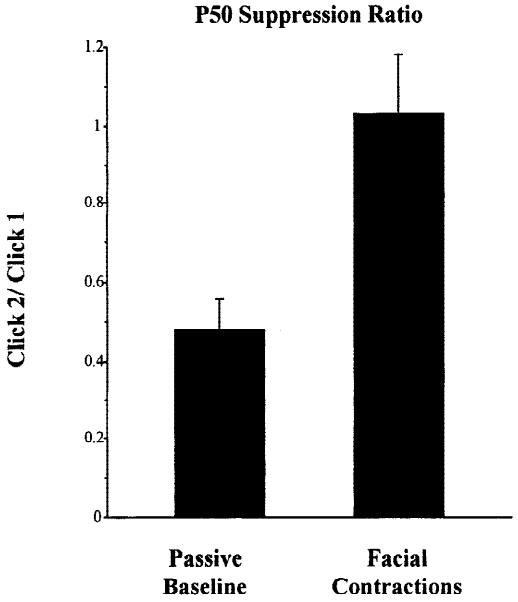

Figure 5. Effects of muscle activity, associated with the facial contractions task, on the P50 suppression ratio.

Research Question IV: Psychological Stress

Silent versions of the MA and social stressor tasks were developed to evaluate the impact of psychological stress on P50 while attempting to control for the potential influence of muscle activity and competing auditory stimuli. Because participants differed in level of self-reported stress experienced during these tasks, however, it was necessary to classify P50 data for each subject into one of two categories: Stress and No Stress. If subjects reported that their level of stress increased above baseline levels during performance of either the silent social stressor or silent MA tasks, those data were assigned to the stress category. If the task did not elicit an increase in stress level, the data were placed in the no stress category. For nine subjects, one condition was reported to be stressful whereas the other condition was not. Of the remaining nine subjects, five participants found both tasks to be stressful, whereas four participants reported no increase in level of stress during performance of either task. For these subjects, a single condition was randomly selected such that the stress category included 14 cases whereas the no stress category was comprised of 13 cases. As these data do not permit a between-subjects comparison, BMDP 5V was used to generate estimates of missing data to be used in a within-subjects ANOVA design (BMDP 2V).

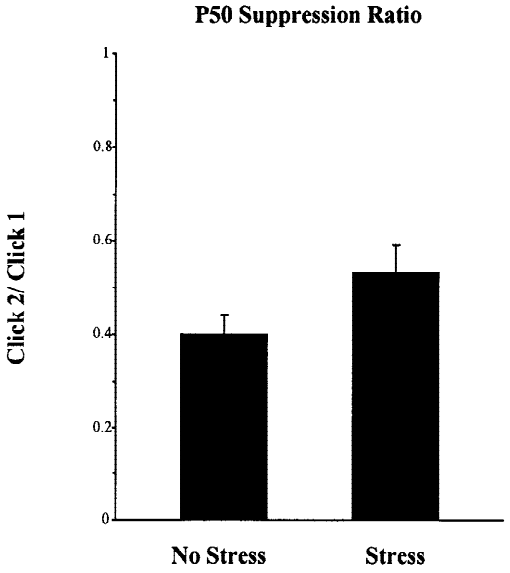

Figure 6. Effects of self-reported psychological stress on the P50 suppression ratio.

When participants reported experiencing increased stress during one of the silent stressor conditions, the P50 suppression ratio was significantly disrupted ($M = 0.53$, $SD = 0.24$) relative to when subjects found a task to be relatively stress free ($M = 0.39$, $SD = 0.17$), $F(1,17) = 5.39$, $p < .04$. This effect is illustrated in Figure 6. Although the pattern of the P50 amplitude data was in the expected direction for the stress (Click 1: $M = 5.56$, $SD = 2.84$; Click 2: $M = 2.47$, $SD = 1.43$) and no stress (Click 1: $M = 5.73$, $SD = 3.02$; Click 2: $M = 1.86$, $SD = 1.62$) categories, the Task $\times$ Click interaction did not reach statistical significance, $F(1,17) = 1.92$, $p < .2$.

