

Normal Electro cortical Facilitation But Abnormal Target Identification during Visual Sustained Attention in Schizophrenia

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Attentional deficits in schizophrenia have been investigated using target identification tasks which conflate the abilities to successfully (1) attend to possible target locations and (2) detect target events. Whether compromised attentional selectivity or abnormal target detection causes schizophrenia subjects' poor performance on visual attention tasks, therefore, is unknown. To address this issue, we measured the neural activity (using electroencephalography) of 17 schizophrenia and 17 healthy subjects during a target identification task. Participants viewed superimposed images (horizontal and vertical bars differing in color) and attended to one image to identify bar width changes in specific locations. Bars were frequency tagged so attention directed to unique parts of the images could be tracked. Steady-state visual evoked potentials (ssVEPs) were used to quantify attention-related neural activity to specific parts of the visual images. Behavioral performance and event-related potentials (ERPs) in response to the target events were used to quantify target detection abilities. For both schizophrenia and healthy subjects, attending to specific parts of the attended image enhanced brain activity related to attended bars and reduced activity evoked by unattended bars. Activity in relation to the spatially overlapping unattended image was unaffected. Schizophrenia patients, however, were impaired on target detection abilities on both behavioral and brain activity measures. Target-related behavioral and brain activity measures were highly correlated in both groups. These findings indicate that deficient target detection rather than compromised attentional selectivity accounts for previously reported visual attention deficits in schizophrenia.

Key words: schizophrenia; visual attention; EEG; visual steady state; P300; sensory gain control

Introduction

Schizophrenia patients exhibit deficits in early visual processing (Potts et al., 2002; Butler et al., 2008; Luck and Gold, 2008). These difficulties are ascribed to directing, maintaining, and regulating visual selective attention (Fuller et al., 2006; Sponheim et al., 2006). A compromised ability of the visual system to respond to relevant at the cost of irrelevant cues is theoretically a mechanism for perceptual problems in schizophrenia (Light and Braff, 1999). Studies supporting selective attention deficits in schizophrenia often rely on target detection tasks like continuous performance (Chen and Faraoane, 2000) and masking (Green and Nuechterlein, 1999) paradigms. Recent work, however, questions which aspect(s) of selective visual spatial attentional processing is (are) impaired in schizophrenia (Luck et al., 2006). In particular, the ability of schizophrenia subjects to maintain states of selective cortical facilitation in the visual domain, independent of target detection and/or identification requirements, is unknown.

In the present study, attentional selection, defined as sus-

tained sensory facilitation in neural mass activity in the visual cortex, and target detection were differentiated to study their separate influences on schizophrenia patients' visual perceptual processing. In current theories of selective attention, sensory facilitation for an attended stimulus can result either from top-down "bias" signals (Kastner and Pinsky, 2004) or as a consequence of similarity between target features (i.e., task demands) and feature preference of a given neuron population (Maunsell and Treue, 2006). Electrophysiological measures of sustained attention-related changes in cortical facilitation are particularly relevant to models of schizophrenia because they are sensitive to electrocortical activity early in processing, can discriminate sensory facilitation to overlapping stimuli (Driver et al., 2001), and are capable of illuminating differences in neural background activity before and during stimulus presentation (Kastner and Pinsky, 2004).

Use of steady-state visual evoked potentials (ssVEPs) allowed us to separately assess cortical facilitation of sensory processing and target identification at attended (and unattended) locations. The ssVEP is an electrocortical response to flickering stimuli where the frequency of brain activity equals the stimulus flicker rate. The experimenter can select the flicker rate of a stimulus, which facilitates identification of neural activity related to the stimulus by means of "frequency-tagging" (Müller et al., 2003).

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Steady-state VEPs are characterized by high signal-to-noise ratios (Mast and Victor, 1991), and multiple stimuli flickering at different frequencies can be presented simultaneously so attention to independent elements within the visual field can be tracked (Morgan et al., 1996; Müller and Hübner, 2002; Müller et al., 2003; Regan and Regan, 2003).

Changes in brain state were tracked using multiple frequency-tagged ssVEP stimuli while schizophrenia and healthy subjects were attending to particular parts of a complex visual display. Subjects were required to identify targets only at attended locations which provided a behavioral index of target identification. Quantifying VEPs to the target events provided a measure of neural activity that was directly related to target identification abilities. This strategy, therefore, allowed us to separate the behavioral and neural equivalents of (1) sustained visual selective cortical facilitation and (2) visual target identification. Present results indicate that the latter process is most clearly disrupted among schizophrenia patients.

Materials and Methods

Participants. Seventeen chronic outpatients with DSM-IV (American Psychiatric Association, 1994) schizophrenia (mean age = 43 years; SD = 8; range = 26–55; 6 females) and 17 healthy (mean age = 41 years; SD = 8; range = 27–54; 7 females) persons participated in this study. All participants were right handed and had normal or corrected-to-normal vision. Subjects were interviewed with the SCID (First et al., 1995) by two psychologists to either verify their clinical diagnosis (schizophrenia) or rule out Axis I disorders (healthy subjects). Participants were absent of neurological hard signs, clinically confounding treatments, history of head trauma, and current psychoactive substance use disorders. All patients were clinically stable (Global Assessment of Functioning $M = 34$, SD = 4) on antipsychotic medications (15 on atypical and 2 on typical) for >8 weeks before participation. A host of previous studies suggest that visual processing deficits observed in schizophrenia are not associated with antipsychotic medication treatments (for a brief discussion, see Butler et al., 2007). Participants were paid \$15/h for participation. The UGA Institutional Review Board approved this study; participants provided informed consent before testing.

