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Event-related potential abnormalities in schizophrenia: A failure to "gate in" salient information?

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ABSTRACT

Sensory gating refers to the central nervous system's ability to filter sensory inputs, and can be measured by comparing the suppression of event-related brain potential (ERP) amplitudes in a paired auditory stimulus procedure. Poor gating scores in schizophrenia may be caused by abnormal responses to the first (S1), the second (S2) or both of the paired stimuli. However, since S1 and S2 responses may index separate psychological phenomenon, corresponding to the ability to "gate in" and "gate out" sensory stimuli respectively, the precise mechanism affected in schizophrenia remains unclear. To examine the extent to which saliency processing abnormalities may contribute to S1 response deficits, standard and rare (15% probability) paired stimuli were presented to 21 participants with schizophrenia and 22 healthy controls. P50 and N100 ERP amplitude as well as low, beta and gamma frequency power were measured to examine the time course and relative contributions of oscillatory activity affecting auditory processing in schizophrenia. In this study, schizophrenia patients exhibited less evoked beta 1 power (12–20 Hz) in response to salient stimuli at S1, and lower N100 amplitude in response to all S1 stimuli. No group differences were found in the low, beta 2 (20–30 Hz), or gamma frequency ranges. These findings suggest aberrant sensory processing during stages of stimulus evaluation and saliency detection in schizophrenia.

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1. Introduction

"Sensory gating" refers to the central nervous system's ability to filter sensory inputs. One method of assessing sensory gating involves measuring mid-latency auditory evoked responses (MLAERs) to paired auditory stimuli. During this procedure, suppression of P50 amplitude to the second stimulus (S2) is ostensibly caused by recurrent inhibitory mechanisms activated by the first (S1) stimulus (Freedman et al., 1987). P50 magnitude of response is most often expressed as a ratio, with amplitude of the response to the second click divided by the amplitude of the response to the first click. Similarly, the N100 also exhibits a pattern of suppression to repeated stimuli. Schizophrenia subjects generally exhibit less sensory gating than healthy subjects for both of these MLAERs

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(Boutros et al., 2004; Clementz et al., 2003; Clementz, 1998; Clementz et al., 1997a; Patterson et al., 2008). Such findings are hypothesized to reflect neuronal gating deficits in schizophrenia that may cause sensory inundation and 'flooding' (Bunney et al., 1999); however much remains to be understood about the neuronal and cognitive mechanisms that influence sensory gating.

To this end, one important line of research aims to determine the factors that contribute to sensory gating scores among both healthy and pathological groups. One possibility is that gating is poor because S2 response amplitude is not suppressed compared to an otherwise normal S1 response. In this case, poor sensory gating indicates a failure of inhibitory neural mechanisms responsible for "gating out" redundant and irrelevant sensory stimuli (Clementz et al., 1997b; Freedman et al., 1987). A second pattern that leads to poor gating scores occurs when S1 response amplitude is abnormally small in the presence of an otherwise normal S2 response (Blumenfeld and Clementz, 2001; Clementz et al., 2003; Johannesen et al., 2005). One interpretation of this pattern is that poor gating is due to a failure of the nervous system to register and/or attend to the S1 stimulus. This conceptualization is consistent with the claim of Boutros and Belger (1999), that ERPs elicited in the paired stimuli procedure reflect the abilities of the nervous system to both (i) filter out extraneous information (as measured by ERP amplitude suppression at S2) and (ii) 'gate in' novel, or salient, information (as measured by ERP amplitude to S1). Interestingly, there is evidence for both "gating in" and "gating out" deficits in schizophrenia during the typical paired stimuli paradigm. However, whether MLAERs associated with "gating in" or "gating out" are differentially affected by manipulations of attention and expectancy (which are known to affect overall sensory gating scores) remains an important empirical question (Clementz et al., 2002; Cullum et al., 1993; Erwin et al., 1998; Guterman et al., 1992; Kogoj et al., 2005; Thoma et al., 2003; Woldorff et al., 1993).