Discussion

Results of this study replicate and extend the findings of White and Yee (1997) in showing that P50 suppression can be reduced during concurrent performance of a mental arithmetic stressor task, as compared to the level of suppression observed during the traditional passive P50 task. Moreover, the factors that were found to influence P50 during the stressor task appear to be relatively specific. The impact of each of the mechanisms considered in the current research will be discussed in turn.

Competing cognitive activity was not found to significantly influence P50 amplitude or its suppression when participants were engaged in merely counting numbers. These data are consistent with prior research on nonpsychiatric subjects by Jerger et al. (1992) and White and Yee (1997) in showing that P50 is not affected by relatively undemanding cognitive activities, such as directing voluntary attention to the click stimuli. Given the low level of cognitive demand or effort associated with each of these tasks, it is possible that interference effects might only have become apparent with a task that places a greater cognitive load on subjects. Such a possibility was addressed in the current study by data obtained from participants who reported experiencing no stress during one of the silent stressor tasks. Although subjects performed the tasks silently, the requirements of the stressor tasks were largely equivalent to those of their oral counterparts, with the exception that subjects did not vocalize their responses during the course of the task. Because each of the stressor conditions (i.e., performing mental arithmetic problems and preparing to deliver a brief speech) is typically associated with an increase in mental workload, any disruptions in P50 suppression can likely be attributed to the cognitive demands of the task. Concurrent performance of the silent stressor tasks did not result in poorer P50 suppression, however, suggesting that P50 is unlikely to be influenced even by a moderate degree of competing cognitive activity.

The *competing auditory stimulation* of listening to someone count numbers was found to reduce P50 amplitude although it did so without influencing P50 suppression. This result is consistent with other research indicating that P50 amplitude, but not P50 ratio, is sensitive to the sound intensity of click stimuli when the stimulus is below the startle-eliciting range (e.g., Griffith et al., 1995; White & Yee, 2001). Similarly, P50 amplitude has been found to be sensitive to background sound intensity levels, whereas the P50 ratio score appears to be relatively immune to these effects (White & Yee, 2001).

The impact of *muscle activity* on P50 and its suppression was found to vary as a function of the basis for the activation. The muscle activity associated with maintaining an upright position, for instance, did not appear to influence P50 amplitude or its suppression. In a study published after the present research was initiated, McCallin, Cardenas, and Fein (1997) likewise reported that P50 amplitude and the P50 suppression ratio did not differ when P50 was recorded in the sitting versus supine position.

The facial muscle activity involved in producing speech, however, was found to influence P50 amplitude. The P50 suppression ratio was not affected. Comparing the ratio scores obtained while subjects counted aloud with the data recorded as subjects sat passively, we did not observe any difference in level of suppression, suggesting that the muscle activity associated with producing speech does not exert a significant impact on P50 suppression. P50 amplitude to Click 1, however, was significantly reduced during the counting task, but this is likely the result of the auditory stimulation associated with hearing oneself count. To investigate such a possibility, the data obtained while subjects were speaking aloud (i.e., oral counting) were contrasted with the data recorded while subjects listened to someone else speak (i.e., passive listening). These two task conditions yielded a similar pattern of results, supporting the possibility that reductions in P50 amplitude during speech are likely the result of auditory stimulation rather than muscle activity. Taken together, these data suggest that the facial muscle activity necessary to produce speech is unlikely to impact P50 amplitude or its suppression. One implication of these findings is that disruptions to P50 suppression observed during performance of the oral MA task cannot be attributed entirely, if at all, to facial muscle activation.

Exaggerated facial movements, in contrast, exerted a pronounced effect by significantly enhancing P50 amplitude to Click 2 and thereby disrupting P50 suppression. These data suggest that suppression of the P50 response may be sensitive to the influence of myogenic activity once a relatively high level of activation is reached. To date, modulation of P50 amplitude to Click 2 has been attributed largely to the noradrenergic system and the involvement of other systems has not yet been thoroughly explored. Evidence supporting a noradrenergic influence on P50 has been provided primarily by studies relying upon the cold-pressor task or the administration of yohimbine (Adler et al., 1994; Johnson & Adler, 1993; Stevens et al., 1993). Although the noradrenergic system is certainly activated by the cold-pressor task, it is likely that other

systems are engaged as well. On the basis of the current data, one such possibility might be involvement of the musculature system when a sufficient level of activation is reached.