Stimuli and procedure. Visual stimuli consisted of two superimposed images that were used in a previous study (Fig. 1) (Chen et al., 2003). Both the horizontal and vertical images were composed of equally spaced parallel bars of 1° visual angle that were equal in luminance (5.5 cd/m^2 against a 0.1 cd/m^2 background). These stimuli have the desirable feature that they are optimal for activating simple cells in primary visual cortex (Hubel and Wiesel, 1962), and require little in the way of visual integration for their optimal registration (for review, see Butler et al., 2008). One image was composed of red and black, and the other of green and black, interleaved bars, so the stimuli certainly engaged both the magnocellular and parvocellular pathways of the visual system (Butler et al., 2008). Each image was 9° square and consisted of 5 colored bars (one middle bar, two peripheral bars, and two outside bars). A centrally located dim gray dot, on which participants fixated, was visible throughout testing. Stimuli were presented on a 21° high-resolution flat surface color monitor with a refresh rate of 100 Hz that was 60 cm from the participants' eyes.

The vertical bars were always identified as the to-be-attended image throughout 2 min trial blocks (Chen et al., 2003). For the attended image, subjects were to identify width changes (65% increase or decrease) in any of the three middle bars (attend-all condition), in the middle bar only (attend-mid condition), or the two peripheral bars bordering the middle bar (attend-peripheral). The attentional manipulation, therefore, allowed for comparisons between broad, narrow, and divided attention conditions, as opposed to simply comparing attend and no-attend conditions (Müller et al., 2003). During each trial block, any of the three middle bars in either the attended or unattended image was randomly and independently selected for a width change. Width changes lasted for ~ 400 ms before the bar returned to its original size; the interval between width changes was randomly selected from a 1–3 s rectangular distribu-

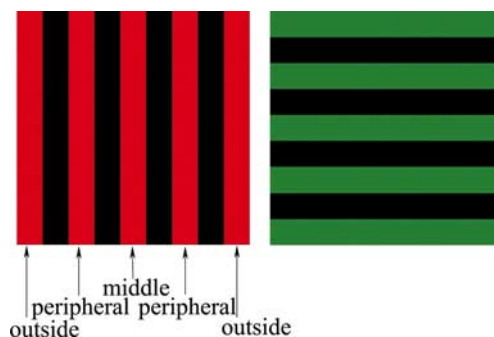


Figure 1. The two images (horizontal and vertical bars) used in this study are shown as spatially distinct, but they perfectly overlapped during testing. Each image included the middle bar, the peripheral bars, and the outside bars.

tion. Target events, defined by a change in widths, would require at least low-level perceptual integration for their detection (Butler et al., 2008). Subjects were to respond to target events with a button press.

The attended image had bars flickering at different frequencies. The middle vertical bar flickered at 7.69 Hz, the peripheral vertical bars flickered at 7.14 Hz, and the outside vertical bars flickered at 6.67 Hz. Unattended horizontal bars flickered at 8.33 Hz. Whether and how attention shifted within the attended image depending on condition (attend-all, attend-mid, attend-peripheral), therefore, could be determined by quantifying the strength of response at the flicker rate of the stimuli. The order of trial block presentations was counterbalanced by color of the attended bars (red or green) and attentional manipulation. We did not randomize either direction of the attended bars or oscillation frequencies of the images because there were no effects associated with these two factors in a previous study (Wang et al., 2007). For each condition (attend-all, attend-mid, attend-peripheral), four 2 min blocks were completed by each participant.

An important requirement when using the “method of multiple stimuli” (Regan and Regan, 2003) is that the tag frequencies be close enough that their differences are undetectable to the observer, differences between them are irrelevant to the sensory system under investigation, and the different frequencies are not harmonically related. In this study, the tag frequencies, which were created by flashing the figure for one refresh and then varying the number of blank refreshes between flashes, were all within a 1.66 Hz range (6.67–8.33 Hz). This has the additional advantage of minimizing possible confounds between attention modulation and tagging frequency (cf. Ding et al., 2006).

EEG recording. EEG data were measured using a 256-channel Geodesic Sensor Net and NetAmps 200 amplifiers (Electrical Geodesics Inc.; EGI). Recordings were referenced to the vertex sensor (Cz). As is standard with high input impedance amplifiers like those from EGI, sensor impedances were $<50 \text{ k}\Omega$. Data were analog filtered from 0.1–100 Hz, digitized at 250 Hz, stored on disk for later off-line analysis, and recorded continuously throughout the 2 min blocks.

Data analysis. Raw data were checked for bad channels ($<5\%$ for any participant), which were replaced using a spherical spline interpolation method (as implemented in BESA 5.1). Data were transformed to an average reference and digitally filtered from 2 to 40 Hz (12 dB/octave rolloff, zero-phase). To ensure that steady state had been adequately established, we used only the last 100 s of each 120 s trial block. The 100 s window yields 0.01 Hz resolution, which was necessary to quantify neural response magnitudes at the specific oscillation frequencies used in the present study. Eye blink artifact correction was achieved by using the ICA toolbox in EEGLAB 4.515 (Delorme and Makeig, 2004) under Matlab (version 7.0, MathWorks). Before computing FFT power, the mean and linear trends were removed (using Matlab) for each EEG channel. Figure 2 shows the head surface maps of FFT power for both the schizophrenia and normal groups, collapsing over all frequencies and all conditions. Maximum ssVEP power was localized at midline sensors over visual cortex. There was no other peak of activity associated with the ssVEP at any other spatial location. FFT power at the frequency of stimulation

