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Attentional Modulation of the P50 Suppression Deficit in Recent-Onset and Chronic Schizophrenia

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Schizophrenia is associated with deficits in P50 suppression to the second stimulus in a pair, a process often conceptualized as a preattentive index of sensory gating. This study assessed the malleability of the deficit by determining whether early attentional control can influence P50 gating across different phases of schizophrenia. Participants included 28 patients in the recent-onset ($n = 16$) or chronic ($n = 12$) phase of illness and 28 healthy comparison subjects. During the standard paradigm, chronic schizophrenia patients exhibited impaired P50 suppression relative to healthy subjects, whereas recent-onset schizophrenia patients were intermediate. Directing voluntary attention toward the initial stimulus yielded substantial improvements in the P50 ratio; recent-onset schizophrenia patients achieved ratio scores comparable to those of healthy participants, whereas chronic patients also improved and could no longer be distinguished clearly from the healthy comparison sample. Directing attention toward the second stimulus enhanced P50 amplitude to the second stimulus across groups, possibly because activation of the inhibitory mechanism was overridden or circumvented by task demands. Thus, P50 suppression may be primarily preattentive under standard conditions, but manipulation of early attention can exert a modulatory influence on P50, indicating that the suppression deficit is malleable in schizophrenia without pharmacological agents.

Keywords: schizophrenia, P50, sensory gating, attention, stage of illness

Individuals with schizophrenia frequently experience difficulty discriminating relevant information from the unimportant (Freedman et al., 1996; McGhie & Chapman, 1961). Confronted with an ever-changing environment and the need to focus selectively while filtering out distracting information, patients with schizophrenia must handle ongoing challenges while attempting to work productively, live independently, and function socially. The capacity to maintain and control attention, frequently referred to as top-down processing, along with the inhibition of responses to distracters, typically achieved with bottom-up processes, are central to effective neurocognitive functioning but are impaired in schizophrenia (Gold, Fuller, Robinson, Braun, & Luck, 2007; Gur et al., 2007). Although often viewed as separate processes involving distinct brain networks (Posner, 2004), these two systems also can interact dynamically, such that attention to sensory stimuli may be modulated by bottom-up and top-down processes (Hillyard, Vogel, & Luck, 1998; Posner, 2004; Woldorff et al., 1993). Given such a relationship between the two systems, it is possible that deficits in one domain are amenable to improvement by intact aspects of the other network among individuals with schizophrenia. If it can be established, for example, that deficits in the inhibitory response to distracting information are responsive to improvement by attentional control systems, this information would provide a potential pathway for future pharmacological interventions and cognitive remediation techniques.

Although neurocognitive dysfunction is extensive in schizophrenia, not all attentional processes are compromised by the illness. Notably, top-down modulation of early auditory attention appears to be spared. Relying on the high temporal resolution offered by event-related potentials (ERPs), Mathalon, Heinks, and Ford (2004) demonstrated that frontally mediated control of attention is intact in schizophrenia patients up until about 75 ms in the processing stream. It is possible, therefore, that early attention can be used to influence disrupted processes occurring within this temporal domain.

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The compromised capacity to gate or inhibit responses to distracting information in schizophrenia has been studied extensively by presenting paired auditory stimuli to assess the degree of suppression of the P50 ERP component to the second stimulus (S2) relative to the response elicited by the first stimulus (S1), when separated by a 500-ms interstimulus interval. The relationship between the two stimuli is often quantified as the S2/S1 ratio, with healthy individuals typically scoring below .50 and schizophrenia patients exceeding this value (Adler et al., 2004; Freedman et al., 2000; Patterson et al., 2008; Waldo et al., 1991). Meta-analytic studies reveal a robust effect size for the P50 deficit in schizophrenia that exceeds most other abnormalities (Bramon, Rabe-Hesketh, Sham, Murray, & Frangou, 2004; Heinrichs, 2001; Patterson et al., 2008). Although deficits in P50 suppression can be restored by pharmacological agents, such as nicotine and a subset of second-generation antipsychotics (Adler, Hoffer, Wiser, & Freedman, 1993; Adler et al., 2004; Light, Geyer, Clementz, Cadenhead, & Braff, 2000; Olincy et al., 2006), it has yet to be established whether voluntary control of attention can be engaged to improve or even normalize P50 gating in schizophrenia. Thus, our objective in the present study was to determine the extent to which early attentional control might improve inhibitory processing of the P50 component of the ERP in schizophrenia within the context of a sensory gating paradigm.

In evaluating another neurophysiological deficit in schizophrenia, we found that enhanced attention to the target stimulus improved eye tracking performance to such a degree that schizophrenia patients with a recent onset of illness were able to track as accurately as healthy individuals (Yee, Nuechterlein, & Dawson, 1998). Similar findings have been obtained in chronic schizophrenia patients (Holzman, Levy, & Proctor, 1976; Iacono, Tuason, & Johnson, 1981), with the level of improvement generally less than that observed in patients closer to their first episode of illness, possibly as a result of degenerative processes, sustained neuroleptic treatment, adaptation to a recurring illness, or other factors associated with the chronic phase of schizophrenia.