It also is possible that making faces in public may have been stressful and as a result, P50 amplitude to Click 2 was influenced not by high levels of muscle activity but by the noradrenergic system. Self-report ratings suggest that this situation is unlikely. With the exception of one subject, none of the participants rated their experience of the facial movement task as particularly stressful. Thus, stress is unlikely to account for the changes in P50 associated with making exaggerated facial movements.

Because movement artifact can also significantly affect recordings of brain electrical activity, a myogenic influence on the EEG also must be considered. A comparison of P50 amplitude to Click 1 between the facial movement and passive baseline conditions, however, suggests that any impact of muscle artifact on P50 is likely to have been modest, as P50 amplitude to Click 1 was not significantly influenced by noise in the recording. Nonetheless, the possibility of differential myogenic contamination of P50 to Click 1 and 2 cannot be eliminated given that the second click typically elicits a smaller signal than the first click in nonpsychiatric subjects and, therefore, may be more susceptible to muscle artifact.

Thus far, the potential influence of cognitive demands, auditory competition, and muscle activity involved in speech on P50 has been examined in an attempt to understand the modulatory effects of the oral MA task on P50 suppression. It appears that none of these factors was sufficient to disrupt the P50 suppression ratio. In contrast, *psychological stress* was found to exert the anticipated effect on P50 suppression. On the basis of the current data, it is difficult to discern the exact means by which P50 suppression was disrupted, as the relative impact on Click 1 versus Click 2 could not be distinguished statistically. Judging from the pattern of mean P50 amplitudes, the data appear to be consistent with results obtained from studies investigating the role of the noradrenergic system and reporting augmentation of the Click 2 response (e.g., Adler et al., 1994; Johnson & Adler, 1993). Such an interpretation is speculative, however, and awaits further empirical confirmation.

Moreover, the effects of psychological stress on P50 do not completely parallel the impact of the oral MA task. It is possible that the factors examined in the present study exerted a cumulative but perhaps nonlinear effect. Specifically, auditory competition may have served to reduce P50 amplitude to both clicks, whereas stress augmented the responses, particularly to Click 2. Whether other variables, such as cognitive competition and facial muscle activation, also played a role by interacting with the factors described appears to be unlikely, although the possibility cannot be ruled out entirely.

In considering these data, one limitation of the present research is that the presence or absence of muscle activity during any of the tasks described can only be inferred, given that EMG recordings were not obtained. Similarly, recordings of autonomic activity were not available in the present study to provide converging validation of stress activation during the MA and stressor tasks. Prior data obtained by White and Yee (1997) have demonstrated that cardiovascular and electrodermal activity are heightened during performance of the oral MA task. Future investigations will be necessary, however, to more clearly delineate the role of muscle activation and stress in P50 suppression.

It also is recognized that some of the predictions in the present study are attempts to confirm the null hypothesis and that failure to observe significant differences between conditions may have been due to a lack of statistical power. This appears to be unlikely for the following reasons. First, the absence of group or task differences in each instance is consistent with available theory. Second, the pattern of results conforms with data obtained in prior research. Finally, a number of highly significant differences were obtained in the present study. If other effects are true and present in the general population but were not observed in the current research, it is likely that they are much smaller than the significant effects obtained in the present study. Additional research certainly will be of considerable assistance in resolving uncertainty around these issues.

In sum, the results of this study have important implications for basic and clinical research on P50. Specifically, psychological stress and heightened facial muscle activation were found to modulate the P50 suppression ratio. Our ability to mimic aspects of the gating deficit associated with schizophrenia underscores the possible role that these factors may play in the P50 gating deficit. The present findings also emphasize the considerable theoretical importance of delineating the mechanisms that underlie P50 suppression in normal and schizophrenia subjects. Some practical implications also must be considered. As we and others have noted previously (e.g., Johnson & Adler, 1993; White & Yee, 1997), it is likely that variability in P50 and its suppression may exist between subjects that cannot be attributed entirely to a diagnosis of schizophrenia. Results of the present study further highlight the need to carefully monitor the psychological state of participants in P50 research to avoid potential and unnecessary confounds.