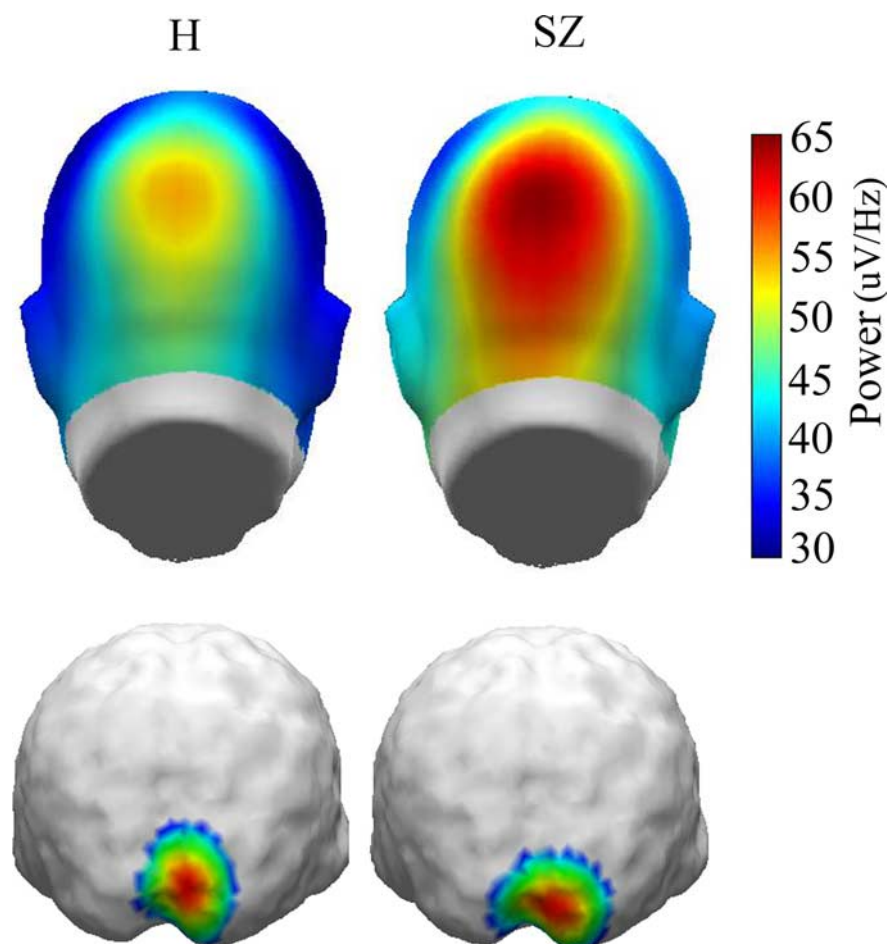


Figure 2. The top row of the figure shows the head surface map of grand average FFT power to the steady-state stimuli (averaged over all frequencies and all conditions for all participants) for both healthy (left) and schizophrenia (right) subjects. The bottom row of the figure shows the sLORETA solutions of time-domain averaged ssVEPs for both healthy and schizophrenia subjects.

averaged over 67 EEG sensors that captured the maximal signal, therefore, was used to quantify strength of sustained visual selective attention (for example, see also Wang et al., 2007).

As can be seen in Figure 3, the nonspecific (not associated with the driving frequencies) brain activity level of the schizophrenia and healthy subjects may be different. To evaluate for this possibility, we calculated the average power in traditional frequency bands (delta: 1–3.5 Hz; theta: 3.5–8 Hz; low alpha: 8–10 Hz; high alpha: 10–12 Hz) excluding the specific driving frequencies if necessary. We also quantified nonspecific brain activity in the more narrow region spanned by the driving frequencies (6.5–8.5 Hz, excluding the driving frequencies themselves). These values were then used in between-group comparisons before testing for selective attention effects on the driving frequencies. In addition, to adjust for possible nonspecific brain activity differences between groups, we subtracted the mean power of 20 bins (± 0.1 Hz) around the unique driving frequencies (6.67, 7.14, 7.69, and 8.33 Hz) from ssVEPs for each subject before making group comparisons on sustained visual selective attention (Srinivasan et al., 1999).

For a measure sensitive to phasic changes in attentional allocation associated with visual target identification, we examined visual event-related potentials (VEPs) elicited by the target events (bar width changes). Individual trials of 700 ms duration (beginning 150 ms before target event onset) were averaged separately for target events that occurred in the middle bar, peripheral bars, or unattended image. Data were initially notch-filtered at 7.5 Hz (± 1.5 Hz) to remove activity associated with the driving frequencies that might otherwise complicate VEP scoring. Trials with activity $>75 \mu\text{V}$ were eliminated from further pro-

cessing. For the attended image, only target events followed by a correct response were included in VEP averages. Grand averages were baseline corrected using the 150 ms preevent period. To maximize signal-to-noise ratios, we collapsed target event VEP averages to three categories: (1) attended objects in the attended image (averaging across middle bar targets in attend-all and attend-mid conditions and peripheral bar targets in the attend-all and attend-peripheral conditions; Total Trials: schizophrenia $M = 118$, $SD = 4.8$; healthy $M = 169$, $SD = 4.5$); (2) unattended objects in the attended image (middle bar targets in the attend-peripheral condition and peripheral bar targets in the attend-mid condition; Total Trials: schizophrenia $M = 90$; $SD = 4.8$; healthy $M = 107$, $SD = 4.3$); and (3) unattended image targets (Total Trials: schizophrenia $M = 232$, $SD = 6.3$; healthy $M = 265$, $SD = 7.0$).