The relative absence of research investigating the malleability of the P50 in schizophrenia patients, aside from pharmacological interventions, can be attributed to two factors. From a theoretical perspective, P50 gating has been conceptualized within the framework of an *automatic, inhibitory process* model (Braff & Light, 2004; Freedman et al., 1996). The prevailing view is that P50 suppression provides an index of sensory gating whereby S1 automatically activates an inhibitory process that then suppresses responsiveness to S2. In schizophrenia patients, the suggestion is that the initial stimulus fails to activate an inhibitory response to the second stimulus and thereby allows S2 to interfere with the processing of S1. The initial stimulus, therefore, is viewed as failing to close off processing of a subsequent auditory event that ensues almost immediately. Under this model, P50 suppression does not require voluntary attention and occurs automatically (Freedman et al., 1987, 1996).

Second, the preattentive nature of P50 suppression is supported by studies in which healthy individuals were instructed to allocate voluntary attention toward each of the two stimuli but without any detectable influence on P50 or its suppression (Jerger, Biggins, & Fein, 1992; White & Yee, 1997). Relying on normal variations in attentiveness among healthy participants, Cardenas, Gill, and Fein (1997) further determined that P50 and its suppression are not affected by differing levels of wakefulness. There is some suggestion, however, that maintaining a running count of S2 may serve to disrupt suppression (Guterman, Josiassen, & Bashore, 1992).

To our knowledge, there have been no investigations examining whether the P50 deficit in schizophrenia is also impervious to attentional manipulations. P50 suppression may be unaffected by voluntary attention in healthy individuals because the inhibitory process is intact and fully functional whereas, in schizophrenia patients, recruitment of voluntary attention could improve the deficit by compensating for a faulty preattentive inhibitory process. Alternatively, allocation of attentional processes might serve to further disrupt a process that is already compromised, depending on how or when voluntary attention is engaged. Because it remains to be demonstrated how voluntary attention might influence P50 suppression in schizophrenia patients, three possible outcomes were evaluated in the current study.

Consistent with the *automatic, inhibitory process* model described above and with available evidence from healthy subjects, voluntary attention directed at either S1 or S2 should have no effect on P50 gating in schizophrenia patients. As an alternative, we examined the possibility that schizophrenia patients fail to allocate sufficient attention toward the incoming, initial stimulus, which, in turn, leads to a failure to activate the P50 inhibitory process. In this case, P50 suppression is not entirely automatic but instead may be enhanced by top-down processes directed toward the auditory channel. Instructing schizophrenia patients to direct attention to S1, therefore, should help to fully engage the P50 inhibitory mechanism and lead to normal levels of P50 suppression. This option is described as a *compensatory attention* model.

A third scenario is that because the automatic P50 inhibitory mechanism is only partially intact in schizophrenia patients, it is easily disrupted when attention is allocated to other stimuli that may be generated internally or externally. Accordingly, impairments in P50 suppression should be exacerbated when voluntary attention is directed toward S2. This possibility, an *attention disruption* model, is not incompatible with the compensatory attention model because both alternatives allow for attentional effects but attribute them to different manners of action.

In the present study, moderating effects of phase of illness on the attentional manipulations also were examined, as the eye tracking results suggest that greater gains with voluntary attention may be achieved with individuals closer to the onset of schizophrenia. Consistent with a *compensatory attention* model, we predicted that directing voluntary attention toward S1 would activate an inhibitory response to S2 and result in improved P50 suppression, with more significant gains observed among patients with a recent onset of schizophrenia than those in the chronic phase. As suggested by an *attention disruption* model, we also hypothesized that because of its tenuous nature in schizophrenia, P50 and its suppression will be further compromised when voluntary attention is directed at the second, interfering stimulus, with the most deleterious effect on chronic patients who also were expected to show greatest P50 impairment overall (Brockhaus-Dumke et al., 2008).

Method

Participants

Written informed consent was obtained from 28 outpatients with a diagnosis of schizophrenia and 28 healthy comparison subjects. Efforts were made to match each patient group with healthy comparison subjects on age, sex, level of parental education, and ethnicity. To examine any effects associated with duration of illness, we classified patients as recent onset ($n = 16$) if they were within three years of their first psychotic episode ($M = 1.4$ years, $SD = 1.0$) and as chronic ($n = 12$) if more than five years had elapsed since their initial psychotic episode ($M = 13.2$ years; $SD = 5.3$). Given possible anticholinergic effects on P50, antiparkinsonian medications were discontinued at least 24 hours prior to testing. The expanded Brief Psychiatric Rating Scale (Ventura et al., 1993) was administered to assess symptom levels during the preceding two-week period. All patients were evaluated in a clinically stable state.

