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Early sensory processing deficits predict sensitivity to distraction in schizophrenia

Jason Smucny, M.S.^{a,b,c}, Ann Olincy, M.D.^{b,c}, Lindsay C. Eichman, B.S.^{b,c}, Emma Lyons, B.S.^{b,c}, and Jason R. Tregellas, Ph.D.^{a,b,c}

^aNeuroscience Program, University of Colorado Anschutz Medical Campus, Aurora CO USA

^bResearch Science, Denver VA Medical Center, Denver, CO USA

^cDepartment of Psychiatry, University of Colorado Anschutz Medical Campus, Aurora CO USA

Abstract

Patients with schizophrenia frequently report difficulties paying attention during important tasks, because they are distracted by noise in the environment. The neurobiological mechanism underlying this problem is, however, poorly understood. The goal of this study was to determine if early sensory processing deficits contribute to sensitivity to distracting noise in schizophrenia. To that end, we examined the effect of environmentally relevant distracting noise on performance of an attention task in 19 patients with schizophrenia and 22 age and gender-matched healthy comparison subjects. Using electroencephalography, P50 auditory gating ratios also were measured in the same subjects and were examined for their relationship to noise-induced changes in performance on the attention task. Positive symptoms also were evaluated in patients. Distracting noise caused a greater increase in reaction time in patients, relative to comparison subjects, on the attention task. Higher P50 auditory gating ratios also were observed in patients. P50 gating ratio significantly correlated with the magnitude of noise-induced increase in reaction time. Noise-induced increase in reaction time was associated with delusional thoughts in patients. P50 ratios were associated with delusional thoughts and hallucinations in patients. In conclusion, the observation of noise effects on attention in patients is consistent with subjective reports from patients. The observed relationship between noise effects on reaction time and P50 auditory gating support the hypothesis that early inhibitory processing deficits may contribute to susceptibility to distraction in the illness.

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Corresponding Author: Jason Smucny, Department of Psychiatry, University of Colorado Anschutz Medical Campus, Aurora, CO 80045, Phone: 303-724-6490, Fax: 303-724-6227, Jason.Smucny@ucdenver.edu.

Disclosures

The authors declare no conflicts of interest.

Contributors

Author JS designed the study, analyzed data, and wrote the manuscript.

Author AO made clinical assessments and analyzed data.

Authors LE and EL collected the data.

Author JT helped write the manuscript.

All authors approved the final draft of the manuscript.

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Introduction

During early investigations of sensory perception in schizophrenia, McGhie and Chapman observed that patients often complained about being overwhelmed by sensory stimuli, as if they were “overflooded” with information to the point where it became impossible to focus on any specific stimulus (McGhie and Chapman, 1961). The investigators hypothesized that patients had a fundamental deficit in “the selective and inhibitory functions of attention,” such that “consciousness would be flooded with an undifferentiated mass of incoming sensory data.” These deficits may contribute to positive symptoms in patients, as they may “attach important meanings to insignificant events” and become sensitive to and suspicious of the environment (Weckowicz, 1958).

Distractibility in patients has since been confirmed in numerous studies that have reported increased error rates as well as increased reaction times on various tasks in the presence of irrelevant stimuli compared to controls (Grillon et al., 1990; Lawson et al., 1967; McGhie et al., 1965a, b; Payne and Caird, 1967; Steffy and Galbraith, 1975). The deficit may be especially pronounced using auditory tasks with auditory distractors (Lawson et al., 1967; McGhie et al., 1965a). Patients whose positive symptoms persist to a greater degree following treatment may be particularly susceptible to auditory distraction (Green and Walker, 1986; Walker and Harvey, 1986).

Deficits in the “inhibitory functions of attention” may arise due to several factors, including pathology of prefrontal-cortical processes involved in the voluntary control of attention (so called “top-down” effects) as well as disruptions in early sensory processes (i.e. “bottom-up” effects). Although the vast majority of research on the neurobiology of schizophrenia has focused on dysfunction in cognitive, “top-down” areas (such as the prefrontal cortex), a growing body of literature suggests that early sensory processing might also be disrupted in the illness (Javitt, 2009). Using electroencephalography (EEG), studies have consistently reported abnormalities in early (often 50 or 100 ms latency) event related potential responses (ERPs) to stimuli in patients with schizophrenia.

