A SPECIFIC RELATIONSHIP BETWEEN MOTION PROCESSING AND NEURAL ACTIVITY DEFICITS IN SCHIZOPHRENIA

by

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(Under the Direction of Brett A. Clementz)

ABSTRACT

Smooth pursuit abnormalities may reflect motion processing deficits in schizophrenia (SZ). There is little evidence, though, for a link between early neural activity supporting motion detection and motion processing ability in SZ. We used motion grating stimuli and dense array EEG data to investigate such a relationship. In the first study, thirteen DSM-IV SZ and 13 healthy subjects performed a simple motion direction discrimination task and only responded to target stimuli. SZ showed enhanced early VERP neural components (P1/N1), but impaired target detection (reduced N400 difference between target and non-target). In a second study, fourteen DSM-IV SZ and 14 healthy subjects performed a velocity discrimination task by indicating which of two gratings was faster (either a 10 deg/s standard or a “test” stimulus that was either faster or slower than the standard) in a two-alternative forced choice design. Speed discrimination of SZ was worse than healthy subjects, indicated by higher speed discrimination thresholds. To the initial grating presentation, there were no significant differences between groups in neural activity (N1/P2) to grating onset. In addition, for both groups, there were lower amplitude VERP responses to the 10 deg/s targets, indicating awareness of the most “typical”

stimulus. These findings indicate normal neural responses to a single motion stimulus among SZ. During presentation of the second motion grating, however, SZ had intact N1 VERP responses but a significantly compromised P2 VERP across all stimulus velocities. Scalp topographies and distributed source analyses indicate this P2 is associated with processing beyond the initial evaluation of stimulus motion. Findings from both studies suggest smooth pursuit and motion analysis deficits in SZ are caused by dysfunction beyond the motion analysis stage.

INDEX WORDS: Schizophrenia, Motion, EEG

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DEDICATION

To my lovely wife and daughter.

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Chapter 1 General introduction

For decades it has been noted that schizophrenia patients have behavior deficits in perceptual, motor, and cognitive functions (Chen et al. 1999a; Chen et al. 2005; Laurens et al. 2005). Among those problems, smooth-pursuit eye movements (SPEM) are a well-documented and consistently observed deficit (Hutton & Kennard, 1998; Clementz & McDowell, 1994). SPEM is a complex behavior that requires subjects to constantly follow a moving stimulus by keeping it on the foveal area. The successful performance of this task requires sufficient motion processing abilities (see, e.g., Lisberger et al., 1987; Stanton et al., 2005), primarily an extrastriate cortex function, and successful use of this perceptual motion information for generation of the correct motor response, primarily a frontal cortex function. Investigating if schizophrenia patients' motion processing abilities are intact, separate from their ability to generate the proper motor response, therefore, is important for understanding the cause of their smooth pursuit-related deficits.

When presented with dynamic random dot patterns, schizophrenia patients require an unusually high proportion of coherently moving dots to discern the pattern's global direction (Stuve et al., 1997; Chen et al., 2003; Chen et al., 2005; Kim et al., 2006; O'Donnell et al., 2006). Schizophrenia patients also are worse at discerning speed differences between two paired moving gratings (Chen et al., 2004; O'Donnell et al., 2006; Slaghuis et al., 2005). In addition, when using stimuli similar to those employed to show smooth pursuit deficits, schizophrenia subjects also have significantly elevated speed discrimination thresholds when compared to healthy persons (Clementz, McDowell, & Dobkins, 2007). These data provide evidence for a

more direct link between the perceptual and eye movement data, and are consistent with the notion that problems during smooth pursuit in schizophrenia may be secondary to or concomitant with a perceptual deficit.

There are also functional neuroimaging data that are at least partially consistent with the conclusion of a perceptual motion processing problem in schizophrenia. Hong et al. (2005) used functional magnetic resonance imaging (fMRI) to measure blood oxygen level-dependent (BOLD) signal change while subjects performed a predictive SPEM task. During the task, subjects needed to follow a horizontally moving dot; visual fixation was used for the baseline against which SPEM-related brain activity was compared. Schizophrenia patients had lower pursuit gain (worse SPEM performance) than healthy subjects in response to target motion. Patients also showed significantly reduced BOLD signal in frontal eye fields (FEF), supplemental eye fields (SEF), anterior cingulate cortex, and medial superior temporal cortex (MST). Brain area MST has been demonstrated to be involved in motion processing from nonhuman primates studies (Newsome & Pare, 1988; Pasternak & Merigan, 1994). Reduced activation in perceptual motion processing regions was also reported by Lencer et al. (2005), who measured BOLD response while subjects performed a SPEM task. They also found that schizophrenia patients had worse SPEM performance than healthy subjects, and that their poor performance was significantly correlated with reduced BOLD signal in extrastriate cortical area V5 (which includes middle temporal area MT and MST).

These findings are consistent with the conclusion that schizophrenia patients have a motion perception deficit attributable to dysfunction in extrastriate cortex area MT (see, e.g., Chen et al.,

2005; Lencer et al., 2005). These data are also consistent with the theory of specific magnocellular pathway dysfunction in schizophrenia (Kim et al., 2006), since this pathway provides majority input to motion area MT (Maunsell et al., 1990). The magnocellular pathway dysfunction in schizophrenia has been reported by studies utilizing M-biased or P-biased stimuli on the basis of different response properties between magnocellular and parvocellular neurons (Butler & Javitt, 2005; Butler et al., 2005; Kim, Zemon, Saperstein, Butler, & Javitt, 2005; Schechter, Butler, Silipo, Zemon, & Javitt, 2003). The magnocellular (M) pathway originates in large ganglion cells in the retina and goes through the lateral geniculate nucleus (LGN), the primary and secondary visual cortices on the way to parietal lobe as the dorsal visual stream (the "where" system). The parvocellular pathway (P) originates in small ganglion cells in the retina and goes through LGN, the primary and secondary visual cortices on the way to inferotemporal lobe as a ventral visual stream (the "what" system). The magnocellular pathway is sensitive to low spatial resolution, low luminance contrast, and non-color stimuli, as well as fast information (high temporal frequency); the parvocellular pathway is sensitive to high spatial resolution, high luminance contrast, and colored stimuli, as well as slow (low temporal frequency) information (Butler & Javitt, 2005).