All recent-onset and six chronic schizophrenia patients were initially recruited for the University of California, Los Angeles, Developmental Processes in Schizophrenic Disorders project. The remaining six chronic patients were participants in the naturalistic follow-up phase of a study of atypical medications conducted at the Veterans Administration Greater Los Angeles Healthcare System. Comparison subjects were recruited from the community and were excluded if they had a history of schizophrenia, schizoaffective disorder, or other major psychopathology; any alcohol or substance abuse in the last three months; or history of a major psychiatric disorder in a first-degree relative. Diagnoses were obtained with the Structured Clinical Interview for *DSM–IV* (First, Spitzer, Gibbon, & Williams, 2001; Ventura, Liberman, Green, Shaner, & Mintz, 1998). Additional exclusion criteria for all participants included neurological disorders, history of a head trauma or loss of consciousness for more than five minutes, and current significant or habitual alcohol or substance abuse. Although one patient from each group smoked 15–20 min prior to the number task, this time interval is sufficient for P50 suppression to return to near baseline values (Adler et al., 1993). All other smokers refrained from cigarettes for at least 45 min before any condition.

Procedure

Baseline data were obtained while participants were seated comfortably and presented with 80 trials of paired high-intensity stimuli. During the attention tasks, four types of stimuli were delivered in random order: (a) moderate-intensity single stimuli, (b) moderate-intensity paired stimuli, (c) high-intensity single stimuli, and (d) high-intensity paired stimuli. A total of 160 trials were presented during each of the attention tasks, with 52% of trials ($n = 82$) comprising high-intensity paired stimuli that were identical to those delivered during baseline. Each of the three remaining types of stimuli accounted for 16% of the total trials per task; the resulting data were not included in any of the subsequent analyses.

During the intensity task, participants were instructed to respond as quickly as possible with a button press whenever they detected a high-intensity stimulus, irrespective of whether the stimulus involved single or paired stimuli; this task served to direct attention to S1. During the number task, participants were instructed to respond as quickly as possible whenever they detected a pair of stimuli, irrespective of stimulus intensity; this task served to direct attention to S2. Order of presentation of the attention tasks was counterbalanced.

Auditory Stimuli

Auditory stimuli were 3 ms in duration, with a 500-ms interstimulus interval and a variable intertrial interval of 9–11 s between pairs. For six chronic patients, two recent-onset patients, and 14 healthy subjects, high-intensity stimuli were delivered at 90-dB sound pressure level (SPL) and moderate-intensity stimuli at 80-dB SPL. Stimuli were presented against 40-dB SPL background white noise over headphones. The auditory stimuli and background noise were created by amplifying white noise generated by a San Diego Instruments Sound Generator board. Stimuli for the remaining six chronic patients, 14 recent-onset patients, and 14 healthy subjects were presented through foam-insert earphones. Sound threshold levels were determined for each ear with high-intensity stimuli at 55 dB above threshold and moderate-intensity stimuli at 20 dB below the sound level of high-intensity stimuli. Auditory stimuli consisted of amplified white noise that was created using the Neuroscan STIM presentation system (Charlotte, NC). Background noise was unnecessary because recordings were obtained in a soundproof chamber rather than the sound-attenuated room used previously that had a background noise level measuring at 46 dB SPL, emanating primarily from the amplifier system in the adjoining room and the ventilation system. As recommended by Veneklasen Associates, consultants in acoustics who provided sound measurements and recommendations on maintaining comparable conditions between rooms, ambient noise in the soundproof chamber was introduced by a small ventilation fan that did not exceed the noise criteria curve of 30. The change in labs and equipment was necessitated by local seismographic retrofitting. To ensure comparability of data across labs, we undertook extensive testing with a separate sample of 16 healthy subjects. Auditory stimuli, for example, were generated using the two methods, whereas electrophysiological data were acquired with the same recording equipment; mean P50 amplitudes to S1 ($M = 3.36$, $SD = 1.64$, vs. $M = 3.34$, $SD = 1.43$) and S2 ($M = 1.24$, $SD = .77$, vs. $M = 1.27$, $SD = .43$) were effectively identical.

Data Acquisition and Analysis

For the first set of participants described above, the electroencephalogram (EEG) was recorded from electrodes placed at Fz, Cz and Pz midline sites and referenced to linked earlobes. Electrooculogram activity was recorded from electrodes placed above and below the left eye. Signals were acquired with a Model 12 Neurodata system (Grass, West Warwick, RI) with half-amplitude analog filters set at 0.1 and 1000 Hz. For remaining participants, EEG recordings were obtained with a high-density cap containing Ag/AgCl sintered electrodes (Falk Minow Services, Herrsching, Germany). Signals were acquired with a SynAmps system (Neuroscan, Charlotte, NC) with filters set at 0.5 and 200 Hz. As with stimulus presentation, the recording systems were assessed for comparability with the separate healthy sample by obtaining data from each unit while using identical auditory stimuli; again, no notable or significant differences

were detected. Chronic patients and healthy subjects also were equally distributed between the two labs. Although data from a greater proportion of recent-onset patients were acquired with a SynAmps system, their P50 data and that of the members of the healthy comparison group reported below (i.e., suppression ratios of $M = .50$, $SD = .29$, and $M = .36$, $SD = .21$, respectively) are largely comparable to data obtained with Grass instrumentation from previous samples of recent-onset patients and healthy comparison subjects (mean ratios of $M = .55$, $SD = .32$, and $M = .38$, $SD = .18$, respectively; see Yee, Nuechterlein, Morris, & White, 1998). Across all participants, the sampling rate was 1000 Hz and only data obtained from Cz are included in this study.