The P50 is an early auditory evoked response to a stimulus that exhibits reduced amplitude when a second stimulus is presented 500 ms following the first. This reduction, usually studied in the auditory domain with repeated pairs of clicks, is referred to as P50 gating and may be a mechanism for automated, early inhibitory control and filtering of responses to repetitive stimuli (Roth and Kopell, 1969), preventing organisms from being overwhelmed by redundant sensory stimulation in the environment (Croft et al., 2001). The magnitude of inhibition is defined as the ratio of the evoked response amplitude to the first stimulus (S1) to the evoked response amplitude of the second stimulus (S2) (i.e. $S1/S2$), or P50 ratio. This inhibition is often reduced or eliminated in patients with schizophrenia, demonstrating a failure in sensory gating that may be related to stimulus “overflooding” (Patterson et al., 2008). Thus, inhibitory failure of S2 suppression may be a mechanism by which patients are more distracted by irrelevant environmental stimuli.

Nonetheless, evidence that P50 gating is associated with related symptomatology (e.g. poor selective attention or perceptual abnormalities) is limited and findings are mixed. Two studies have found an association between poor sensory gating and attentional deficits (Cullum et al., 1993; Erwin et al., 1998). In contrast, another study found no association between perceptual abnormalities (assessed by interview) and P50 ratio (Jin et al., 1998). Associations between P50 ratio and working memory as well as processing speed have also been reported (Potter et al., 2006). However, to our knowledge, no study has examined the relationship between distractibility (defined here as impaired selective attention) in schizophrenia and P50 gating.

In the present study, we examined the effect of an environmentally relevant noise distraction on performance of an auditory attention task in schizophrenia patients and healthy comparison subjects. The distracting urban noise stimulus is a mixture of common sounds from the environment simulating what a person may experience in a real-life urban setting, including multiple conversations and noises recorded from a party, music, and conversations from the radio (Tregellas et al., 2009). To determine if early sensory processing contributes to the effects of distracting noise on attention, P50 auditory gating ratios were measured and examined for their relationship to noise-induced changes in performance on the attention task. We hypothesized that patients would show more pronounced performance deficits during noise, and that the magnitude of this deficit would be associated with impaired sensory gating. Additionally, given previous suggestions that distractibility may be related to positive symptoms, we hypothesize that both noise effects and P50 gating would be associated with BPRS measures of hallucinations and delusions in patients.

Methods

This study was approved by the Colorado Multiple Institutional Review Board. Only decisionally capable subjects with schizophrenia were eligible for study participation.

Subjects

Participants included 19 outpatients who met DSM-IV criteria for schizophrenia (13 Male, 6 Female, 6 smokers, average age 47 years, standard deviation 11 years, range 20–62 years) and 22 healthy comparison subjects recruited from the local community (13 Male, 9 Female, no smokers, average age 42 years, standard deviation 14 years, range 22–64 years). Patients were recruited by referral from a psychiatrist involved in the study (A.O.) and by other local clinicians and mental health professionals. Groups were not significantly different with respect to gender (Mann-Whitney $U = 190$, $df = 39$, $p = 0.54$) or age ($t = 1.28$, $df = 39$, $p = 0.21$). Exclusion criteria included a current diagnosis of substance abuse, neurological disorders, or head trauma. BPRS (24-item) scores were determined by a clinician (A.O.); all patients were stable and were not being hospitalized at the time of scoring. Scores were unavailable for two patients. One patient was being treated with conventional antipsychotics, two patients with a combination of conventional and atypical antipsychotics, and the remaining patients with atypical antipsychotics. Healthy comparison subjects were excluded for Axis I disorders including schizophrenia, bipolar disorder, depression, anxiety, and lifetime substance dependence as well as a first-degree family history of psychosis. After complete description of the study to the subjects, written informed consent was obtained. Subjects were compensated for participation.

Task Description

All subjects first underwent a hearing test to ensure they did not have a substantial difference (greater than 10 dB) in hearing between each ear.