Magnocellular pathway dysfunction was indicated by the fact that schizophrenia patients usually showed deficits to M-biased stimuli but not to P-biased stimuli. In relation to motion processing in schizophrenia, Kim et al. (2006) proposed that motion processing deficits in schizophrenia are caused by impaired bottom-up early magnocellular pathway input to motion processing areas such as MT. Within their studies, subjects performed one of two tasks: a

coherence dot motion threshold task or an incoherent dot motion task. Both tasks required subjects to judge the speed difference between base speed and test speed. The only difference is that in the coherence dot motion task all dots move coherently in the same direction; in incoherent dot motion task the direction of each dot is randomly chosen from eight possible directions. The results indicated no difference on motion discrimination thresholds between the two tasks among schizophrenia patients, although both thresholds were higher than among healthy subjects.

Kim et al. (2006) also measured steady-stage visual evoked potentials (ssVEPs) when subjects were exposed to magnocellular-biased stimuli (low luminance contrast) and parvocellular-biased stimuli (high luminance contrast). Significant correlations were found between elevated motion discrimination thresholds and reduced amplitude of the magnocellular-biased ssVEPs among schizophrenia patients, but not for ssVEP amplitude of the parvocellular-biased stimuli. Kim et al. (2006) drew three conclusions from their findings: (1) Schizophrenia patients have motion processing deficits, revealed by elevated motion detection thresholds; (2) No difference between motion detection thresholds during the coherence and incoherent dot motion tasks indicate relatively normal late-stage motion processing (e.g., at the level of MT/V5) among schizophrenia patients. MT is responsible for decoding motion patterns (Kim et al., 2006) separately for coherent and incoherent motion stimuli. If there is a dysfunction in MT locally, therefore, there should be threshold differences between coherent and incoherent motion task; (3) The significant correlation between amplitude of the magnocellular-biased ssVEPs and elevated motion discrimination in schizophrenia suggest that motion-processing

deficits in schizophrenia are a result of impaired bottom-up magnocellular input to motion processing areas such as MT rather than local dysfunction within those regions.

A possible complication for a theory of specific magnocellular pathway dysfunction in schizophrenia is that schizophrenia patients have accurate saccades to slowly moving smooth pursuit targets (Clementz, 1996b; Kim et al., 1997), indicating that at least some MT-supported functions are normal in schizophrenia (Dursteler & Wurtz, 1988; Newsome et al., 1985). Also, Chen (2003) reported that schizophrenia patients showed no difference from healthy people when doing a simple motion direction detection task at slow speed (10 degree/second), and concluded that schizophrenia patients had intact motion information processing at least during the early perceptual stage. Whether there is a perceptual motion problem in schizophrenia, and at what stage in the motion processing neural circuitry this dysfunction is manifest, therefore, has not been consistent demonstrated.

In addition, existing brain imaging studies among schizophrenia subjects on adequacy of the neural circuitries supporting motion processing activities have had insufficient temporal resolution to determine when abnormalities in the processing stream might occur. Motion perception is a dynamic, time-varying process, so concluding that there is a perceptual motion problem in schizophrenia requires adequate evidence at a sufficient time scale. Compared to behavior measurement (absent time information) and fMRI (low-time resolution), complementary studies with high-time resolution EEG measurement will be helpful for determining when in the course of stimulus processing abnormalities may occur in schizophrenia.

The present paper will investigate the dynamic character of motion processing in schizophrenia by utilizing high-temporal resolution EEG. To most effectively address the relevant scientific issues, the studies will assess strength of visual event-related potentials (VERPs) to motion stimuli. The VERPs, a useful index of neural activity, is an electrical response of visual cortex in relation to discrete and transit sensory stimuli (Hillyard & Kutas, 1983). The main advantage of using VERPs to study specific motion processing deficits in schizophrenia is that they afford a high temporal resolution view of the processing of motion information in the brain. The temporal resolution of VERP analysis is much higher than that of other neuroimaging methods like functional MRI and PET (i.e., it is on the order of milliseconds).

There are two studies included in present project. In the first study, the motion-processing deficit in schizophrenia will be evaluated by using a simple motion direction detection task. In the second study, a traditional velocity discrimination task will be used (e.g., Clementz et al., 2007). This project will add to the schizophrenia literature by providing complementary high time resolution brain activity data during motion processing. This study is important because the use of a *combination* of neurophysiological and behavior measurements will enhance our understanding of underlying neurophysiological mechanisms of motion deficits in schizophrenia and provide adequate and greater power concerning when in the course of stimulus processing motion deficits may be manifest in schizophrenia.

Chapter 2 STUDY 1

Introduction

This study was conducted to extend findings from Chen's studies on the "late-stage" proposal. The "late-stage" motion processing theory was proposed by Chen and his colleagues (2004) to resolve the conflict among inconsistent findings on motion processing deficits in schizophrenia. According to this theory, the motion deficits in schizophrenia occurr at a late-stage of motion processing and functional failures in the late-stage of motion processing caused the smooth-pursuit deficit since continuous spatial and temporal integration of motion information is required during SPEM. Moreover, no deficits in schizophrenia during simple saccade eye movements tasks (i.e., saccades to moving targets; Clementz, 1994) are due to the fact that discrete spatial information at an early stage of processing is sufficient to perform such tasks (Chen et al., 2004).