Most sensory gating studies have relied on time domain ERP amplitude measurements. However, recent studies employing spectral frequency analyses have provided additional information about auditory sensory processing in schizophrenia. For instance, poor gating may, in part, reflect attenuated neural activation in response to S1 (i.e., "gating in" deficits) in the 1–20 Hz bandwidth (Blumenfeld and Clementz, 2001; Johannesen et al., 2005). Consistent with data demonstrating that beta activity reflects encoding, salience detection and consolidation of sensory information, Hong et al. (2008) found that beta activity in response to S1 predicted stronger gating and P50 suppression to S2 (Bibbig et al., 2001; Kisley and Cromwell, 2006; Hong et al., 2008). Neural activity in the gamma frequency range, previously associated with immediate sensory registration, contributes to the morphology of the P50 ERP component (Kopell et al., 1999; Clementz and Blumenfeld, 2001), but the findings regarding the contribution of gamma activity to auditory sensory gating deficits in schizophrenia are unclear. Some studies have failed to find differences in the gamma band response between healthy and schizophrenia participants (Clementz and Blumenfeld, 2001; Clementz et al., 1997a), whereas others have reported decreased gamma and low

frequency responses to S1 in schizophrenia (Johannesen et al., 2005) as well as a selective reduction in gamma band suppression in association with higher ratings of subjective perceptual disturbance (Johannesen et al., 2008). Therefore, it is important to further evaluate the frequency composition of EEG activity elicited by manipulations of the paired stimuli paradigm. Given the emerging data on the functional significance of oscillatory activity within specific frequency ranges (Deiber et al., 2007; Kisley and Cromwell, 2006; Klimesch, 1999; Krishnan et al., 2005; Palva and Palva, 2007; Pantev et al., 1991; Pesonen et al., 2007; Schack et al., 2005; Tallon-Baudry, 2003; Trautner et al., 2006; Whittington et al., 1997), it is likely that assessing activity in these bands will provide information about the underlying neurophysiological and cognitive deficits in those with schizophrenia.

Therefore, the primary aims of the present study were to characterize the frequency composition of the MLAER electrophysiological response and explicate the nature of the differences between schizophrenia and healthy subjects with respect to the frequency composition of responses at S1 and S2 in the paired stimuli paradigm. First, we examined the effects of stimulus salience on MLAER responses, and predicted that (i) salient stimuli (infrequent paired clicks of a deviant pitch) would augment evoked response amplitudes across all participants, but (ii) schizophrenia subjects would have less augmentation than controls to rare stimuli. Second, we sought to determine whether differences in schizophrenia are better explained by difficulty "gating in" salient sensory information at S1 or to difficulty "gating out" redundant sensory information at S2, and predicted that (iii) schizophrenia subjects would have "gating in" deficits as indicated by reduced S1 amplitudes to both frequent and rare stimuli. Third, we examined which frequency band best accounted for S1 and gating deficits in schizophrenia, and predicted, based on previously reported associations between beta frequency activity and salient stimulus processing, that (iv) low beta (12–20 Hz) frequency information would best account for stimulus-driven salience effects. These finding provide a more comprehensive characterization of the neurophysiological and cognitive processes that best account for poor auditory gating in schizophrenia.

2. Materials and methods

2.1. Participants

The participants were 21 individuals (3 females, mean age = 36, SD = 13) meeting criteria for schizophrenia ($N = 17$) or schizoaffective disorder ($N = 4$) based on the Structured Clinical Interview for DSM-IV (1994) and 22 healthy persons (6 females, mean age = 38, SD = 11) free from any Axis I or Axis II disorders (ratings done by authors C. A.B. and A.S.). None of the participants met criteria for alcohol dependence within the past 2 years or substance abuse within 6 months prior to testing. Exclusion criteria included head injury, learning disability, hearing impairment, verbal IQ less than 75, and alcohol or illicit substance use within 24 h prior to testing. The number of individuals who smoked cigarettes within 24 h of testing did not differ between groups, and participants were not permitted to smoke during the 40 min preceding testing, thus minimizing possible acute

effects of nicotine on ERP amplitudes (Adler et al., 1993). Findings reported below were unchanged when smoking status was used as a statistical covariate.