Subjects performed an auditory version of the Sustained Attention to Response Task (SART) (Seli et al., 2012). For the SART, single-digit numbers were presented sequentially, and the subject was asked to respond (with a spacebar press) after each auditory stimulus (60 dB, presented in the right ear with headphones (Bose Acoustic Noise Canceling)) except for the number '3,' in which case the subject was asked to withhold from responding. The predictable nature of the stimuli minimized the requirement for stimulus-driven motor response inhibition (Dockree et al., 2004); the task also required minimal involvement of frontal executive components such as working memory or conflict monitoring (O'Grada et al., 2009). The task consisted of 126 trials (with each trial being the presentation of a single

number), with a 250 ms stimulus duration and 900 ms intertrial interval. Subjects were asked to respond as quickly and accurately as possible to help induce attentiveness.

Blocks of distracting urban noise stimuli (80 dB, presented in the left ear, 10 s duration) were pseudo-randomly dispersed over half of the trials.

Auditory Stimuli

For the auditory SART, synthetic audio recordings for the numbers 1–9 were downloaded from www.modeltalker.com. Number stimuli were adjusted to have the same onset with Adobe Audition.

For task-overlaid noise distraction, urban noise stimuli were mixed as described previously (Tregellas et al., 2009). Briefly, clips included segments from two talk radio shows, two classical musical pieces, sounds from a neighborhood block party, which included multiple background conversations and sounds from children playing, traffic sounds, a refrigerator motor cycling on and off, and frequent knocking sounds from glasses being set on countertops. Volumes of all of these elements were mixed so that no one element was readily identifiable. The subjective experience of the sound mixture was that of standing in a busy crowd of people, in which multiple conversations were occurring, with a low level of indistinguishable background music and other sounds.

Behavioral Data Analysis

Performance measures for the task were 1) %errors of commission, or the frequency of a spacebar press during presentation of the number '3' when no responses were required, 2) %errors of omission, or the frequency of the absence of a spacebar press during any number except for '3,' when responses were required, and 3) reaction time. The effect of noise on each measure was calculated by subtracting the mean value for each subject during noise from the mean value in silence. The primary measure of interest was reaction time, as previous studies have demonstrated greater effects of distracting noise on reaction time in patients compared to controls (Grillon et al., 1990; Payne and Caird, 1967).

No significant associations between age, gender, or smoking status were observed on any measures of interest; thus, results were not adjusted for these factors.

The dependent measures (percent errors of commission, percent errors of omission, and reaction time) were each entered into a 2×2 repeated measures ANOVA with distraction condition (noise or silence) as a within-subjects factor and diagnosis (patient or control) as a between-subjects factor. Significant condition X diagnosis interactions were followed with post-hoc tests (Fisher's Least Significant Difference (LSD)).

Pearson's correlation coefficients were used on normally distributed data (e.g. gating data). Spearman's correlation coefficients were used on non-normally distributed data (e.g. BPRS data). Correlations focused on the Hallucinations and Unusual Thought Content subscales of the BPRS, based on the hypothesis that these scores would be related to distractibility and sensory gating. All correlation analyses were two-sided. All analyses were conducted using SPSS (IBM, New York).

P50 Gating Measurement and Analysis

P50 auditory sensory gating was measured and analyzed as described previously (Adler et al., 1992). Briefly, EEG activity was recorded from a gold disk electrode affixed to the vertex, referenced to linked ears. The electroculogram was simultaneously recorded between the right superior orbit and lateral canthus. EEG recording and analysis was performed using

LEA2003 software (Rave Wave Systems, Inc.). The P50 wave of the auditory evoked response was measured in a paired-stimulus (conditioning-testing) paradigm, measuring the P50 wave amplitudes, and then calculating the P50 ratio (the ratio of the test amplitude to the conditioning amplitude), with lower values indicative of better sensory gating.

Clicks were presented binaurally with headphones (Sony MDR V-600) and LEA2003 hardware (Rave Wave Systems, Inc). The click stimulus intensity was set to 50 dB above the subject's threshold to optimize the evoked potential response while minimizing startle. The clicks were presented in pairs separated by 500 ms, with 10 s between click pairs. Click pairs were presented in five blocks of 16 conditioning-test trials. Total recording time was approximately 30 min.