For providing supporting evidence to this theory, Chen et al. (2004) examined velocity discrimination performance in schizophrenia under different contrast levels. During the experiment, they presented subjects with two motion gratings and required that subjects do the velocity discrimination task (standard speed versus. test speed) in two contrast conditions: low contrast (4 times detection threshold) and high contrast (20 times detection threshold). Besides a higher velocity discrimination threshold in schizophrenia patients, the most important result was that schizophrenia patients did not show the threshold difference between low- and high-contrast stimuli, while healthy subjects showed significant decreased threshold at high-contrast compared to low-contrast. This result provided direct evidence for the "late-stage" theory since previous

animal studies have shown neural responses to motion stimuli increased with stimulus contrast at early stage but not at late stage of motion processing (Pasternak & Merigan, 1994; Sclar et al., 1990). Therefore, the contrast independence of velocity discrimination performance found in schizophrenia patients suggested that their motion processing deficits occur at a late stage (after V5).

To investigate further the "late-stage" theory, Chen et al. (2003) compared local and global motion direction judgment performance in schizophrenia. The local motion direction task (a moving grating) doesn't require integrating the motion information across space because of the uniform motion distribution. On the contrary, the global motion direction task (coherence motion detection of random dot patterns) requires integrating at least a significant portion of the random dots since dot motion directions are not the same across space. Previous animal studies suggested that global motion processing occurs at a later stage (i.e.in MT/MST or beyond; Born & Tootell, 1992; Movshon & Newsome, 1996). As a result, comparing the performance of schizophrenia patients between local- and global motion direction tasks will indicate whether the motion deficit happened at early perceptual stage or late information integration stage. During the experiment, Chen et al. (2003) measured thresholds for detecting the motion detection of a random dot pattern (global motion processing) and the motion detection of a grating (local motion processing) in both schizophrenia and normal subjects. The results indicated that schizophrenia subjects had elevated thresholds in the random dot task but no difference on the grating detection task compared with normal subjects. Based on these results, they concluded that the global processing of motion is compromised in schizophrenia patients at a later processing stage (at MT/MST or

beyond) but is intact in primary visual cortex (V1). A follow-up study (comparing schizophrenia patients to their first-order relatives and bipolar disorder patients) conducted by same research group (Chen et al. 2005) further indicated the global motion processing deficit was unique to patients and might serve as a marker to define presence of the illness.

Based on the discussion hereinbefore, it seems that schizophrenia patients have normal performance on tasks involving only perceptual processing (e.g. motion grating direction judgment). This conclusion, however, may be correct only for centrally-presented motion stimuli (Chen et al., 2003; Chen et al. 2005). In STUDY 1, we will evaluate this possibility by presenting stimuli peripherally (left and right) and determine whether the performance is normal in schizophrenia patients and whether there are lateralized differences on motion stimulus processing in schizophrenia patents. The latter possibility would have special interest since there have been heated discussions concerning lateralized dysfunctions in schizophrenia since the 1960s (Flor-Henry, 1969, 1978). Usually, lateralized dysfunction in schizophrenia is indicated by generalized abnormal neural activities in left hemisphere across cognitive domains (Crow, 1997; Gur & Chin, 1999; Sommer et al., 2001; Wright et al., 2000). However, a recent study (Caligiuri et al., 2005) suggested that lateralized cognitive dysfunctions in schizophrenia may differ across tasks. For example, they found hemispheric differences in schizophrenia during a recognition memory test (worse performance for right hemisphere-related face recognition than for left hemisphere-related word recognition) but no hemispheric differences during a covert orienting of visual attention task. In STUDY 1, by comparing the performance and neural activities for left and right motion stimuli directly, it will be determined if there is lateralized dysfunction of

motion processing in schizophrenia. To best of our knowledge, this examination on neural correlates of motion-related lateralized dysfunction has not been done before either due to the centrally-presented motion stimuli or lack of necessary neuroimaging techniques.

The task used for STUDY 1 was similar to that used by Chen (Chen et al., 2003): subjects were instructed to do a simple motion direction detection task during which they only needed to tell the direction of a motion grating and only needed perceptual motion information to perform the task without needing to judge the speed of the stimuli. Also, only slow velocity stimuli (5 deg/sec and 10 deg/sec) were utilized since previous studies have shown contrast information could be utilized to make velocity judgment for fast velocity stimuli since fast velocity stimuli have lower contrast than slow velocity stimuli (Pantle, 1978). Another important manipulation in STUDY 1 is to make the target's motion direction (requiring response) opposite and less frequent than the non-target's motion direction (not requiring response) to get a strong oddball effect. By comparing the behavior and neural responses of this oddball effect between groups, we will be able to determine if schizophrenia patients have a deficit on target detection and the neural correlates of this dysfunction.

In summery, STUDY 1 will provide complementary evidence of normal motion perceptual processing in schizophrenia and answer the question whether there are lateralized differences on motion stimulus processing in schizophrenia. The following hypotheses will be tested: (1) schizophrenia patients will show similar performance and neural activities as normal people. (2) There will be no lateralized difference in schizophrenia.

Methods

Participants

Thirteen chronic outpatients with DSM-IV (American Psychiatric Association, 1994) schizophrenia (Mean Age=43 yrs; SD=8; range=26-55; 6 females) and 13 healthy (Mean Age=41 yrs, 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 (11 on atypical and 2 on typical) for >8 weeks prior to participation. A host of previous studies suggest that visual processing deficits observed in schizophrenia are not associated with antipsychotic medication treatments (see, e.g., Butler et al., 2007, for a brief discussion). After the study, participants were paid $15/hr for participation. The UGA Institutional Review Board approved this study and participants provided informed consent prior to testing.