Component latency identification was performed using programs written in Matlab. To identify components above baseline noise level, global field power (GFP) plots were derived for every subject and condition. The only identifiable component in the GFP plots for all subjects in all conditions was the P300 (see Results). Given the 6–9 Hz notch filter, with this frequency range overlapping the frequency range for the P100/N100/P200 (Moratti et al., 2007) it is not surprising that these components were not present; the P300 component, however, occupies a lower frequency range. The latency for the P300 component for each condition was determined from the peak in the GFP plots. The magnitude of the P300 was determined based on averaging GFP values at the peak latency (± 20 ms) from 45 sensors located over posterior parietal/occipital regions that best captured this component.

After VEP analyses calculated on voltage data at the sensors, we used standardized low-resolution brain electromagnetic tomography (sLORETA; Pascual-Marqui, 2002) to estimate brain regions involved in determining the (1) ssVEP for schizophrenia and healthy participants and (2) the brain regions accounting for between-groups differences on P300 observed in the sensor space data. sLORETA is a modification of minimum norm least squares (Hämäläinen and Ilmoniemi, 1994) that uses the standardization of the minimum norm inverse solution to infer high probability regions of brain activation given the measured EEG data. sLORETA solutions yield pseudostatistics that are not appropriate for determining strength of activity, but they provide accurate information about the regions of activity that can account for the voltage pattern recorded at the sensors (e.g., Soufflet and Boeijinga, 2005).

The sLORETA calculations were performed using CURRY (Version 5.0, Neuroscan). An averaged magnetic resonance (MR) image from the Montreal Neurological Institute (Collins et al., 1994) was used to construct a realistic head model (Fuchs et al., 2002) before source localization. The MR images were segmented into skin surface, inside of the skull, and cortex. A three-compartment boundary element method (BEM) model was then constructed; standard homogeneous conductivities were assumed for the skin, skull, and brain (0.33 , 0.0042 , $0.33 \Omega^{-1} \cdot \text{m}^{-1}$). For this BEM model, the average triangle edge lengths were 7.5 mm for the skin, 5.1 mm for the skull, and 3.1 mm for the brain compartment. Before source analysis calculations, the fiducial locations from the EEG data collection session were matched to the fiducial locations on the averaged segmented skin surface (using a least squares fitting procedure in CURRY). The sLORETA solutions were projected to the cortical surface.

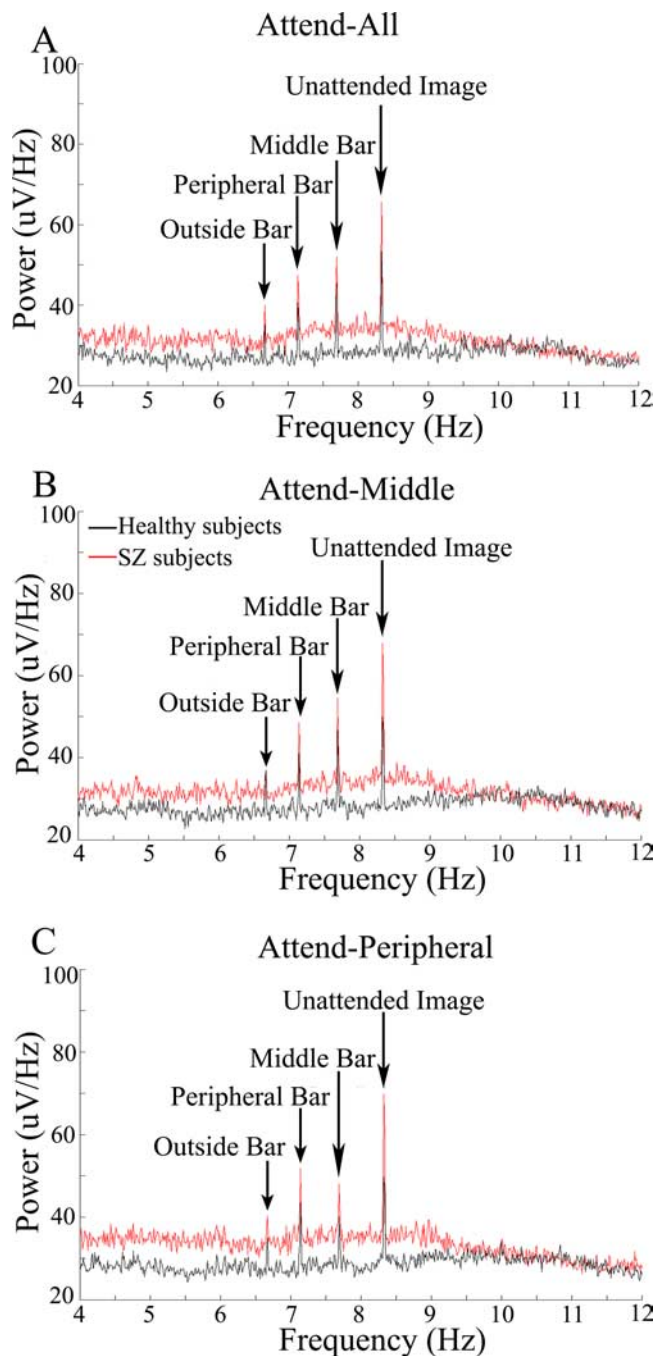


Figure 3. An example of power spectra averaged over the 67 EEG channels that captured the peak ssVEP power (healthy subjects: black line; schizophrenia subjects: red line). In this example, the red vertical middle bar, peripheral bars, and outside bars flickered at 7.69 Hz, 7.14 Hz, and 6.67 Hz, respectively. The green horizontal bars flickered at 8.33 Hz. Participants attended to the red vertical bars, and were asked to identify width changes in the red middle and peripheral bars (**A**, the attend-all condition), red middle bar only (**B**, the attend-mid condition) or red peripheral bars only (**C**, the attend-peripheral condition).