Trials contaminated by subject movement were excluded and data were subtracted from a 200-ms prestimulus baseline. After we corrected for eye movement artifact (Miller, Gratton, & Yee, 1988), single EEG trials were digitally filtered with a bandpass of 10–50 Hz to measure P50. For the intensity and number tasks, only trials with a correct behavioral response to high-intensity paired stimuli contributed to the ERP average. Trials with moderate-intensity stimuli were not examined further. P50 was identified as the most positive point between 40 and 70 ms after stimulus presentation. P30 amplitude and latency were scored as the maximum positivity occurring 20 to 40 ms after the stimulus. The maximum negativity between the P30 and P50 latencies was then used to measure P50 amplitude. P50 to S1 exceeded 0.5 μV for all participants and could be scored reliably. Reaction time was obtained from a button press made with the thumb of the dominant hand and recorded from S1 for the intensity task and S2 for the number task.

Statistical Analysis

Preliminary analyses were conducted with lab as a factor to further verify comparability of the data. After determining that lab did not emerge as a significant main effect for any dependent variable and never interacted significantly with other factors, we merged the data. Additionally, no significant group differences were detected between the older and younger healthy comparison groups. Yoking of patient groups to separate comparison groups was eliminated in favor of a single, combined healthy sample to maximize the sample size for group contrasts. Although none of the P50 measures were associated with normal aging, P50 amplitude to S1 during the baseline correlated negatively with age in schizophrenia patients. We therefore undertook a hierarchical multiple regression analysis with group, age, and their interaction. The absence of significant interaction effects confirmed that age was not a confounding variable. Analyses of variance (ANOVAs) were conducted with the Greenhouse–Geisser method to adjust degrees of freedom. Post hoc analyses relied on Newman–Keuls and *t* tests for between-group and within-group contrasts, respectively.

N100 was analyzed to examine comparability with the pattern of effects obtained previously (Jerger et al., 1992; White & Yee, 1997) and to verify along with the behavioral performance data that attention had been engaged. Because group differences were not detected, with the exception of healthy participants exhibiting a larger response to S1 during the intensity condition, these data are not included in the present article. Similarly, P50 latency was examined but no significant findings involving group or experimental conditions were obtained.

Results

Demographic and Clinical Characteristics

As indicated in Table 1, the patient groups were matched to their healthy comparison group on age, sex, level of parental education, and ethnicity with a single exception. Relative to the chronic schizophrenia patients, older healthy comparison subjects were significantly younger, $F(1, 22) = 12.90$, $p = .01$. Education levels were significantly higher in the young healthy comparison sample than in the recent-onset schizophrenia patient group, $F(1, 30) = 6.43$, $p = .05$, and in the older comparison group relative to chronic schizophrenia patients, $F(1, 22) = 8.90$, $p = .01$. In comparison to chronic schizophrenia patients, recent-onset patients had a significantly shorter duration of illness, $F(1, 23) = 75.64$, $p = .001$; were on a significantly lower dosage of antipsychotics, $F(1, 23) = 11.13$, $p = .01$; and had significantly lower Brief Psychiatric Rating Scale scores, $F(1, 26) = 7.29$, $p = .05$.

Behavioral Performance

Behavioral data appear in Table 2. The groups did not differ in mean percentage of correct responses during the intensity task, $F(2, 50) = 0.65$, $p = .53$, or number task, $F(2, 50) = 2.17$, $p = .12$. Healthy comparison subjects were significantly faster in mean reaction time than were those in the patient groups during the intensity task, with recent-onset schizophrenia patients providing significantly slower performance than subjects in either of the other two groups, $F(2, 53) = 30.57$, $p = .001$. During the number task, recent-onset patients were significantly slower again in performance than were chronic schizophrenia patients and healthy comparison subjects, who did not differ from one another, $F(2, 53) = 18.60$, $p = .001$.

P50 Suppression Ratio

Grand-average ERP waveforms are presented in Figure 1. To assess for differences in P50 suppression prior to manipulating voluntary attention, we compared the three groups during the typical, passive P50 baseline condition. A significant main effect of group, $F(2, 53) = 3.85$, $p = .028$, revealed impaired P50 suppression in chronic schizophrenia patients ($M = .61$, $SD = .36$) relative to healthy subjects ($M = .36$, $SD = .21$), whereas recent-onset patients were intermediate ($M = .50$, $SD = .29$) and did not differ statistically from the other two groups.[1]

Mean P50 suppression ratio scores for each task condition are displayed in Figure 2. As predicted, directing voluntary attention to S1 eliminated any group differences; recent-onset ($M = .35$, $SD = .25$) and chronic schizophrenia patients ($M = .52$, $SD = .38$) exhibited levels of P50 suppression that were statistically indistinguishable from those of healthy comparison subjects ($M = .34$,

[1] Because clozapine can improve P50 suppression (Adler et al., 2004; Light et al., 2000), associations with medication type were examined and revealed poorer suppression in chronic schizophrenia patients receiving clozapine ($n = 8$; $M = .75$, $SD = .32$) than those on other atypical antipsychotic medications ($n = 4$; $M = .32$, $SD = .30$), $F(1, 11) = 5.12$, $p = .047$, possibly reflecting selection of clozapine for patients with a more severe course of illness.