Stimuli and Procedure

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. A centrally-located fixation cross was visible throughout testing; subjects were instructed to remain fixated on this cross throughout testing. The relevant visual stimulus was a vertical grating (20 cd/m^2 against a 0.1 cd/m^2

background) with its spatial luminance (100% depth) modulated by a sinusoidal waveform (spatial frequency of 0.5 cycles/deg; whole grating occupied 2.5 × 3 deg of visual angle. see Figure 1). The gratings when they appeared were centered 5 deg to the left or right of central fixation. Each trial started with a 1500ms (+/- 150ms) fixation period. The grating randomly appeared either to the left or right of fixation. The grating bars moved horizontally (via temporally modulating the bars), either towards or away from fixation, at either 5 or 10 deg/sec for the 500 ms of their presentation (although the grating itself remained in the same spatial location during a trial). Subjects were instructed to respond with a key press when the gratings moved away from fixation (25% of trials). Each participant completed 640 trials (320 trials for each differential speed; half in each direction).

EEG Recording. EEG data were measured using a 256-channel Geodesic Sensor Net and NetAmps 200 amplifiers (Electrical Geodesics Inc.; EGI, Eugene, OR). Recordings were referenced to the vertex sensor (Cz). As is standard with high input impedance amplifiers like those from EGI, sensor impedances were below 50 kΩ (the EGI manufacturer recommended value when using high input impedance amplifiers). Data were analogue-filtered from 0.1-100 Hz, digitized at 500 Hz, stored on disk for later off-line analysis, and recorded continuously throughout the testing. Horizontal eye movements were monitored through eye channels.

Behavioral Data Analyses

The d-prime, response bias and reaction time were calculated for each moving speed and for each group.

EEG Data Analyses

Raw data were checked for bad channels (less than 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 1-50 Hz (12 db/octave rolloff, zero-phase). Eye blink and cardiac artifact correction was achieved by using the ICA toolbox in EEGLAB 4.515 (DeLorme and Makeig, 2004) under Matlab (Version 7.0, MathWorks, Natick, MA).

Only the visual event-related potentials (VERPs) elicited by the non-target events (moving gratings towards center) without a key press response (correct rejections) and target events (moving gratings away from center) with a key press response (correct detection) were included in the analyses. The events trials with an eye movement to the peripheral target were removed from analysis. Individual trials of 800 ms duration (beginning 200 msec before event onset) were averaged separately for nontargets and targets. Trials with activity greater than 75 μV were automatically eliminated from further processing. Grand averages were baseline corrected using the 200 ms pre-event period.

Two approaches were used to evaluate VERP responses to the grating stimuli. First, frequency (spectral power) characteristics of the VERPs were assessed. The averaged response for each condition for each subject was submitted to a 125-sample moving window (corresponding to 250 msec, resulting in ±125 msec time uncertainty for each window). A window was created for each sample point, and each window was multiplied by a 125-sample Hanning filter. The real and imaginary parts of the Fourier components were then estimated for each window for each individual sensor. Spectral power was determined from the real parts of

the Fourier components for each frequency step and each shifted time window leading to a time-frequency representation of the data with 4 Hz resolution. Spectral power values for sensors over the back half of the head were then averaged within-subjects, and were used to create time-frequency plots (see Figure 2). Differences between schizophrenia and healthy subjects' time-frequency representations were created (see Figure 2), which revealed two clear time ranges of between-groups differences on spectral power (one near 200 ms and one near 400 ms post-stimulus-onset). To quantify between-groups differences at these time points, the mean spectral power for each subject from 1-8 Hz was averaged for a 20 ms time window centered on the peak latency of each of these spectral power differences.

The second approach used to evaluate VERP responses to the grating stimuli involved more traditional component latency and amplitude quantification. 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 components in the GFP plots for all subjects in all conditions were the P1, N1, P2 and N400 (see Figure 3). The latency for the P1, N1 and P2 component for each condition were determined from the peak in the GFP plots. The magnitudes of the P1 and N1 in μV were determined based on differences between maximum positive and maximum negative potentials (averaged over 5 sensors that included and surrounded this peak, see Figure 4) at the peak latency of the component (±4 ms). The magnitudes of the P2 in microvolts were determined based on maximum positive voltage (averaged over 5 sensors that included and surrounded this peak, see Figure 4) at the peak latency (±4 ms). The magnitudes of the N400 difference between

target and non-target waveforms (target minus nontarget) in microvolts were determined based on maximum negative voltage (averaged over 15 sensors that best captured the component, see Figure 5) averaged from 400ms to 500ms following stimulus onset.

After VERP analyses calculated on voltage data at the sensors, we used L2 minimum norm (Hämäläinen & Ilmoniemi, 1994) to estimate brain regions involved in determining the brain regions accounting for between-groups differences on each component observed in the sensor space data. For the minimum norm approach, the source configuration is fixed *a priori* (fixed source locations are specified on the surface from which EEG signals emanated; e.g., the cerebral cortex). Given the measured data, source strength values are estimated for each location at each time point. In BESA 5.1, 713 locations are evenly distributed on the surface of a smoothed standard MRI of the brain. At each location, sources are located 10% and 30% below the cortical surface (for a total of 1426 sources). The source used at each location in the final analyses is the one with the largest magnitude.

Results

Behavioral Results

A Group (schizophrenia, healthy) by grating speed (5 deg/s and 10 deg/s) by stimulus location (left, right) repeated-measures ANOVA was used to test for differences on d-prime, response bias, and reaction time.

For d-prime, the main effect of Group, $F(1,24)=12.7$, $p=.002$, was significant. There were no other significant effects involving group membership. There were no significant effects involving group membership on either response bias or reaction time. On d-prime, healthy

participants (M=4..1, SD=0.3) were better than schizophrenia patients (M=3.2, SD=0.3) at detecting target events.

EEG Results

There was no difference between groups on total usable trials for non-targets (schizophrenia M=453, SD=31; healthy M=463, SD=19) and targets (schizophrenia M=147, SD=23; healthy M=156, SD=5).