All but one patient with schizophrenia was taking antipsychotic medication (2 typical, 18 atypical), thus group size was too small for statistical comparison between medication subgroups. There were no significant correlations between any electrophysiological variable and chlorpromazine equivalent dosage.

2.2. Stimuli and procedures

One-hundred and thirty paired stimuli were presented binaurally while participants were seated in a sound attenuated room. Stimuli were two different paired auditory sounds: (1) standard click pairs (85% probability; $N = 110$ trials, 3 ms duration, peak intensity 81 dB SPL as measured by a Simpson Model 886 sound level meter, fast mode, "A" weighting, SOA = 500 ms) and (2) rare 1000 Hz paired tone pips (15% probability, 3 ms duration, rise/fall of .75 ms, peak intensity 81 dB SPL, SOA = 500 ms). Inter-trial interval varied randomly between 7 and 11 s (mean = 9 s). Stimuli were presented against a 58 dB SPL white-noise background. To keep all participants alert, subjects were asked to respond by button press to the rare paired tone pips.

2.3. EEG recordings and data processing

Electroencephalographic activity was collected from 29 recording sites (1000 Hz A/D rate; 0.10 Hz high pass, 200 Hz low pass; gain = 10 K; nose reference; impedances ≤ 10 kΩ) using sintered Ag–AgCl electrodes.

2.3.1. ERP peak measurement

P50 responses at Cz were segmented (−50 to 400 ms), baseline corrected, ocular artifacts were corrected (Gratton et al., 1983), and remaining trials with values exceeding ±100 µV were excluded from analyses. A 1–50 Hz (24 dB/octave) bandpass filter was applied to averaged data and peak amplitude was defined as the difference in µV between the most positive point 40 to 80 ms after stimulus onset and the point of maximum deflection on the preceding negative trough (Fig. 1).

Responses to the second click were measured within ± 15 ms of the response to the first click. The amplitude of the N100 response was defined as the most negative point 80 to 150 ms after stimulus onset (referenced to baseline).

2.3.2. Spectral frequency power

Frequency bands of interest were identified as low (1–12 Hz), beta 1 (12–20 Hz), beta 2 (20–30 Hz) and gamma (30–50 Hz). We did not further subdivide the low frequency band because the ISI of 500 ms does not allow for reliable measurement of low frequency activity. Raw EEG recordings were segmented into 700 ms epochs (250 ms baseline), and subjected to the same ocular correction and artifact rejection criteria as the peak amplitude analyses. The time-varying spectral power, $W_x = |\omega(t,f) * s(t)|^2$ was computed for each frequency (f) by convolving the average ERP signal, $s(t)$, with a complex-valued Morlet's wavelet, $\omega(t; f)$,

$$\omega(t,f) = A \cdot e^{2i\pi f t} \cdot e^{-t^2/2\sigma_t^2} \qquad (1)$$

where $\sigma_f = 1/(2\pi\sigma_t)$, and $A = \sigma_t^{-1} \cdot (2/\pi)^{1/2}$ is a Gabor normalization factor (Tallon-Baudry and Bertrand, 1999). In the context of Eq. (1), A yields the instantaneous amplitude (Hermann et al., 2005, p. 240). The family of wavelets used were characterized by the constant ratio $f/\sigma_f = 7$. Signal power was computed over the range of frequencies from 1 to 70 Hz in 1 Hz steps.