REFERENCES

Adler, L. E., Gerhardt, G. A., Franks, R., Baker, N., Nagamoto, H., Drebing, C., & Freedman, R. (1990). Sensory physiology and catecholamines in schizophrenia and mania. *Psychiatry Research, 31,* 297–309.

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., Hoffer, L., Nagamoto, H. T., Waldo, M. C., Kisley, M. A., & Griffith, J. M. (1994). Yohimbine impairs P50 auditory sensory gating in normal subjects. *Neuropsychopharmacology, 10,* 249–257.

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.

Bickford, R., Jacobson, J., Thane, D., & Cody, R. (1964). Nature of average evoked potentials to sound and other stimuli in man. *Annuals of the New York Academy of Sciences, 112,* 204–223.

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

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.

Franks, R. D., Adler, L. E., Waldo, M. C., Alpert, J., & Freedman, R. (1983). Neurophysiological studies of sensory gating in mania: Comparison with schizophrenia. *Biological Psychiatry, 18,* 989–1005.

Freedman, R., Adler, L. E., Bickford, P., Byerley, W. Coon, H., Cullum, C. M., Griffith, J. M., Harris, J. G., Leonard, S., Miller, C., Myles-Worsley, M., Nagamoto, H. T., Rose, G., & Waldo, M. (1994). Schizophrenia and nicotinic receptors. *Harvard Review of Psychiatry, 2,* 179–192.

Freedman, R., Adler, L. E., Gerhardt, G. A., Waldo, M. C., Baker, N., Rose, G. M., Drebing, C., Nagamoto, H., Bickford-Wimer, P., & Franks, R. (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., McRae, K., Cawthra, E., & Waldo, M. (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., 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., Polymeropoulos, M., Holik, J., Hopkins, J., Hoff, M., Rosenthal, J., Waldo, M. C., Reimherr, F., Wender, P., Yaw, J., Young, D. A., Breese, C., Adams, C., Patterson, D., Adler, L. E., Kruglyak, L., Leonard, S., & Byerley, W. (1997). Linkage of a neurophysiological deficit in schizophrenia to a chromosome 15 locus. *Proceedings of the National Academy of Sciences*, *94*, 587–592.

Gratton, G., Coles, M. G. H., & 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.

Jerger, K., Biggins, C., & Fein, G. (1992). P50 suppression is not affected by attentional manipulations. *Biological Psychiatry*, *31*, 365–377.

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., Budnick, B., & Braff, D. L. (1992). Sensory gating deficits in schizophrenia: New results. *American Journal of Psychiatry*, *149*, 488–493.

Leonard, S., Adams, C., Breese, C. R., Adler, L. E., Bickford, P., Byerley, W., Coon, H., Griffith, J. M., Miller, C., Myles-Worsley, M., Nagamoto, H. T., Rollins, Y., Stevens, K. E., Waldo, M., & Freedman, R. (1996). Nicotinic receptor function in schizophrenia. *Schizophrenia Bulletin*, *22*, 431–445.

McCallin, K., Cardenas, V. A., & Fein, G. (1997). P50 event-related brain potential amplitude and suppression measurements recorded with subjects seated versus supine. *Biological Psychiatry*, *41*, 902–905.

Miller, G. A., Gratton, G., & Yee, C. M. (1988). Generalized implementation of an eye movement correction procedure. *Psychophysiology*, *25*, 241–243.

Smith, D. A., Boutros, N. N., & Schwarzkopf, S. B. (1994). Reliability of P50 auditory evoked potential indices of auditory gating. *Psychophysiology*, *31*, 495–502.

Stevens, K. E., Meltzer, J., & Rose, G. M. (1993). Disruption of sensory gating by the alpha-2 selective noradrenergic antagonist yohimbine. *Biological Psychiatry*, *33*, 130–132.

Waldo, M. C., & Freedman, R. (1986). Gating of auditory evoked responses in normal college students. *Psychiatry Research*, *19*, 233–239.

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.

White, P. M., & Yee, C. M. (1997). Effects of attentional and stressor manipulations on the P50 gating response. *Psychophysiology*, *34*, 703–711.

White, P. M., & Yee, C. M. (2001). P50 sensitivity to physical and psychological influences. Submitted for publication.

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.

(Received August 14, 1998; Accepted October 17, 2000)