Time-Frequency Results. A Group (schizophrenia, healthy) by Grating speed (5 degree/s and 10 degree/s) by Stimulus location (left and right) by Event type (target and non-target) repeated-measures ANOVA was used to test for two FFT components of interest (early and late). For the early (200 ms) FFT component, there were only significant main effects of group, $F(1,24)=12.0$, $p=.002$, with schizophrenia patients (M=5.4 μV, SD=0.8) having larger responses than healthy subjects (M=4.4 μV, SD=0.8), and of event type, $F(1,24)=6.8$, $p=.016$, with subjects having larger responses to targets (M=5.0 μV, SD=0.9) than to non-targets (M=4.8 μV, SD=1.0). For late (400 ms) FFT component, there were only significant main effects of group, $F(1,24)=13.8$, $p=.001$, with schizophrenia patients (M=4.6 μV, SD=0.8) having larger responses than healthy subjects (M=3.7 μV, SD=0.4), and of event type, $F(1,24)=15.6$, $p=.001$, with subjects having larger responses to targets (M=4.4 μV, SD=0.9) than to non-targets (M=3.9 μV, SD=0.8).

VERPs. A Group (schizophrenia, healthy) by Grating speed (5 degree/s and 10 degree/s) by Stimulus location (left and right) by Event type (target and non-target) repeated-measures ANOVA was used to test for differences on the latency and amplitude of the three early VERP

components (P1, N1, P2). For P1 latency, there was a significant main effect of event type, $F(1,24)=5.0, p=.034$, with subjects having faster responses to targets (M=90 ms, SD=7) than to non-targets (M=94 ms, SD=8). For P1 amplitude, there were only significant main effects of group, $F(1,24)=8.8$, $p=.007$, with schizophrenia patients (M=4.0 μV, SD=1.2) having larger responses than healthy subjects (M=2.8 μV, SD=0.8), and of event type, $F(1,24)=21.8$, $p<.001$, with subjects having larger responses to targets (M=3.7 μV, SD=1.2) than to non-targets (M=3.1 μV, SD=1.2). Inspection of the P1 topographies and minimum norm solutions (see Figure 4) indicate that the between-groups difference on P1 amplitude was accounted for by greater visual cortex activity contralateral to the visual field of stimulus presentation among the schizophrenia subjects.

For N1 latency, there were no significant effects involving group membership. For N1 amplitude, there were significant main effects of group, $F(1,24)=8.2$, $p=.009$, with schizophrenia patients (M=-5.2 μV, SD=1.1) having larger responses than healthy subjects (M=-3.9 μV, SD=1.2), and of event type, $F(1,24)=11.9$, $p=.002$, with subjects having larger responses to targets (M=-4.8 μV, SD=1.2) than to non-targets (M=-4.3 μV, SD=1.2). Inspection of the N1 topographies and minimum norm solutions (see Figure 4) indicate that the between-groups difference on N1 amplitude was accounted for by greater superior visual cortex activity in the hemisphere contralateral to visual field of stimulation among the schizophrenia subjects. There were no significant effects involving group membership on either P2 latency or P2 amplitude.

For the late component, a Group (schizophrenia, healthy) by Grating speed (5 degree/s and 10 degree/s) by Stimulus location (left and right) repeated-measures ANOVA was used to test for

differences on the N400 (target minus nontarget) amplitude differences. There was only a significant main effect of group, $F(1,24)=6.0$, $p=.022$, with schizophrenia patients (M=-0.3 μV, SD=0.2) having a smaller difference between target and nontarget responses than healthy subjects (M=-0.6 μV, SD=0.4). Inspection of the N400 topographies and minimum norm solutions (see Figure 5) indicate that the between-groups difference on N400 difference amplitude was accounted for by greater superior parietal cortex activity among the healthy subjects.

Relationships Between Behavior and Brain Activity

Pearson correlations were used to investigate relationships between behavioral responses (d-prime) and brain activity measures that differentiated the groups (FFT power, P1/N1 amplitude and N400 amplitude difference). The only significant correlations involved the N400 amplitude difference (see Figure 6). For schizophrenia patients, the N400 amplitude difference was significantly correlated with d-prime, $r(13)=-0.6$, $p=.022$. This significant correlation showed that schizophrenia subjects had better target discrimination ability as N400 amplitude difference between targets and nontargets increased. This same correlation was not statistically significant for the healthy subjects (d-prime $r(13)=-0.2$, $p=.211$). Although the strength of these correlations was larger among schizophrenia patients, their magnitudes did not significantly differ between-groups, $0.9<|Z|<1.1$, $p>.05$.

Discussion

In STUDY 1, contrary to the first hypothesis, schizophrenia patients showed unexpected abnormal motion processing indicated by poor target detection performance. And this

compromised motion processing can't be easily attributed to early magnocellular pathway processing deficits (Kim et al., 2006) because we found enhanced early VERP components (P1 and N1) for schizophrenia patients. The enhanced P1 and N1 in schizophrenia were striking and inconsistent with previous studies in which reduced P1 and intact N1 were reported (Butler et al., 2007; Doniger et al., 2002; Foxe et al., 2001). For example, Foxe et al. (2001) presented schizophrenia and normal subjects with successively less fragmented line drawings of common objects and instructed subjects to press a key when they felt they could identify the objects. Recorded VERPs indicated there was no amplitude difference on the N1 component between groups but there was a smaller P1 in schizophrenia. This finding was replicated by a follow-up study using a similar task (Doniger et al. 2002).

One possible explanation for the surprising P1/N1 enhancement is that more specific activation of M-pathway neurons (peripherally as opposed to a centrally-presented moving stimulus) revealed that schizophrenia patients increase sensory amplification of motion signals, perhaps as an effort to enhance signal-to-noise ratio for stimulus processing relative to their constitutionally higher state of low frequency background brain activity in visual cortex (Clementz, Wang, & Keil, 2008).

Stronger early sensory amplification, however, did not lead to normal target detection response in schizophrenia reflected by impaired behavior performance and reduced N400 differences between target and non-target stimuli. In addition, strong associations between behavioral and brain indicators of target detection indicated that impaired performance among schizophrenia patients was a consequence of an inability to generate a neural correlate of target

detection (the N400 in superior parietal cortex) well after the initial registration of the motion stimulus.