Trials (evoked response pairs) were rejected during recording if they contained muscle startle artifact or eye blinks as indicated by an EEG or electro-oculographic voltage of $\pm 35 \mu\text{V}$ at 50 ms after stimulus or if there was evidence of drowsiness in the EEG, as indicated by repetitive waves greater than $20 \mu\text{V}$. The average waveform for each block of trials was then traced; tracings were rejected if they lacked an identifiable P50 waveform in the conditioning block, or if the electrocular waveform grossly outweighed (1.5x or greater average amplitude) the P50 waveform in the conditioning block. No difference was observed between the number of accepted trials between patients and controls. The grand average P50 potential of accepted blocks of trials for each subject was identified and measured by using a previously described computer algorithm (Adler et al., 2004). Subjects were given no special instructions concerning the clicks they were hearing. Recordings were obtained from 18 patients and 20 comparison subjects. Data from one patient and one comparison subject were unusable due to excessive eye movement artifacts.

Results

Attention Task

Behavioral data are presented in Table 1. For errors of commission, a significant main effect of group was observed ($F(1,39) = 20.8$, $p < 0.001$), with patients making more errors than controls. No main effect of distraction ($F(1,39) = 0.94$, $p = 0.34$), or distraction (noise or silence) X diagnosis (patient or control) interaction ($F(1,39) = 0.01$, $p = 0.92$) was observed. Similarly, for errors of omission, a significant main effect of group was observed ($F(1,39) = 11.2$, $p = 0.002$), with patients making more errors than controls. No main effect of distraction ($F(1,39) = 0.65$, $p = 0.42$) or distraction X diagnosis interaction ($F(1,39) = 0.06$, $p = 0.81$) was observed.

For reaction time, no main effect of group was observed ($F(1,39) = 0.0$, $p = 0.99$). However, a significant main effect of distraction ($F(1,39) = 4.33$, $p = 0.044$) as well as a significant distraction X diagnosis interaction ($F(1,39) = 5.16$, $p = 0.029$) were both observed. Post-hoc tests showed that the significant interaction was driven by significantly increased reaction times during noise (relative to silence) in patients ($p = 0.005$) but no effect of noise on reaction times in controls ($p = 0.89$) (Figure 1).

Across all subjects, no relationship was observed between noise-induced changes in %errors of commission and changes in reaction time ($R = 0.10$, $F(1,39) = 0.41$, $p = 0.52$) or noise-induced changes in %errors of omission and changes in reaction time ($R = 0.048$, $F(1,39) = 0.091$, $p = 0.76$).

P50 Sensory Gating

P50 auditory sensory gating ratios were greater in patients, relative to comparison subjects ($t = 2.62$, $df = 34$, $p = 0.02$) (Table 1). Across all subjects, gating ratio was positively

correlated with noise-induced changes in reaction time on the attention task ($R = 0.45$, $F(1,34) = 8.87$, $p = 0.005$; Figure 2). Within the patient group alone, gating ratio was also positively correlated with noise-induced changes in reaction time ($R = 0.48$, $F(1,15) = 4.51$, $p = 0.05$). Within the control group alone, gating ratio was not correlated with noise-induced changes in reaction time ($R = 0.10$, $F(1,17) = 0.18$, $p = 0.67$). When gating ratio was used as a covariate, the difference in noise-induced reaction time between patients and controls was no longer significant ($F(1,33) = 0.58$, $p = 0.45$).

The relationships between P50 response to the first (conditioning, or S1) and second (test, or S2) stimuli and the effect of noise on reaction times were also examined. Across all subjects, S1 was not significantly associated with noise-induced changes in reaction time ($R = 0.11$, $F(1,34) = 0.39$, $p = 0.53$). In contrast, across all subjects, S2 was significantly associated with noise-induced changes in reaction time ($R = 0.42$, $F(1,34) = 7.36$, $p = 0.010$). Within the patient group alone, S2 was also significantly associated with the effect of noise on reaction time ($R = 0.64$, $F(1,15) = 10.2$, $p = 0.006$). Within the control group alone, S2 was not correlated with noise-induced change in reaction time ($R = 0.27$, $F = 1.32$, $p = 0.27$).