To identify the latency of the peak power within each frequency band, the raw EEG was segmented from −100 to 500 ms and averaged across S1, S2, standard and rare trials for each frequency band separately. The 'frequency extraction' procedure in Brain Vision Analyzer software (Brain Products, Munich, Germany) converted the data into power within a specified frequency range at each time point. We then measured the latency at which the power peaked for each subject, and used that average (± 1.5 standard deviations) to define the region that we analyzed our wavelet-based time–frequency data. This approach allowed us to define the window used in our time–frequency analysis based on the points in which activity within that frequency band was largest. For low frequency data the analysis window spanned from 118–310 ms; for beta 1 activity it was 20–167 ms; for
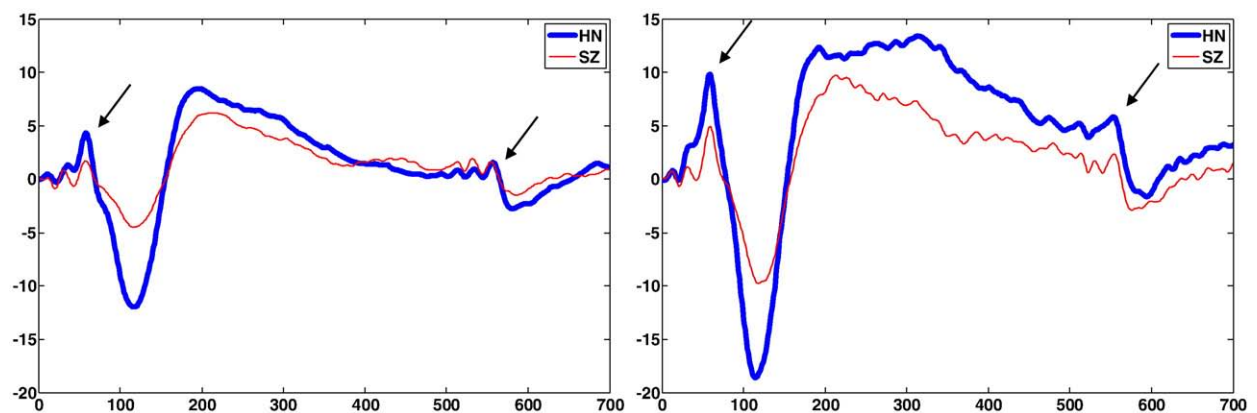

Fig. 1. ERP waveforms (1–50 Hz filter) for each diagnostic group. The left panel shows the waveforms in response to 'standard' stimuli and the right panel shows the waveforms in response to 'rare' stimuli.

beta 2 activity it was 23–157 ms; and for gamma it was 32–74 ms.

2.4. Statistical analyses

A square root transformation was applied to the P50 peak amplitude data to better approximate a normal distribution. Statistical outliers were determined as participants with values at least three times the interquartile range of the corresponding participant group (Brenner et al., 2004), and were eliminated from further analyses. There were no more than six outliers in a given analysis (three Sz and three controls). Difference scores were computed across click stimuli (S1–S2), rather than the S2/S1 ratio, because it is a more psychometrically reliable index of P50 evoked response attenuation (Smith et al., 1994). Within and between-group contrasts were conducted using Repeated measures ANOVA, with Diagnosis (SZ, HC) as the between-group factor and Stimulus (S1, S2) and Salience (rare, standard) as within-group factors.

3. Results

3.1. Behavioral responses

Button-press responses to the presentation of the rare stimuli did not differ between groups (control = 98.6% correct; SD = .03; schizophrenia = 95.7% correct; SD = .06).

3.2. P50 ERPs

Repeated Measures ANOVA yielded: a main effect of Salience, $F(1,37) = 32.8$, $p = .001$, $\eta_p^2 = .47$, indicating larger responses to rare compared to standard paired stimuli; a main effect of Stimulus, $F(1,37) = 71.9$, $p = .001$, $\eta_p^2 = .66$, indicating larger responses to S1 than to S2; and a Salience × Stimulus interaction, $F(1,37) = 11.2$, $p = .002$, $\eta_p^2 = .23$, reflecting greater S1 amplitude to rare compared to standard stimuli for both groups (Table 1). For the S1–S2 amplitude difference score, there was a main effect of Salience, $F(1,39) = 12.2$, $p = .001$, $\eta_p^2 = .24$, indicating a larger difference between S1 and S2 in response to rare compared to standard paired stimuli for both groups[1]. Repeated measures ANOVAs were repeated using only those 'standard' trials that immediately preceded a rare trial, thereby ensuring the same number of trials contributed to the average waveform for both trial types. These analyses resulted in a main effect of Stimulus, $F(1,36) = 26.1$, $p = .001$, $\eta_p^2 = .42$, and a Salience × Stimulus interaction, $F(1,36) = 15.8$, $p = .001$, $\eta_p^2 = .31$, when using S1 and S2 amplitudes. Results using the S1–S2 difference score did not change when this procedure was applied. There were no group differences in P50 gating.