Table 1
Demographic and Clinical Characteristics of Participants

Characteristic	Healthy comparison subjects: Younger sample (n = 16)			Healthy comparison subjects: Older sample (n = 12)			Recent-onset schizophrenia patients (n = 16)			Chronic schizophrenia patients (n = 12)		
	n	*M*	*SD*	*n*	*M*	*SD*	*n*	*M*	*SD*	*n*	*M*	*SD*
Gender												
Female	5			0			6			1		
Male	11			12			10			11		
Ethnicity												
African American	5			0			5			0		
Asian American	1			0			1			0		
Caucasian	5			12			6			12		
Hispanic	5			0			4			0		
Antipsychotics												
Risperidone							12			2		
Aripiprazole							2			0		
Olanzapine							2			1		
Clozapine							0			9		
Age (years)		23.8	4.6		32.3	3.3		24.3	3.7		43.6	10.4
Education (years)		14.9	1.5		15.7	1.4		13.3	2.0		13.5	2.1
Parental education (years)		13.6[a]	2.1		14.7	2.8		12.6	4.6		15.3	2.4
Medication dosage (mg/day, in chlorpromazine equivalents)								222	68.2		613[b]	467.8
24-item BPRS total score								29.3	7.3		36.7	7.1

Note. BPRS = Brief Psychiatric Rating Scale.
[a] n = 15. [b] n = 9; data are unavailable for three patients.

SD = .23), as indicated by the absence of a main effect for group during the intensity task, $F(2, 53) = 2.12$, $p = .13$. The number task, in contrast, interfered with P50 suppression to a similar degree across recent-onset patients ($M = .66$, $SD = .78$), chronic patients ($M = .72$, $SD = .40$), and healthy subjects ($M = .54$, $SD = .34$), given levels significantly elevated from baseline as reflected by a main effect for condition, $F(1, 53) = 4.67$, $p = .035$, and the absence of a main effect for group, $F(2, 53) = 0.64$, $p = .53$.

In terms of the magnitude of P50 suppression differences between patients and healthy participants during the passive baseline condition, chronic schizophrenia patients exhibited the larger effect size (Cohen's $d = 0.95$) compared with a medium effect size ($d = 0.58$) for recent-onset patients. Directing attention to the initial stimulus served to eliminate any differences between recent-onset schizophrenia patients and healthy individuals ($d = 0.04$) while reducing the effect size in chronic patients ($d = 0.64$). Likewise, the amount of interference introduced by directing attention to S2 exerted less of an impact on recent-onset patients ($d = 0.22$) than chronic patients ($d = 0.50$) relative to healthy comparison subjects.

P50 Amplitude

Mean P50 amplitudes are shown in Figure 3. To evaluate the extent to which group differences in passive baseline ratio scores reflect the response elicited by each of the paired stimuli and to provide a difference score measure of P50 suppression, we undertook a repeated-measures ANOVA for the effects of group and stimulus (S1 vs. S2). The main effect of stimulus, $F(1, 53) = 78.89$, $p = .001$, was modified by a significant Group × Stimulus interaction, $F(2, 53) =$

Table 2
Behavioral Performance

Task	Healthy comparison subjects (n = 28)		Recent-onset schizophrenia patients (n = 16)		Chronic schizophrenia patients (n = 12)	
	M	*SD*	*M*	*SD*	*M*	*SD*
Intensity						
% correct	94.3	8.0	91.6	11.9	96.4[a]	7.2
RT (ms)	561	201	1171	326	751	237
Number						
% correct	97.0	2.8	98.0	3.5	96.6[a]	5.1
RT (ms)	265	91	598	278	377	145

Note. RT = reaction time.
[a] Performance accuracy data are missing from three participants because of computer error.