Calculating source estimates for the P300 was straightforward because, after averaging over trials, there was one P300 component that represented the typical response to target stimuli. Such was not the case, however, for the ssVEP because no such trial averages were created for quantification purposes. To allow for estimate of ssVEP source generators, the following procedure was used. First, separate time-domain averages of the ssVEPs were obtained for each flicker frequency using a moving window technique. For each frequency, a four-cycle window was moved in steps of one cycle (120 ms, 130 ms, 140 ms, 150 ms for the 8.33, 7.69,

7.14 and 6.67 Hz rates, respectively). Second, the sources for these moving window averages were estimated, with the sLORETA solutions being averaged over all four peaks for the different flicker rates (Fig. 2).

Results

Behavioral responses

Correct responses were button presses happening 100–1000 ms after target onset (bar width change). A group (schizophrenia, healthy)-by-attention-condition (attend-all, attend-mid, attend-peripheral) repeated-measures ANOVA (with Huyhn-Feldt adjusted degrees of freedom) was used to test for differences on d' and correct response reaction times. For d' , both main effects of group, $F_{(1,32)} = 11.8$, $p = 0.002$, and attention condition, $F_{(2,64)} = 172.6$, $p < 0.001$, $\epsilon = 1.0$, were significant. The group-by-attention-condition interaction was also significant, $F_{(2,64)} = 5.9$, $p = 0.005$, $\epsilon = 1.0$. Analysis of simple main effects indicated that healthy participants (attend-all $M = 2.0$, $SD = 0.5$; attend-mid $M = 3.2$, $SD = 0.4$; attend-peripheral $M = 2.3$, $SD = 0.4$) were better than schizophrenia patients (attend-all $M = 1.7$, $SD = 0.5$; attend-mid $M = 2.5$, $SD = 0.5$; attend-peripheral $M = 1.8$, $SD = 0.6$) at detecting target events especially during the attend-mid, $t_{(32)} = 4.7$, $p < 0.001$, and attend-peripheral conditions, $t_{(32)} = 3.1$, $p = 0.004$. For reaction times, there were also significant main effects of group (schizophrenia patients $M = 575$ ms, $SD = 72$; healthy $M = 514$ ms, $SD = 43$), $F_{(1,32)} = 8.9$, $p = 0.006$, and attention condition (attend-all $M = 542$ ms, $SD = 67$; attend-mid $M = 529$ ms, $SD = 73$; attend-peripheral $M = 563$ ms, $SD = 73$), $F_{(2,64)} = 10.2$, $p < 0.001$, $\epsilon = 0.95$. Schizophrenia patients were slower to respond than healthy subjects; both groups were fastest at detecting targets during the attend-mid condition and slowest during the attend-peripheral condition.

Brain activity

Nonspecific brain activity

A group (schizophrenia, healthy)-by-attention-condition (attend-all, attend-mid and attend-peripheral) repeated-measures ANOVA (with Huyhn-Feldt adjusted degrees of freedom) was used to test for differences on nonspecific brain activity. There were significant main effects of group for delta, theta, and 6.5–8.5 Hz driving frequency range power (schizophrenia $M = 34.5$, $SD = 6.5$; healthy $M = 27.7$, $SD = 3.3$), $F_{(1,32)}$ values > 14.8 , p values < 0.001 . There was also a significant group difference on low alpha power (schizophrenia $M = 30.9$, $SD = 4.0$; healthy $M = 28.5$, $SD = 5.5$), $F_{(1,32)} = 6.1$, $p = 0.019$, but not on high alpha power. There were no other significant effects on nonspecific brain activity. In all cases where there were significant effects of group, schizophrenia patients had higher nonspecific brain activity power.

Adjusted ssVEP activity

As expected, and replicating earlier ssVEP work, the sLORETA source projection of ssVEP amplitude pointed to a restricted area in early visual cortex, contributing most strongly to the scalp measured potential. A group (schizophrenia, healthy)-by-attention-condition (attend-all, attend-mid, attend-peripheral) repeated-measures ANOVA (with Huyhn-Feldt adjusted degrees of freedom) was used to test for differences on adjusted ssVEP power for each object (outside bar, peripheral bars, middle bar, unattended image) separately (see Fig. 4). For the outside bars and unattended image the main effects of group, $F_{(1,32)}$ values < 0.6 , p values > 0.465 , and attention condition, $F_{(2,64)}$ values < 2.6 , p values > 0.082 , ϵ values = 1.0, and the group-by-attention-condition interactions, $F_{(2,64)}$ values < 0.10 , p values > 0.905 , $\epsilon = 1.0$, were not significant. For both the peripheral bars and

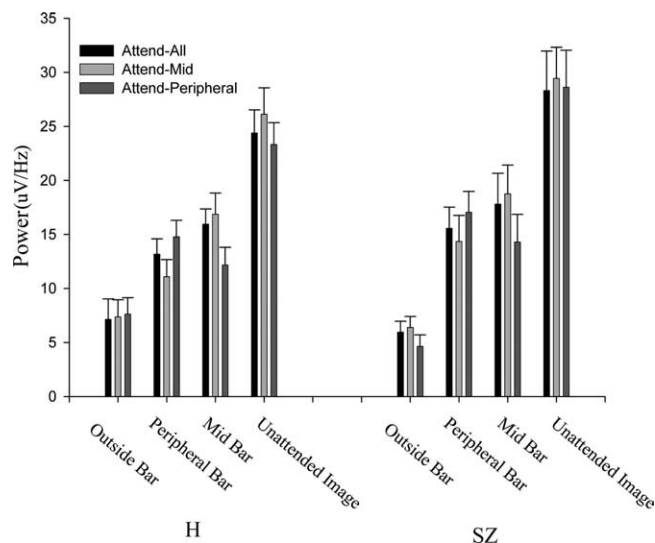


Figure 4. Mean amplitude (plus SE) of the ssVEP for healthy and schizophrenia subjects in the different attention conditions. The labels on the x-axis refer to the different stimulation locations that had unique stimulation frequencies. Note that ssVEP amplitude to the unattended image is higher because there are more stimuli (5 total bars, so greater overall neural activity) contributing to this response.