3.3. N100 ERPs

Repeated Measures ANOVA revealed: a main effect of Salience, $F(1,40) = 118.7$, $p = .001$, $\eta_p^2 = .75$, indicating larger responses to rare compared to standard paired stimuli; a main

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[1] Analysis of the P50 responses and difference score in response to frequent stimuli using different filter parameters (10–50 Hz) also did not yield significant group differences.

Table 1
Untransformed ERP amplitudes (in uV) and power values (in uV^2).

	S1 M (SD)	S2 M (SD)	S1–S2 M (SD)	S2/S1 (SD)
P50 ERP				
Frequent				
HN	4.62 (2.58)	1.55 (.89)	2.97 (2.47)	.94 (2.45)
SZ	4.28 (2.46)	2.35 (2.11)	1.94 (3.14)	.73 (.71)
Rare				
HN	7.97 (4.23)	2.86 (2.46)	5.34 (4.63)	.39 (.36)
SZ	8.01 (4.72)	2.92 (2.36)	5.09 (4.58)	.50 (.45)
N100 ERP				
Frequent				
HN	− 14.51 (6.76)	− 3.25 (3.19)	− 11.25 (5.40)	.200 (.16)
SZ	− 8.93 (3.91)	− 2.77 (1.90)	− 6.16 (3.78)	.337 (.30)
Rare				
HN	− 24.54 (10.66)	− 5.99 (3.81)	− 18.550 (9.57)	.215 (.13)
SZ	− 16.14 (8.40)	− 5.11 (3.96)	− 11.028 (8.33)	.281 (.34)
Low power (1–12 Hz)				
Frequent				
HN	4.78 (5.07)	1.56 (2.82)	3.22 (6.11)	
SZ	3.69 (3.66)	1.98 (2.82)	1.71 (5.28)	
Rare				
HN	5.98 (5.39)	.73 (1.12)	5.26 (5.68)	
SZ	4.28 (1.90)	1.37 (1.83)	2.91 (2.70)	
Beta 1 power (12–20 Hz)				
Frequent				
HN	2.94 (4.78)	1.92 (3.63)	1.01 (5.85)	
SZ	3.13 (3.36)	1.55 (3.74)	1.58 (5.32)	
Rare				
HN	9.31 (7.76)	1.74 (2.76)	7.57 (8.60)	
SZ	4.03 (4.54)	1.44 (1.79)	2.59 (4.49)	
Beta 2 power (20–30 Hz)				
Frequent				
HN	2.34 (4.43)	1.90 (3.61)	.439 (4.11)	
SZ	2.65 (3.37)	2.02 (4.28)	.628 (5.22)	
Rare				
HN	3.47 (4.05)	2.67 (2.76)	.800 (3.81)	
SZ	3.79 (4.52)	1.32 (2.00)	2.47 (3.91)	
Gamma Power (30–50 Hz)				
Frequent				
HN	5.52 (7.79)	2.64 (6.21)	2.88 (7.57)	
SZ	2.98 (5.78)	1.14 (2.18)	1.84 (5.67)	
Rare				
HN	7.38 (10.76)	2.12 (3.68)	5.26 (8.91)	
SZ	6.28 (12.83)	2.30 (4.22)	3.98 (9.22)	