Although both groups showed increased N400 for targets compared to non-targets, this occurred against the background of schizophrenia patients having larger N400s regardless of stimulus type. As a result, despite the presence of an 'oddball' effect among schizophrenia patients, their target to nontarget N400 ratio was considerable smaller than it was for healthy subjects (Healthy: 1.7; Schizophrenia: 1.1). Impaired target detection performance in schizophrenia, therefore, may have been due to inappropriately large signal amplification, regardless of stimulus type, resulting in a proportionately reduced ability to neurophysiologically differentiate targets from nontargets. The neural source of the N400 (Figure 5) was in superior parietal cortex which is part of neural network associated with target-related brain activation during visual oddball tasks (Ardekani et al., 2002) and attention-regulation associated with identifying task-relevant stimuli (e.g., Simons et al., 2002).

In summary, the present study indicates that schizophrenia patients have a difficulty with target detection that accounted for their behavioral deficiencies in this motion direction detection task. Consistent with Chen et al.'s (2004) hypothesis, this difficulty is not easily attributed to a problem with the earliest stages of visual motion processing. The patients demonstrated a difficulty generating a target-specific parietal cortex response, regardless of stimulus location, that was highly correlated with subsequent behavioral performance.

These results, therefore, suggest that schizophrenia patient may have a stimulus classification difficulty during motion detection tasks that is independent of any difficulty with

generating the proper neural response to motion stimuli at the earliest levels of stimulus processing.

Chapter 3 STUDY 2

Introduction

STUDY 2 was conducted to reevaluate motion processing in a velocity discrimination task by using high time resolution EEG to measure the neural correlates of this ability among schizophrenia patients. The velocity discrimination task has been widely used as a straightforward means for assessing motion analysis (see Nakayama, 1985) that is closely related to actual smooth pursuit abilities (Kowler & McKee, 1987). Previous behavioral studies have demonstrated abnormal velocity discrimination in schizophrenia (Chen et al. 1999a; Chen et al. 1999b; Clementz, McDowell, & Dobkins, 2007).

Chen et al. (1999a) investigated motion perception in schizophrenia by measuring contrast sensitivity for velocity discrimination. In their experiment, subjects were presented two consecutive moving gratings with a short interval (500 ms) between gratings and were required to report which of two gratings was moving faster. The test speed was randomly picked from 5 to 15 degree/sec. The results showed schizophrenia patients had significantly higher thresholds than normal controls for the discriminating velocity differences between the two stimuli.

To strengthen this finding, Chen et al. (1999b) compared task performances between schizophrenia patients, their first-degree relatives, and normal subjects using the same velocity discrimination task while controlling two confounding non-velocity cues: position and contrast. Previous studies had shown that at slow velocities, position information is utilized to make velocity judgments (McKee, 1981; Nakayama & Tyler, 1981); at fast velocity, however, contrast information is utilized to make velocity judgments since fast velocity stimuli have lower

contrasts than slow velocity stimuli (Pantle, 1978). During the experiment, Chen et al. eliminated the position and contrast cues by randomly varying the presentation time and contrast of the moving gratings. The results indicated that velocity discrimination thresholds in schizophrenia and their relatives were still significantly higher at slow and fast velocity compared to the normal group.

Combined with first study, therefore, Chen (1999a; 1999b) suggested there was a primary motion perception deficit in schizophrenia. Our group (Clementz, McDowell, & Dobkins, 2007) replicated this deficit of compromised speed discrimination in schizophrenia by using smooth pursuit-like stimulus (moving dot stimuli). During the task, subjects were instructed to make a speed judgment between base speed (12 or 24 degree/sec) and test speed. As expected, higher speed discrimination thresholds in schizophrenia were found and indicated that schizophrenia patients had abnormalities of motion perception even when using smooth pursuit-like stimuli.

STUDY 2 will build upon and extend the design of Clementz et al. (2007) by directly measuring brain activity during the velocity discrimination task. Two important issues specifically related to velocity discrimination among schizophrenia patients will be investigated. Firstly, compared to a simple motion direction task like was used for STUDY 1, it is necessary to evaluate the differences in neural activity during velocity discrimination between paired stimuli (velocity discrimination tasks usually involve comparisons between two paired events). With the behavior measurements utilized in previous studies, it is impossible to tell whether neural activity differences occur in relation to both, or only one, of the stimulus presentations on an individual trial. Additional, like for STUDY 1, it is impossible to tell, without high temporal

resolution brain imaging data, whether abnormalities in neural processing of motion information occurs early or late among schizophrenia patients. By examining the VERPs associated with each motion stimulus separately, we will determine when neural abnormalities arise among schizophrenia patients that lead to difficulties with velocity discrimination judgments.

Secondly, during a velocity discrimination task, subjects must keep information about a first stimulus "in mind" for comparison with the second stimulus. Therefore, it is important to consider whether higher-level cognitive factors (e.g. working memory) could account for group differences on motion processing. Avila et al. (2006) suggested that initial velocity perception may be unaffected in schizophrenia, and that schizophrenia patients' problems with pursuit may "reflect an inability to accurately generate, store, and/or access these 'remembered' velocity signals" (p. 599). In addition, schizophrenia patients have working memory impairments that are modality independent and may be manifest at brief delay intervals, although typically not as short as the 500 ms interval we will use in STUDY 2 (Lee & Park, 2005). In order to fully evaluate this high level confounding factor, we will determine whether there are between-group differences in memory-related activation by evaluating VERP components and corresponding neural sources in relation to both standard and test stimuli.