middle bars, the main effects of group, $F_{(1,32)}$ values < 0.6 , p values > 0.465 , and the group-by-attention-condition interactions, $F_{(2,64)}$ values < 0.10 , p values > 0.905 , $\epsilon = 1.0$, were not significant. There were significant main effects of attention condition, however, for both the peripheral and middle bars, $F_{(2,64)}$ values > 7.6 , p values < 0.002 . Further analyses showed that for the peripheral bars, power was higher during the attend-all than during the attend-mid condition, $t_{(33)} = 2.1$, $p = 0.040$, and was higher during the attend-peripheral condition than during both the attend-all, $t_{(33)} = 2.4$, $p = 0.020$, and attend-mid conditions, $t_{(33)} = 3.3$, $p = 0.003$. For the middle bar, power was higher, but not significantly so, during the attend-mid than during the attend-all condition, $t_{(33)} = 1.1$, $p = 0.262$. Middle bar power was also higher during the attend-all, $t_{(33)} = 3.4$, $p = 0.002$, and attend-mid conditions, $t_{(33)} = 3.9$, $p < 0.001$, than during the attend-peripheral condition.

VEPs

As can be discerned from Figure 5, for all subjects in both groups above-baseline P300 components were evident only if target events occurred at the attended locations. The groups did not differ on P300 latency (schizophrenia $M = 356$ ms, $SD = 38$; healthy $M = 361$ ms, $SD = 42$). A between-groups t test on P300 amplitudes, however, indicated that healthy subjects ($M = 1.1$ μV , $SD = 0.3$) had significantly larger responses than did schizophrenia patients ($M = 0.8$ μV , $SD = 0.3$), $t_{(32)} = 2.1$, $p = 0.047$. Inspection of the P300 topographies, surface laplacians and sLORETA solution (Fig. 5) indicate that the between-groups difference on P300 amplitude was accounted for by amplitude differences, but not topographical shifts, with greater left superior parietal activity among the healthy subjects. According to the sLORETA model, this region generally contributed most strongly to the scalp-measured P300 in both groups, which supports that schizophrenia participants engaged the same underlying cortical regions as controls, but to a lesser degree.

Relationships between behavior and brain activity

Pearson correlations were used to investigate relationships between behavioral responses (d' and reaction time) and brain ac-

tivity measures that differentiated the groups (nonspecific power and P300 amplitude) (Fig. 6). There were no significant associations between behavior and nonspecific power. On the relationship between d' and P300 amplitude, both the schizophrenia, $r_{(17)} = 0.7$, $p = 0.005$, and healthy groups, $r_{(17)} = 0.8$, $p < 0.001$, had better target discrimination ability as P300 amplitude increased. Similarly, on the relationship between reaction time and P300 amplitude, both schizophrenia, $r_{(17)} = -0.6$, $p = 0.011$, and healthy groups, $r_{(17)} = -0.6$, $p = 0.010$, were faster to respond on correct trials as P300 amplitude increased. The magnitude of these relationships did not differ between the groups.

Discussion

This study investigated subcomponents of sustained selective visual processing in schizophrenia. First, using ssVEPs we assessed task-related changes in oscillatory neural activity related to specific locations among arrays of overlapping bars. This design allowed us to measure sustained selective visual processing of features competing for resources with spatially overlapping distractors, a near real-world demand to the visual system. Schizophrenia patients effectively allocated perceptual resources to specific features in the visual field, as indicated by normal modulation of the ssVEP as a function of attention instruction. Second, using VEPs to target events, we assessed target detection ability that was related to, but measured independently of, sustained selective attention. Schizophrenia patients' target detection ability was impaired, as manifest in both brain activity and behavior. Successful sustained selective visual attention, most likely determined by top-down bias signals and indexed by prolonged cortical facilitation for the attended visual feature, did not translate into successful target detection, as indexed by attenuated neural responses to targets and poor behavioral identification of their occurrence. The implications for understanding the neurophysiological and perceptual correlates of schizophrenia pathology are discussed below.

Behavioral and neurophysiological work indicates that schizophrenia patients have difficulty on tasks requiring several aspects of visual selective attention (Carter et al., 1997; Potts et al., 2002; Butler et al., 2008; Luck and Gold, 2008). The present study complements this literature by examining sustained selective processing of overlapping features and the related but separate target detection process. Schizophrenia patients successfully directing visual resources to specific spatial locations, indicating intact regulation of top-down control and intact amplification of large-scale neural signals to relevant stimuli embedded in a complex array. Particularly striking was schizophrenia patients' ability to divide attention effectively between a central to-be-ignored bar and two adjacent but peripheral bars that were separated by 4° of visual angle (center-to-center).

In the context of biased competition models of attention (Desimone, 1996), stimuli are envisioned as competing for resources, with both bottom-up and top-down modulations leading to one stimulus receiving in-depth processing (Kastner and Ungerleider, 2000). In particular, sustained attentional selection based on prior knowledge of relevant visual coordinates is related to bias signals affecting initial input to cortex from the lateral geniculate nucleus (Kastner and Ungerleider, 2000) and reflect parsing of the visual world by top-down control into to-be-attended and to-be-ignored components. Such guidance of attention to relevant stimuli has been reported as deficient among schizophrenia patients in spatial cueing and visual search tasks, often leading to the assumption that their initial attention control is impaired (Luck and Gold, 2008). In the present study of sus-

tained selective attention, individuals with schizophrenia could establish and maintain stimulus-specific cortical facilitation over time. Combined with studies of low-level vision (Dakin et al., 2005), this finding highlights the importance of studying specific aspects of selective attention (Kastner and Pinsk, 2004) rather than assuming a more general attention deficit in schizophrenia.