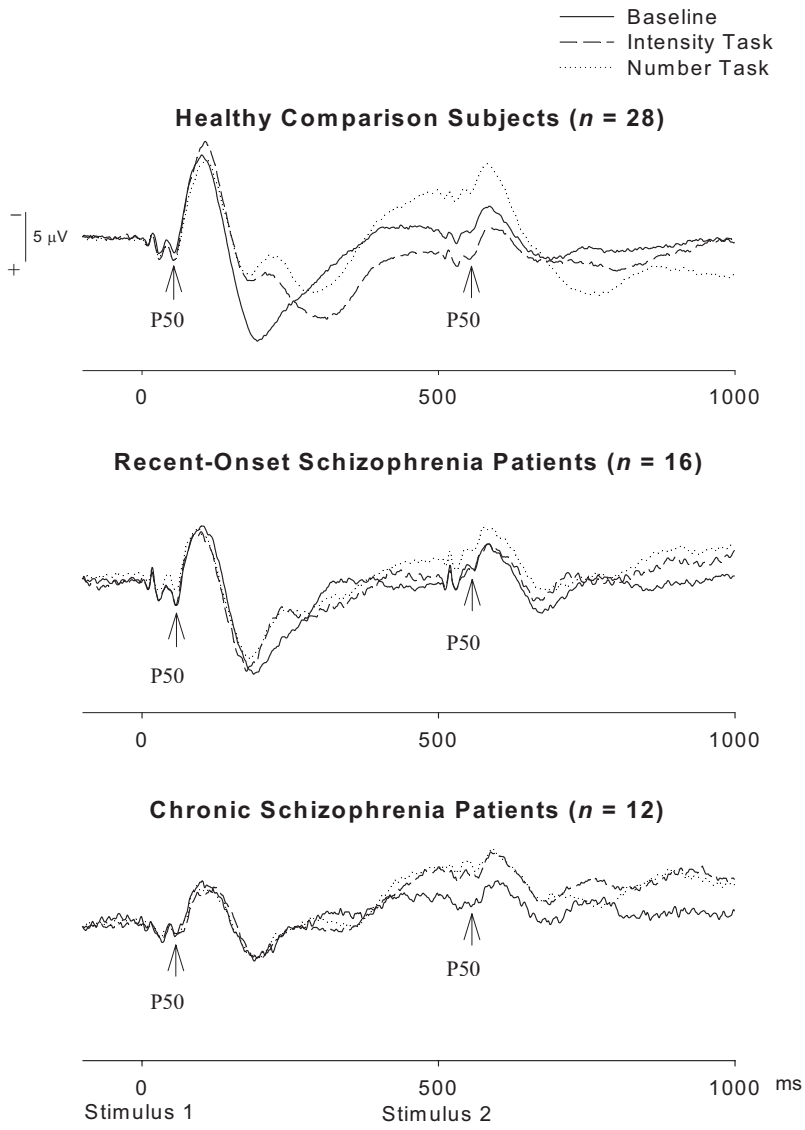

Figure 1. Grand average event-related potential waveforms at the Cz recording site.

3.54, $p = .036$. Post hoc comparisons determined that P50 amplitude to S1 was comparable between recent-onset schizophrenia patients ($M = 4.67$, $SD = 2.91$) and healthy comparison subjects ($M = 4.26$, $SD = 2.08$) but reduced in chronic patients ($M = 2.82$, $SD = 1.03$). Although the relative magnitude of P50 amplitude to S2 was in the expected direction for recent-onset ($M = 1.99$, $SD = 1.06$) and chronic schizophrenia patients ($M = 1.63$, $SD = 0.90$) relative to healthy individuals ($M = 1.53$, $SD = 1.10$), the group difference did not reach statistical significance. Thus, there appears to have been greater mediation of the P50 ratio score by the smaller S1 response in the chronic group.

To examine a priori hypotheses concerning the specific impact of voluntary attention on P50 within each group while again providing a difference score measure of P50 suppression, we conducted Condition (baseline vs. intensity task vs. number task) × Stimulus (S1 vs. S2) ANOVAs for each sample. These within-subjects analyses further serve to mitigate any differences that may have resulted from obtaining ERP recordings in two different settings, as the data for any given participant were always obtained in the same location.

P50 amplitude in healthy comparison subjects exhibited condition, $F(2, 54) = 5.80$, $p = .006$; stimulus, $F(1, 27) = 100.59$, $p = .001$; and Condition × Stimulus, $F(2, 54) = 3.75$, $p = .034$, effects. In keeping with the pattern of directed attention, P50 to S1 was significantly larger during the intensity task than during baseline. Similarly, P50 to S2 was enhanced when attention was directed to the second stimulus during the number task relative to levels observed during baseline and the intensity task.

Among recent-onset schizophrenia patients, P50 amplitude showed significant effects for stimulus, $F(1, 15) = 25.92$, $p = .001$, and for the Condition × Stimulus interaction, $F(2, 30) = 4.26$, $p = .027$. Consistent with hypothesized improvements in P50 suppression as a result of directing attention to S1, P50 to S2 was significantly inhibited or reduced during the intensity

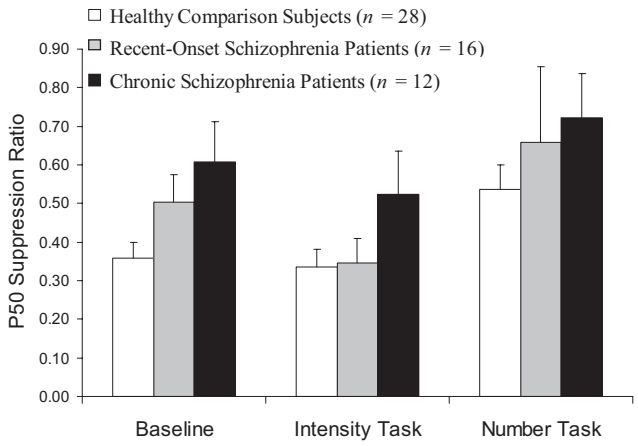

Figure 2. Mean P50 suppression ratios.

task relative to the other conditions. P50 to S1, however, remained comparable to baseline levels during the intensity task. Directing attention to S2 during the number task had the unanticipated impact of significantly reducing P50 to S1 relative to baseline levels.