It will be useful and necessary in the current study, therefore, to assess whether higher level cognitive control rather than basic perceptual abilities determines group differences in motion perception. With the help of high time resolution EEG, two aspects of velocity discrimination performance will be assessed separately: (1) initial motion perceptual information processing (2) high order cognitive processing involved in the velocity discrimination phase (probably

involving working memory). Based on previous results, and the results of STUDY 1, the following hypotheses will be tested: (1) schizophrenia patients will show higher velocity discrimination thresholds than normal persons; (2) schizophrenia participants will show a late stage dysfunction indicated by normal early VERPs and abnormal late VERPs; (3) this late-stage motion processing deficit will be indicated by reduced activity in areas beyond V5.

Methods

Participants

Sixteen chronic outpatients with DSM-IV (American Psychiatric Association, 1994) schizophrenia (Mean Age=43 yrs; SD=8; range=26-55; 6 females) and 15 healthy persons (Mean Age=41 yrs, SD=8; range=27-54; 7 females) participated in this study. The screening and interview process were same as for STUDY 1. All participants were right-handed and had normal or corrected-to-normal vision. All patients were clinically stable (Global Assessment of Functioning M=34, SD=4) on antipsychotic medications (12 on atypical and 2 on typical) for >8 weeks prior to participation. After the study, participants were paid $15/hr for participation. The UGA Institutional Review Board approved this study and participants provided informed consent prior to testing. Three participants (2 healthy, 1 schizophrenia) did not meet a minimal performance criterion of 60% correct and were not used in data analysis.

Stimuli and Procedure

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. A centrally-located diamond was visible throughout testing; subjects were instructed to remain fixated on this diamond throughout

testing. The relevant visual stimulus was a vertical grating (20 cd/m^2 against a 0.1 cd/m^2 background) with its spatial luminance (100% depth) modulated by a sinusoidal waveform (spatial frequency of 0.5 cycles/deg; whole grating occupied 2.5 × 5 deg of visual angle. see Figure 7). The gratings, when they appeared, had their inside edge at central fixation. To simulate motion, the grating bars moved horizontally (via temporally modulating the bars) away from fixation at the appropriate velocity for the 500 ms of their presentation (although the grating itself remained in the same spatial location during presentation). A standard 2-alternative forced-choice design was used (see Clementz, McDowell, & Dobkins, 2007). Each trial consisted of a "standard" speed (10 degree/sec) and a "test" speed that randomly differed from the standard by –30%, -20%, -10%, 0%, 10%, 20%, 30% [differential speed = (test speed – standard speed)/standard speed]. A trial began with the central fixation diamond. After a brief time interval, the grating randomly appeared either to the left or right of fixation for 500 msec. After a 500 ms delay, with only the central fixation diamond visible, a second grating was displayed for 500 ms. At the end of each trial, subjects reported which of the two gratings they judged was moving faster. No feedback was provided on response accuracy. The presentation order of the two types of gratings (standard, test), location (left, right), and the speed of the test stimulus was randomized across trials. Each participant completed 420 total trials (60 trials for each differential speed; half in each direction), meaning that they viewed 840 total moving gratings.

EEG Recording. EEG data were measured using a 256-channel Geodesic Sensor Net and NetAmps 200 amplifiers (Electrical Geodesics Inc.; EGI, Eugene, OR). Recordings were

referenced to the vertex sensor (Cz). As is standard with high input impedance amplifiers like those from EGI, sensor impedances were below 50 kΩ (the EGI manufacturer recommended value when using high input impedance amplifiers). Data were analogue-filtered from 0.1-100 Hz, digitized at 500 Hz, stored on disk for later off-line analysis, and recorded continuously throughout the testing.

Behavioral Data Analyses

For each test speed, the percentage of trials for which the subject perceived the test speed as faster than standard speed was calculated (from 0% to 100%) and fit with a cumulative normal function using probit analysis (Clementz, McDowell, & Dobkins, 2007; Finney, 1971; McKee et al., 1985) to obtain a speed discrimination threshold (threshold equals half the difference in differential speeds corresponding to the 25% and 75% levels of the psychometric function). The "bias" (the percent speed difference yielding 50% reports of test speed being faster than the standard) was also calculated for each subject.

EEG Data Analyses

Raw data were checked for bad channels (less than 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 1-50 Hz (12 db/octave rolloff, zero-phase). Eye blink and cardiac artifact correction was achieved by using the ICA toolbox in EEGLAB 4.515 (DeLorme and Makeig, 2004) under Matlab (Version 7.0, MathWorks, Natick, MA). Trials with activity greater than 75 μV were automatically eliminated from further processing.

The same two approaches as were used in STUDY 1 were used to evaluate VERP responses to the grating stimuli. First, the averaged response for each condition for each subject was submitted to 50-sample Hanning window (corresponding to 200 ms, resulting in ±100ms time uncertainty for each window). A window was created for each sample point, and each window was multiplied by a 50-sample Hanning filter. The real and imaginary parts of the Fourier components were then estimated for each window for each individual sensor. Spectral power was determined from the real parts of the Fourier components for each frequency step and each shifted time window leading to a time-frequency representation of the data with 5 Hz resolution. Spectral power values for sensors over the back half of the head were then averaged within-subjects, and were used to create time-frequency plots (see Figure 8). Differences between schizophrenia and healthy subjects' time-frequency representations were created (see Figure 8), which revealed two clear time ranges of between-groups differences on spectral power (one near 200 ms and one near 300 ms post-stimulus-onset). To quantify between-groups differences at these time points, the mean spectral power for each subject from 1-10 Hz was averaged for a 20 ms time window centered on the peak latency of each of these spectral power differences.

The second approach used to evaluate VERP responses to the grating stimuli involved more traditional component latency and amplitude quantification. 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 components in the GFP plots for all subjects in all conditions were the N1, P2, and

N300 (see Figure 9). The latency for the N1, P2 and N300 component for each condition were determined from the peak in the GFP plots. The magnitudes of the P2 in microvolts were determined based on maximum positive voltage (averaged over 5 sensors that included and surrounded this peak) at the peak latency (±4 ms). The magnitudes of the N1 and N300 in microvolts were determined based on maximum negative voltage (averaged over 5 sensors that included and surrounded this peak) at the peak latency (±4 ms). After VERP analyses calculated on voltage data at the sensors, we used L2 minimum norm (Hämäläinen & Ilmoniemi, 1994) to estimate brain regions involved in determining the brain regions accounting for between-groups differences on each component observed in the sensor space data.