effect of Stimulus, $F(1,40) = 137.3$, $p = .001$, $\eta_p^2 = .77$, indicating larger responses to S1 than S2; and a Stimulus × Diagnosis interaction, $F(1,40) = 9.9$, $p = .003$, $\eta_p^2 = .20$, reflecting greater S1 amplitude by the healthy control group. Finally, there was a Salience × Stimulus interaction, $F(1,40) = 40.7$, $p = .001$, $\eta_p^2 = .51$, indicating greater S1 amplitude to rare compared to standard stimuli for both groups. For the S1–S2 difference scores, there was a main effect of Salience, $F(1,40) = 40.7$, $p = .001$, $\eta_p^2 = .51$, indicating a larger difference between S1 and S2 in response to rare compared to standard paired stimuli for both groups.

3.4. Time frequency analyses

Repeated Measures ANOVA compared groups on power values for each frequency band separately (see Table 1).

Within the low frequency (1–12 Hz) range, there was a main effect of Stimulus, $F(1,36) = 41.94$, $p = .001$, $\eta_p^2 = .54$, that indicated greater power in response to S1 compared to S2 (Fig. 2). There were no significant findings using the difference scores.

Within the beta 1 frequency range (12–20 Hz), analyses revealed a main effect of Salience, $F(1,36) = 13.31$, $p = .001$, $\eta_p^2 = .27$, indicating greater beta power in response to rare stimuli, and a main effect of Stimulus, $F(1,36) = 21.44$, $p = .001$, $\eta_p^2 = .37$, that indicated greater power in response to S1 compared to S2. A Salience × Diagnosis interaction, $F(1,36) = 5.92$, $p = .020$, $\eta_p^2 = .14$, indicated less beta 1 power in schizophrenia than in controls in response to rare stimuli. A Salience × Stimulus interaction, $F(1,36) = 9.48$, $p = .004$, $\eta_p^2 = .21$, indicated greater beta 1 power in response to rare S1 stimuli. Finally, there was a Salience × Stimulus × Diagnosis interaction, $F(1,36) = 11.41$, $p = .002$, $\eta_p^2 = .24$. To better understand this interaction, separate analyses were performed in response to standard and rare stimuli. For standard stimuli there was a main effect of Stimulus, $F(1,36) = 4.93$, $p = .033$, $\eta_p^2 = .12$, that indicated greater power in response to S1. For rare stimuli there was a main effect of Stimulus, $F(1,36) = 21.36$, $p = .001$, $\eta_p^2 = .37$, and a significant Stimulus × Diagnosis interaction, $F(1,36) = 5.48$, $p = .025$, $\eta_p^2 = .13$, that indicated lower beta 1 power in response to S1 to rare stimuli by the schizophrenia group. For the S1–S2 difference scores, there was a main effect of Salience, $F(1,40) = 10.89$, $p = .002$, $\eta_p^2 = .21$, and a Salience × Diagnosis interaction, $F(1,40) = 5.96$, $p = .019$, $\eta_p^2 = .13$. These findings indicated less change in beta 1 power from S1 to S2 in response to rare stimuli pairs in schizophrenia (Fig. 2).

Within the beta 2 frequency range (20–30), analyses revealed a main effect of Salience, $F(1,34) = 8.80$, $p = .005$, $\eta_p^2 = .21$, that indicated greater beta 2 power in response to rare stimuli, and a main effect of Stimulus, $F(1,34) = 6.36$,

$p = .017$, $\eta_p^2 = .16$, indicating greater power in response to S1 compared to S2 (Fig. 2). There were no significant findings using the difference scores.

Gamma frequency power analyses revealed a marginally significant main effect of Salience, $F(1,38) = 4.06$, $p = .051$, $\eta_p^2 = .10$, indicating greater gamma power in response to rare compared to standard stimuli, and a main effect of Stimulus, $F(1,38) = 12.79$, $p = .001$, $\eta_p^2 = .25$, indicating greater gamma power in response to S1 compared to S2 (Fig. 2). There were no significant findings using the difference scores.