Chronic schizophrenia patients exhibited significant P50 effects for condition, $F(2, 22) = 7.14$, $p = .008$, and stimulus, $F(1, 11) = 38.27$, $p = .001$, and an effect that approached significance for the Condition × Stimulus interaction, $F(2, 22) = 3.66$, $p = .06$. Given a priori hypotheses, planned comparisons were conducted to determine the influence of attention during each experimental condition. Directing attention to the initial stimulus during the intensity task served to augment P50 amplitude to S1 relative to baseline levels as hypothesized but failed to significantly impact P50 to S2. During the number task, voluntary attention to S2 resulted in significant increases in P50 to S1 compared with baseline and to S2 relative to response levels elicited during baseline and the intensity condition.

Discussion

Although P50 suppression has been regarded primarily as a preattentive process, the present results demonstrate that voluntary attention can exert a modulatory influence, thereby providing further evidence for the potential malleability of the P50 deficit in schizophrenia. As might be expected of intact inhibitory processes in healthy participants, there was no appreciable impact on the P50 suppression ratio when voluntary attention was directed toward the initial stimulus. In recent-onset schizophrenia patients, however, directing attention toward S1 suppressed P50 to S2 while exerting no significant impact on the initial response, resulting in a mean P50 ratio score at a level typically observed only in healthy populations. These data therefore demonstrate that P50 suppression deficits among recent-onset patients can be transiently normalized without the aid of pharmacologic agents.

Improved P50 ratio scores also were observed in chronic schizophrenia patients during the intensity task, although gains were more modest and the amplitude data were less clearly indicative of suppressed responsiveness to S2. Instead, P50 to S1 increased to a mean level comparable to that of the healthy subjects while P50 to S2 did not change from baseline levels. Attempts to evaluate the pattern and significance of these data underscore the difficulty associated with inferring an inhibitory response from paired stimuli (Smith, Boutros, & Schwarzkopf, 1994). Specifically, changes in the ratio score resulting from alterations in P50 to S1 do not necessarily support the engagement of inhibitory processes; the improved ratio score in chronic schizophrenia patients could be attributed to an enhanced response to S1 alone rather than any true change in the relationship between responses. A plausible alternative interpretation is that inhibition of the S2 response in chronic patients was improved by attention to S1, with inhibitory processes leading to no appreciable change in P50 to S2 despite augmentation of P50 to S1.

A similar situation is encountered in recent-onset schizophrenia patients when attention was directed toward S2 during the number task, with changes in P50 to S1 contributing to increases in the P50 ratio. Given the complex pattern of findings obtained in the present study and continued reliance on the ratio measure of P50 suppression, researchers conducting future studies should attempt to not only consider factors that might influence S1 or S2 amplitudes but also ascertain the extent to which these determinants influence P50 suppression. Beyond conceptual implications, discriminating between actual inhibition of the P50 and other alterations to the P50 ratio measure is a methodological necessity (White & Yee, 2006).

In chronic schizophrenia patients, direction of attention toward the second stimulus more definitively resulted in poor suppression, with P50 to S2 exceeding baseline levels. It appears, therefore, that voluntary attention may have served to override or prevent activation of the inhibitory mechanism during the number task. This pattern of effects may be adaptive, in that assigning significance to the second stimulus allows the S2 to be processed fully rather than gated in an obligatory manner. Results from the healthy group

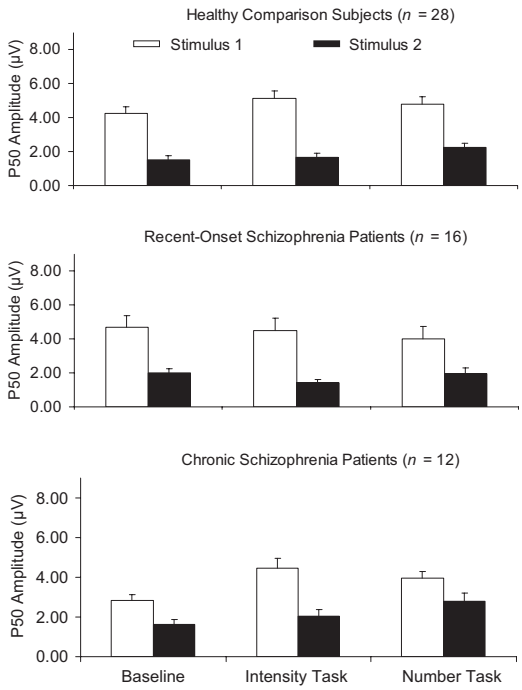

Figure 3. Mean P50 amplitude to paired stimuli.

during performance of the number task revealed similar effects on the P50 ratio and contrast with prior data obtained with the same experimental manipulation in which voluntary attention had no significant impact (White & Yee, 1997). Earlier data suggest that a similar pattern of disruption was present but not statistically significant, possibly due to a smaller sample of 13 participants coupled with a modest experimental effect size among nonpsychiatric subjects. Thus, similar to psychosocial stress (White & Yee, 1997; Yee & White, 2001), it appears that voluntary attention can interfere with P50 and its suppression even in healthy individuals (Guterman et al., 1992).