Early visual processing deficits have been reported in schizophrenia (Butler et al., 2008), with some specific functions reported as being intact or even enhanced among patients (Dakin et al., 2005). Some of those findings suggested deficiency in the magnocellular (m) pathway of the human visual system in schizophrenia as expressed in reduced sensory gain control. Our stimuli most likely engaged both the magnocellular and parvocellular (p) portions of the visual stream. Individuals with schizophrenia were able to maintain states of stimulus-selective cortical facilitation despite possible problems in the magnocellular part of their visual system. It should be emphasized however, that our EEG-derived dependent variables are good indices of neural mass activity, but may lack specificity with respect to m- or p-pathway activation. In future studies, it would be useful to determine whether a dysfunction of sustained selective cortical facilitation could be identified using stimuli biased for m- versus p-pathway activation. It would be especially important to demonstrate among schizophrenia patients (1) normal sustained cortical facilitation and target detection abilities using p-pathway-specific stimuli, and (2) deficient sustained cortical facilitation and target detection abilities using m-pathway-specific stimuli.

Previous tests of neural modulation of visual selective attention in schizophrenia required detecting a transient target (for review, see Luck and Gold, 2008). The advantage of the approach used here is that assessment of neural modulations associated with visual selective attention was independent of target identification. We isolated two aspects of selective attention: (1) sustained cortical facilitation in neural masses representing specific aspects of the visual scene, and (2) transient responses to the occurrence of targets. The former was assessed via strength of the sustained ssVEP to frequency-tagged stimuli at different and overlapping spatial locations under different attentional requirements; the latter was assessed by strength of the transient P300 VEP to target events. The similarity between-groups on amplitude modulation of the ssVEP was not reflected in either the behavioral data, where patients showed marked decreases in accuracy and speed, or amplitude of the visual P300, which was reduced among patients as a consequence of decreased parietal cortex activity. There were also strong associations between behavioral and brain indicators of target detection, indicating that impaired performance was not a consequence of a generalized deficit or poor signal-to-noise ratio of the electrophysiological data. These findings provide a link between brain activity and behavioral deficiency, which is rarely demonstrated in the schizophrenia literature (Camchong et al., 2006).

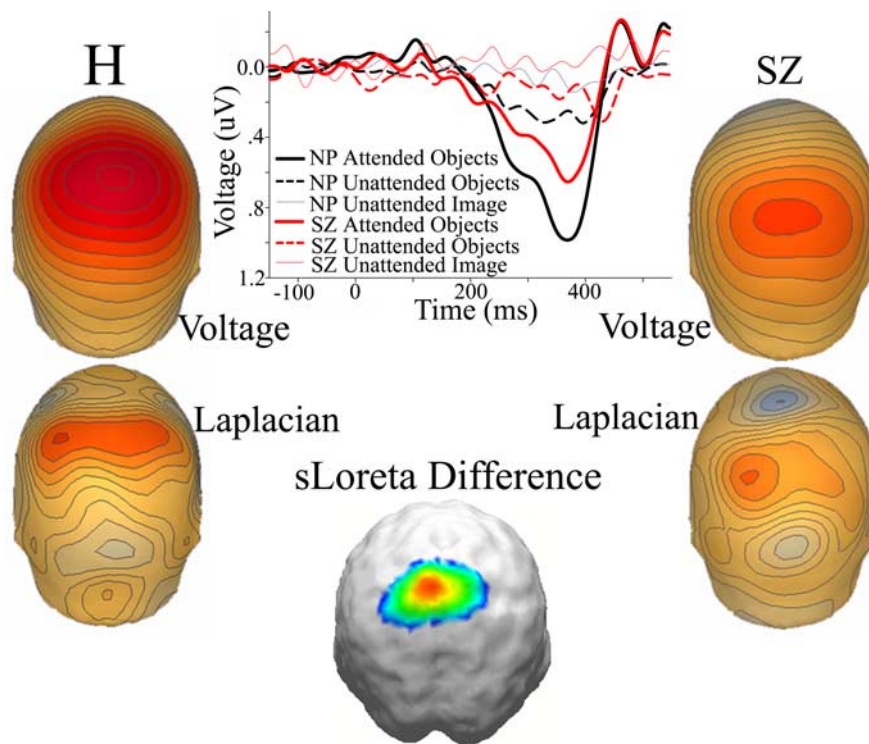


Figure 5. The top portion of the figure shows the grand average VEP waveforms for healthy (black line) and schizophrenia (red line) subjects. They show separate averages for the VEPs to the attended objects (solid line), unattended objects (dashed line), and unattended image (light solid line), respectively. The back views of the head on the far left (healthy subjects) and right (schizophrenia patients) show the grand average voltage and surface Laplacian topographies for the P3 component (same scale for both groups). The bottom middle image shows the sLORETA solution of the P3 amplitude difference between healthy and schizophrenia subjects, and indicates stronger activity among healthy persons specifically in the left superior parietal region.