3.5. Time frequency and N100 amplitude correlations

Bivariate correlations were performed between beta 1 power and N100 amplitude for each group separately. Within the control group N100 amplitude at S1 in response to rare stimuli was significantly correlated with beta 1 power at S1 in response to rare stimuli ($r = .467$, $p = .044$). Within the schizophrenia group N100 amplitude at S1 in response to frequent stimuli was significantly correlated with both beta power at S1 in response to frequent ($r = .536$, $p = .018$) and rare stimuli ($r = .567$, $p = .011$). In addition, within the schizophrenia group N100 amplitude difference score to frequent stimuli was negatively associated with beta 1 power at S1 in response to rare stimuli ($r = -.600$, $p = .008$).

4. Discussion

Individuals with schizophrenia exhibited less neural activity in the beta 1 frequency range (12–20 Hz) in response to rare, more salient stimuli, an effect that was driven by the low magnitude of their response to the initial stimulus in a dual-click procedure. The N100 analyses revealed a similar pattern of smaller S1 amplitudes in the schizophrenia group resulting in schizophrenia patients having less N100 "gating"
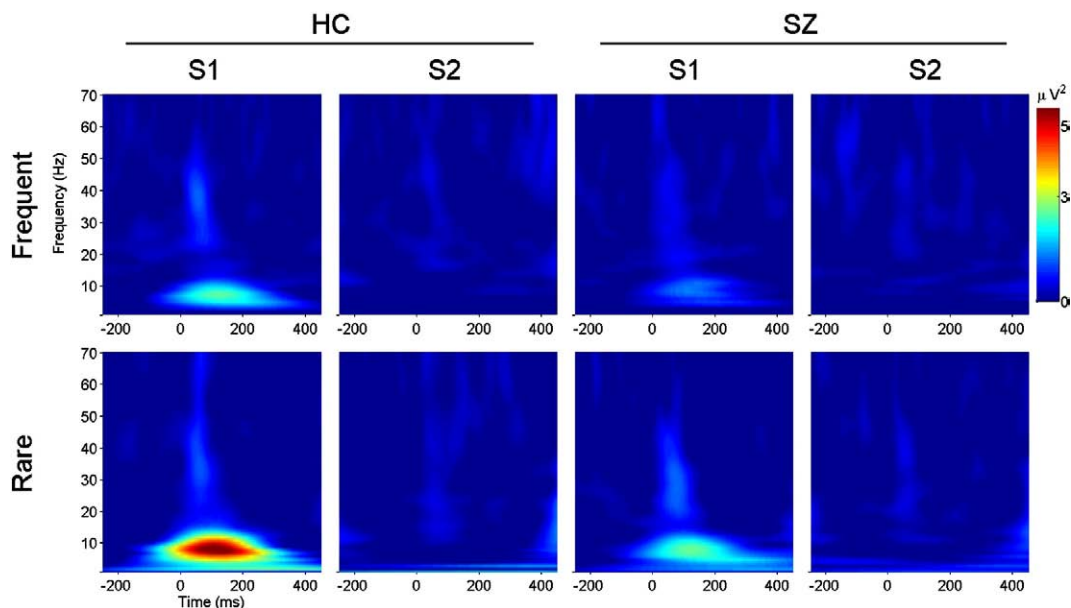
Fig. 2. Wavelet-based time–frequency transforms of the averaged ERP waveform. The upper panels show power over time in response to standard stimuli, and the lower panels show power over time in response to rare stimuli. Data from the healthy control group is shown on the left (S1 and S2 in columns) and the data from the schizophrenia group is shown on the right (S1 and S2 in columns). Patients demonstrated reduced beta 1 power (12–20 Hz) in response to rare S1 stimuli.

than the healthy controls, although this finding was not specific to rare stimuli. Correlations between N100 amplitude and beta 1 activity reflect a relationship between these two measures; with N100 amplitudes to S1 (both frequent and rare stimuli) positively correlated with beta 1 power to S1 (both frequent and rare stimuli). Interestingly, the salience-driven deficits in schizophrenia were not seen in the low (1–12 Hz), beta 2 (20–30 Hz) or gamma frequency (30–50 Hz) range, and P50 amplitude gating did not differ between groups. Taken together, the present findings suggest a possible functional differentiation between sensory registration and mechanisms associated with sensory processing during stages of stimulus evaluation and saliency detection that may be dysfunctional in schizophrenia (Clementz et al. 2008).