Stage of illness also was implicated in the basic P50 deficit and its malleability. A pattern of increasing disruption was observed during the passive paradigm from healthy to recent-onset to chronic groups and may be related to course of illness. On the basis of consideration of the effect sizes, there was some suggestion that patients in the initial stage of schizophrenia achieved more substantial gains in improving P50 suppression than did those in the chronic phase. Additionally, when attention was directed toward S2, the magnitude of disruption to P50 suppression may have been diminished in recent-onset patients relative to patients who had progressed to the chronic phase. It is possible that our ability to distinguish statistically between the patient samples was constrained by medication differences and sample size. Two thirds of chronic schizophrenia patients, compared with none of the recent-onset patients, were treated with clozapine, which may have a more pronounced effect in ameliorating the P50 deficit than other antipsychotic medications (Adler et al., 2004). Although we did not replicate this finding, clozapine could have exerted a normalizing effect on one of the underlying P50 mechanisms, such that suppression in chronic patients was already enhanced to some degree. Without clozapine, the P50 deficit might have been substantially greater in chronic schizophrenia patients and, therefore, potentially less amenable to improvement and more susceptible to disruption from voluntary attention than in recent-onset patients.

Another aspect of the study that may have influenced our findings was reliance on different laboratories. However, significant efforts were made to calibrate one laboratory against the other, and these efforts appear to have been successful, given that differences were not detected after multiple attempts. As noted above, one other factor reducing any influence of the laboratory change is that a significant proportion of the statistical analyses relied on a within-subjects design.

Taken together, results from the present study suggest that reductions in P50 amplitude to the second of two auditory stimuli may reflect preattentive inhibitory mechanisms during a standard passive paradigm. Directing early voluntary attention toward S2, however, was sufficient to alter P50 suppression in healthy individuals. Among schizophrenia patients, early voluntary attention exerted a considerable influence on P50 amplitude and therefore on the P50 ratio score, ranging from enhancing P50 to S1 and decreasing the P50 ratio to augmenting P50 to S2 and increasing the ratio score. Under some circumstances, therefore, it is possible that the P50 ratio may reflect the effects of early voluntary attention, either compensatory or disruptive in manner, rather than a strictly preattentive inhibitory mechanism. In a departure from the prevailing *automatic, inhibitory process* model of sensory gating in schizophrenia (Freedman et al., 1996), the current data offer support for compensatory and disruptive effects of attention.

It is noteworthy that the magnitude of the P50 deficit in schizophrenia patients has been found to be associated with the degree of attentional difficulties on clinical and neuropsychological measures (Cullum et al., 1993; Erwin, Turetsky, Moberg, Gur, & Gur, 1998; Yee, Nuechterlein, Morris, & White, 1998). One implication of these findings is that although directing early voluntary attention to S1 has the potential to improve P50 suppression, attentional processes may be compromised to such a degree that the automatic call of attention to the first of two identical stimuli is no longer functioning for some schizophrenia patients, particularly those in the chronic phase. If attention is sufficiently spared, however, voluntary direction of early attention to task-congruent stimuli may provide an opportunity to override or circumvent certain sensory gating deficits. It is possible that failures to detect the P50 deficit in some studies of schizophrenia may result when relatively loud and, therefore, attention-enhancing stimuli are used.

An important next step toward deciphering the contribution of these various processes will be to characterize the neuronal mechanisms that underlie P50 suppression and its attentional modulation in schizophrenia. The pattern of effects obtained in the present study is consistent with results of recent research examining the neural network associated with P50 gating during the standard paired-stimulus paradigm. Applying EEG source localization, we and others determined that a distributed neural network involving the superior temporal gyrus, hippocampus, thalamus, and dorsolateral prefrontal cortex (DLPFC) is involved in the generation of P50 in schizophrenia patients and healthy individuals (Tregellas et al., 2007; Williams, Yee, Nuechterlein, & Subotnik, 2009). The groups may differ, however, in the neural generators associated with the gating response. In healthy individuals, we observed hippocampal and, to a lesser degree, DLPFC involvement, whereas in schizophrenia patients, only DLPFC activity was detected. Evidence for a modulatory influence of attention on P50 suppression further underscores potential interactions between the prefrontal cortex and other cortical or subcortical systems in sensory gating, particularly in schizophrenia patients.

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