How could the sustained ssVEP to target locations be normal in schizophrenia, but the neural response to targets at those same locations show deficits? First, in the present study, sustaining attention to the proper stimulus features at the neural level (measured with frequency-tagged steady-state stimuli) mainly required activation of simple cells in cortical layer 4 of primary visual cortex (Hubel and Wiesel, 1962; Carandini, 2006). These overlapping grating stimuli flickering at different frequencies were optimal for activating V1 cells receiving the earliest input from thalamus. Their proper modulation under different attention conditions was likely determined by top-down control via reciprocal connections between visual cortex and lateral geniculate nucleus (Hamker, 2005; Sherman, 2005; Kastner et al., 2006). Our results indicate that, at least when using stimuli optimal for activating simple cells in V1, the initial geniculocortical input pathway can function normally among schizophrenia patients. We used an ssVEP stimulation frequency that has been associated with normal electrocortical processing in schizophrenia patients (Krishnan et al., 2005); adding an attention manipulation resulted in amplitude modulation among patients that was also well within the range of the healthy participants. Sensory processes tapped by the present task, as well as their sustained attentional modulation, appear to be functioning normally in schizophrenia.

Second, detection of target events in this study required integrated neural processing in addition to the accurate ability to selectively attend to the proper stimulus features. Target events were changes in bar widths, which should activate complex cells. Integrated neural processing, which Butler et al. (2008) described as “the process of linking the output of neurons that individually code local . . . attributes of a scene into global . . . complex struc-

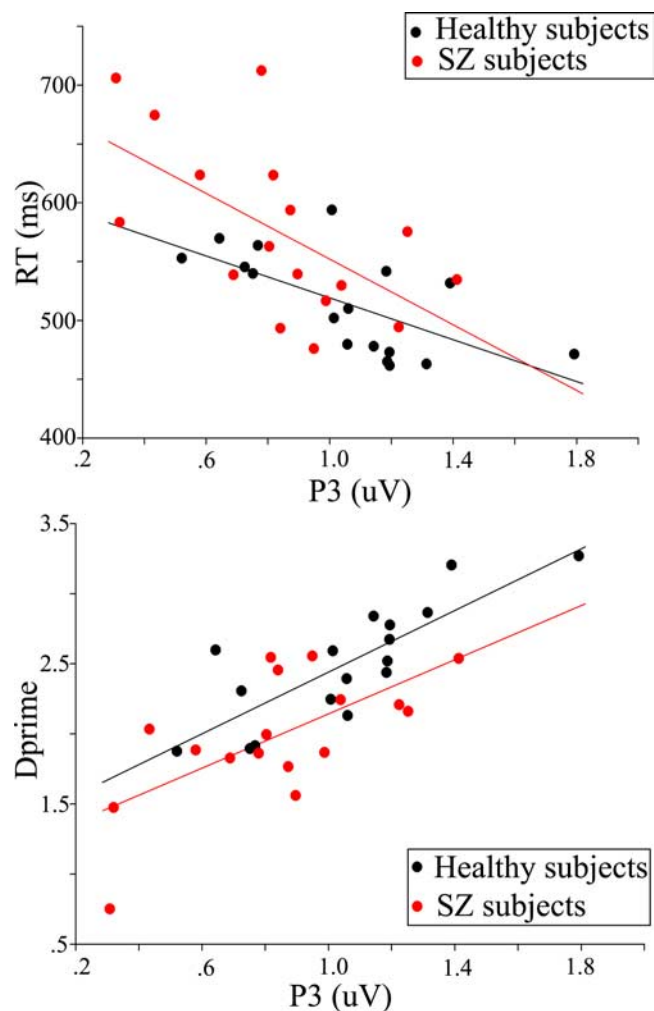


Figure 6. Bivariate scatter plot of relationships between behavioral responses (upper plot: reaction time; lower plot: d') and P3 amplitude for healthy (black dots) and schizophrenia (red dots) subjects. The best fitting regression lines are also included for both groups.

ture, more suitable for guidance of behavior,” may be the critical attribute determining manifestation of visual attentional abnormalities in schizophrenia. Complex cells, with primary distribution in cortical layers 2 and 3 of V1, are sensitive to edges of a particular orientation, although they are less sensitive to specific spatial locations (Riesenhuber and Poggio, 1999). Integration of information from multiple simple cells determines the response properties of complex cells (Wurtz and Kandel, 2000). Consistent with Butler et al. (2008), schizophrenia patients’ abnormalities in behavioral and neural indicators of target detection may indicate dysfunction of a supragranular integrative process.

Nonspecific, ongoing oscillatory activity <10 Hz (in the theta and low alpha ranges) was higher in schizophrenia than in healthy subjects, replicating previous observations (Clementz et al., 1994; Winterer et al., 2000; Krishnan et al., 2005). Traditionally, alpha and theta have been considered to recruit different neuronal pools when measured with EEG/MEG (Schürmann and Başar, 1994; Pizzagalli et al., 2003), and to index unique cognitive processes or states of the nervous system (Pfurtscheller, 1992; Makeig and Jung, 1996; Klimesch et al., 2005). Recent work on the microscopic (cellular) level yields evidence for a direct link between relative amounts of alpha/theta composition in the EEG and corticothalamic inputs in the same neuronal architecture (Hughes and Crunelli, 2005). Pharmacological activation of

mGluR1a (a metabotropic glutamate receptor subtype) leads to increased alpha activity. Deactivation at the same synapses leads to a dose-response-related decrease in the idling frequency of these neurons and, therefore, a relative increase in amount of theta activity (Hughes et al., 2004). A decrease in corticothalamic input via mGluR1a receptors, a possibility among schizophrenia subjects (Pietraszek et al., 2007), may determine relative alpha/theta concentrations in the spontaneous EEG. The level of background brain activity may be determined by different neural processes from those generating evoked and/or steady-state responses. The implications of these possibilities for understanding the neural correlates of cognitive functioning in schizophrenia have yet to be fully investigated (Pietraszek et al., 2005), but it may be an issue worth pursuing in subsequent investigations (Brody et al., 2003).

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