Clinical Correlates

In patients, noise-induced increase in reaction time was significantly associated with unusual thought content (i.e. delusional thoughts) on the BPRS (Spearman's $\rho = 0.57$, $p = 0.018$). P50 ratios showed a nearly significant positive correlation with unusual thought content on the BPRS (Spearman's $\rho = 0.49$, $p = 0.056$). No significant correlation was observed between noise-induced increase in reaction time and the Hallucinations subscore on the BPRS (Spearman's $\rho = 0.23$, $p = 0.38$). A significant correlation was observed between P50 ratio and the Hallucinations subscore (Spearman's $\rho = 0.55$, $p = 0.03$).

Discussion

The primary goals of the present study were to determine if real-life distracting noise differentially affected performance on an auditory attention task in schizophrenia patients, relative to comparison subjects, and to determine if task effects were related to early sensory processing and positive symptoms. Results suggest that patients were more sensitive to the effects of distracting noise, as evidenced by a greater effect of noise on reaction time in the attention task in patients relative to comparison subjects. The magnitude of increase was significantly associated with impaired P50 sensory gating and the magnitude of neural response to the second click (but not the first click) in the P50 paradigm. Additionally, noise effects were significantly related to delusional thoughts in patients; P50 gating ratios were nearly-significantly related. A significant correlation was also observed between P50 ratio and hallucinations.

The relative increase in reaction time in patients during noise was not associated with a change in accuracy, however, as no correlation was observed between the effect of noise on errors of commission and omission and the effect of noise on reaction time. As such, the reaction time increase in noise was likely driven by an increase in stimulus processing and/or motor response time and not a change in overall task strategy.

The increased reaction time during noise in schizophrenia is consistent with previous studies using attention tasks. Payne and Caird (1967) found that distracting noises, and particularly "meaningful" distractors (recorded conversations and laughter), caused significantly greater reaction times in patients compared to controls when subjects were asked to give a motor response to a tone. Grillon et al. (1990) found that auditory distractors ("unusual, computer-generated sounds") caused a greater increase in reaction time in patients than controls. The latter study attributed this effect to a relative increase in processing resources devoted to the

distracting stimuli in patients compared to controls, as evidenced by differences in P300 ERP amplitude evoked by the noises. It was unclear if P50 gating deficits contributed to the effect.

Reaction times consist of a stimulus perception component as well as a stimulus response component. The increased reaction times during noise in patients in the present study suggest that one or both of these neurobiological processes are adversely affected during distraction in schizophrenia. Functional neuroimaging studies have reported decreased response in sensory association cortices during auditory processing tasks in schizophrenia (Kreitschmann-Andermahr et al., 1999; Wible et al., 2001). In addition, previous work has demonstrated a negative correlation between reaction time and neuronal response in sensory areas (Mohamed et al., 2004; Oguz et al., 2003). One may thus speculate that the increase in reaction time observed in the present study reflects the relative inability of patients to appropriately recruit processing resources in these areas during noise distraction. Future imaging studies will be needed to test this hypothesis.

The effect of noise was significantly associated with P50 auditory gating ratios. Furthermore, the effect of noise was significantly associated with P50 amplitude after S2, but not S1. This finding suggests a contribution of early sensory processing deficits to the effect of noise distraction on attention in schizophrenia, particularly due to dysfunction of inhibitory “gating out” mechanisms during repetitive stimulation. The finding that dysfunction in early processing of sensory information in schizophrenia may contribute to cognitive control deficits has important ramifications for the treatment of cognitive symptoms of schizophrenia. Metanalytic studies have shown that classical methods of cognitive rehabilitation, i.e. behavioral training designed to improve “higher order” cognition in patients, show modest effect sizes, poor stability, and limited applicability to real-life situations (Hayes and McGrath, 2000; McGurk et al., 2007; Silverstein and Wilkniss, 2004). More recent approaches have been designed to improve efficiency of “lower order” sensory processing and thus foster more effective engagement of top-down processes (Fisher et al., 2009; Popov et al., 2011). Although these approaches are novel and their effectiveness not well characterized, basic auditory training in patients improves auditory gating as well as verbal learning and memory (Fisher et al., 2009; Popov et al., 2011). The effects observed in the present study may represent a baseline by which to compare the therapeutic effects of these types of interventions.