In particular, our finding that schizophrenia patients exhibited less S1 beta 1 power to rare stimuli may indicate deficits in the stimulus evaluation stage of sensory encoding. This deficit, along with sensory gating deficits in the later stages of information processing (N100 and P200), is consistent with a problem in the nervous system's ability to detect and respond to salient or important information ("gating in") in schizophrenia (Boutros et al. 2004). In addition, increased stimulus saliency as manipulated by ISI (Kisley and Cromwell, 2006) and/or expectancy (Clementz et al., 2002) has been associated with increased beta activity in healthy controls, while less beta activity in response to S1 has been associated with aberrant sensory gating scores in healthy controls and patients with schizophrenia (Hong et al., 2004; Hong et al., 2008). Finally, in-vitro hippocampal stimulation studies suggest that beta oscillations may reflect encoding and evaluation of a percept (Haenschel et al., 2000; Hong et al., 2004; Traub et al., 1999). Taken together, these findings suggest that oscillatory activity in the beta range represents a measure of stimulus-driven salience detection that is altered in schizophrenia. While it is impossible to disentangle the effect of salience alone from the different physical characteristics of the rare stimuli that make it salient, this issue does not nullify the group differences that are the main finding of this report.

P50 ERP amplitude was larger to rare compared to standard paired stimuli, indicating sensitivity to salience. However, the P50 gating score did not significantly differ between groups. This finding, along with that of the gamma band results, may indicate intact sensory registration in patients with schizophrenia. There are, however, several alternative interpretations of this result including: (1) the range of P50 gating scores across studies is large and may be related to a number of methodological factors (Blumenfeld and Clementz, 2001; Bunney et al., 1999); (2) the effect size of our P50 peak-picked results is small compared to those of our N100 and frequency band results, suggesting lower discriminative power in P50; (3) reductions in P50 and evoked gamma responses may reflect pathophysiology that is present in only select subgroups of patients with schizophrenia (Johannesen et al., 2008); (4) the atypical medications taken by the majority of the patients in this study may further reduce the schizophrenia–normal effect size differences (Adler et al., 2004; Light et al., 2000); and (5) the use of rare tone pairs in a button-press target detection procedure, interspersed within the standard click pairs, may have altered

the fundamental nature of the dual-click procedure. Future studies that clarify these issues, using larger sample sizes, are warranted.

In summary, previous investigations have identified at least two stages of auditory processing: stimulus registration (i.e., encoding that a stimulus has been presented) and evaluation (i.e., classifying the nature of the stimulus) (Boutros and Belger, 1999). There is evidence to suggest that neural oscillatory activity within the gamma and beta frequency ranges, respectively, may support these functions. The current study evaluated these functions in patients with schizophrenia using a modified dual-click procedure. We found that individuals with schizophrenia exhibited reduced N100 amplitude in response to the initial click stimulus and reduced beta 1 activity (12–20 Hz) in response to the initial salient stimulus. Patients did not significantly differ from healthy comparison subjects in P50 amplitude, low, beta 2 or gamma activity. These findings extend previous research by investigating the difference in neural response to both standard and salient, or rare, paired stimuli within a more detailed frequency band analysis than has previously been reported in the literature (Blumenfeld and Clementz, 2001; Johannesen et al., 2005). While P50 ERP amplitudes were increased to rare stimuli in both groups, beta 1 activity (12–20 Hz), which is associated with stimulus saliency and evaluation, exhibited sensitivity to diagnosis. These findings suggest that aberrant stimulus evaluation, especially as it relates to stimulus salience detection, may be considered a primary mechanism underlying sensory processing-related EEG abnormalities in schizophrenia.

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