The effects of noise distraction on the attention task were significantly associated with delusional thoughts as measured by the BPRS, consistent with previous studies showing an association between distractibility and positive symptoms in schizophrenia patients (Green and Walker, 1986; Walker and Harvey, 1986). To place this finding, along with the P50 gating findings in a unified framework, it is possible to speculate that delusional thought content, gating deficits, and distractibility are possibly all indicative of hippocampal inhibitory dysfunction in schizophrenia. Current hypotheses suggest that inhibitory dysfunction in the hippocampus may play a key role in generating delusional thought content through spreading of spurious associations (Tamminga et al., 2010). Electrophysiological and neuroimaging studies have identified the hippocampus as a site of inhibitory processing during suppression of the test P50 response (i.e. the evoked P50 response to the second click) during paired click stimuli (Bak et al., 2011; Grunwald et al., 2003), and abnormalities in hippocampal structure (reduced volume) (Thoma et al., 2008) and function (overactivation during noise) (Tregellas et al., 2009) have been proposed to underlie gating deficits in schizophrenia. Finally, overactivity of the hippocampus may be related to distractor sensitivity (Wolf et al., 2008). Given these converging lines of evidence, results of the present study may further support the involvement of the hippocampus as a primary site of pathology in schizophrenia.

In the present study, we interpret the P50 potential as a pre-attentive (bottom-up dependent) response, in agreement with the majority of the current literature. A limitation of this interpretation, however, is that the magnitude of P50 suppression may also be influenced by top-down modulation. For example, P50 response to either the conditioning or test stimulus may increase when instructed to pay attention to either stimulus (Yee et al., 2010). In this study, we did not provide instructions on how subjects should respond to either click, in order to make the task as “passive” as possible. However, we cannot rule out the possibility of different levels of attentiveness between groups and consequent top-down influences on P50 ratio. Indeed, on the behavioral task, patients made more errors than controls across all conditions, suggesting that patients may have a general attentive deficit (in addition to increased distractibility during noise).

In conclusion, the present findings suggest that patients are more susceptible to auditory distraction during attention, as evidenced by increased reaction time. The observation that these effects are positively correlated with P50 auditory gating suggests that early sensory processing deficits contribute to higher-level cognitive deficits in schizophrenia. These findings inform the current debate in schizophrenia research as to the contribution of “top down” versus “bottom” up mechanisms in the illness. Additionally, the observation that both sensory gating and the effect of noise on the attention task were correlated with positive symptoms suggests that the measures examined in this study may be useful as biomarkers for therapeutic development.

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Figure 1.
Comparison of the effect of noise on RT between schizophrenia patients and healthy controls. $\pm$ symbols represent the standard error of the mean.

Figure 2. Correlation between gating ratio and the effect of noise on RT during the task. Statistics: Across all subjects, $R = 0.45$, $F(1,34) = 8.87$, $p = 0.005$; patient group alone, $R = 0.48$, $F(1,15) = 4.51$, $p = 0.05$.

Table 1

Behavioral and EEG Data.

	Controls	S.D.	Patients	S.D.
p50 Conditioning Amplitude (μV)	3.35	1.27	2.82	2.11
p50 Test Amplitude (μV)	0.89	0.71	1.45	1.41
p50 Ratio (Conditioning/Test)	0.28	0.19	0.60	0.48
%Errors of Commission in silence	5.30	7.95	21.0	16.5
%Errors of Commission in noise	7.20	7.39	23.4	18.5
Change in %Errors of Commission (noise – silence)	1.89	11.9	2.34	16.0
%Errors of Omission in silence	2.72	4.81	12.4	14.2
%Errors of Omission in noise	2.16	6.20	11.4	11.6
Change in %Errors of Omission (noise – silence)	–0.56	2.96	–1.00	8.34
RT in silence (ms)	413	72.0	391	110
RT during noise (ms)	411	82.3	435	84.6
Change in RT (noise – silence) (ms)	–1.91	47.1	43.7	79.5