Individual trials of 800 ms duration (beginning 200 msec before target event onset) were averaged across left and right location since there were no VERP topographies difference between left and right stimuli (see Figure 10) Then to investigate influence of speed/presenting order and discrimination difficulty on motion processing separately, trials were averaged in two ways. Firstly, trials were averaged to six categories on the basis of different combination of speed and presentation order: (1) First presented standard speed (10 degree/s); (2) Second presented standard speed; (3) First presented slower speed (speeds differing from the standard by –30%, -20%, -10%); (4) Second presented slower speed; (5) First presented faster speed (speeds differing from the standard by 10%, 20%, 30%); and (6) Second presented fast speed. Secondly, paired stimuli from individual trials were averaged to four categories on the basis of velocity discrimination difficulty defined by velocity difference between target speed and standard speed, regardless of whether the standard or test came first: (1) speeds differing from the standard by

0%; (2) speeds differing from the standard by ±10%; (3) speeds differing from the standard by ±20%; (4) speeds differing from the standard by ±30%. Grand averages were baseline corrected using the 200 ms pre-event period.

Results

Behavioral Results

Schizophrenia subjects (M= 22.2%, SD=12) had significant higher speed discrimination thresholds than the healthy subjects (M= 15%, SD=5.1), $t(26)=2.07, p<.05$. The shallower psychometric function for the schizophrenia patients in Figure 11 reflects the poorer speed discrimination performance. There was not a group difference on "bias", the percent speed difference yielding 50% reports of test speed being faster than the standard, $t(26)=0.99, p=0.329$.

EEG Results

Time-Frequency Results. A Group (schizophrenia, healthy) by presentation order of the standard grating (first, second) by speed (slow, fast and standard) repeated-measures ANOVA (with Huyhn-Feldt adjusted degrees of freedom) was used to test for two FFT components of interest (early and late). For the early FFT component, there was only a significant main effect of Speed (fast M=4.3, SD=0.9; slow M=4.2, SD=0.9; standard M=4.1, SD=0.9), $F(2,52)=4.0$, $p=0.0325$, $\varepsilon=0.8$. Further analyses showed that the early FFT component power for the faster speed was higher than for the standard speed, $t(27)=2.4$, $p=.02$; the early FFT component power for the slower speed was also higher, but not significantly so, than the standard speed, $t(27)=1.4$, $p=0.17$. For late FFT component, there were significant main effects of Group (schizophrenia

M=3.4,SD=0.6; healthy M=2.9, SD=0.6), F(1,26)=4.3, p=0.0477; presentation order (first grating M=3.3, SD=0.9; second grating M=3.0, SD=0.6), F(1,26)=6.7,p=0.0155, and Speed (fast M=3.2, SD=0.7; slow M=3.1, SD=0.7; standard M=3.0, SD=0.7), F(2,52)=5.2,p=0.01, ε=0.8. Further analyses showed late FFT component power for fast speed was higher than standard speed, t(27)=3.1, p=.004, and late FFT component power for slow speed was also higher than standard speed, t(27)=2.5, p=0.02.

VERPs. Two repeated-measures ANOVAs were done separately on the VERPs from the two ways of averaging described in Methods section.

First, a Group (schizophrenia, healthy) by presentation order of the standard grating (first, second) by speed (slow, fast and standard) repeated-measures ANOVA (with Huyhn-Feldt adjusted degrees of freedom) was used to test for differences on the latency and amplitude of the three VERP components (N1, P2 and N300). For N1 latency, there was a significant main effect of Speed (fast speed M=146, SD=8; slow speed M=147, SD=9; standard speed M=149, SD=9), F(2,52)=3.9, p=0.0351, ε=0.8. Further analyses showed N1 latency for fast speed was shorter than standard speed, t(27)=-2.9, p=.007, and N1 latency for slow speed was also shorter, but not significantly, than the standard speed, t(27)=-1.8, p=0.08. For N1 amplitude, there were significant main effects of Speed (fast speed M=-3.9, SD=1.5; slow speed M=-3.8, SD=1.3; standard speed M=-3.6, SD=1.4), F(2,52)=4.0, p=0.0242, ε=1.0, and presentation order (first grating M=-3.4, SD=1.8; second grating M=-4.1, SD=1.9), F(1,26)=11.1, p=0.0026. Further analyses showed N1 amplitude for fast speed was higher than standard speed, t(27)=2.8, p=.009, and N1 amplitude for slow speed was also higher, but not significantly, than standard speed,

t(27)=1.7, p=0.1. For P2 latency, there was only a main effect of presentation order (first grating M=200, SD=12; second grating M=196, SD=13), F(1,26)=8.8, p=0.0065. For P2 amplitude, there was a significant main effect of presentation order, F(1,26)=5.2, p=0.0318, and a significant presentation order by group interaction, F(1,26)=6.0, p=0.0215. Further analysis showed that healthy participants (M=3.2, SD=1.8) had higher P2 amplitude than schizophrenia patients (M=2.6, SD=1.6) in response to the second grating. However, healthy participants (M=3.2, SD=1.8) and schizophrenia patients (M=3.2, SD=1.7) did not differ in P2 response to the first grating. Inspection of the P2 topographies and minimum norm solutions (see Figure 12) indicate that the between-groups difference on P2 amplitude was accounted for by greater bilateral inferior parietal cortex activity among the healthy subjects.

For N300 latency, there were significant main effects of Group (schizophrenia M=270, SD=12; healthy M=285, SD=20), F(1,26)=5.5, p=0.0271, presentation order (first grating M=289, SD=17; second grating M=266, SD=23), F(1,26)=44.26, p<0.0001, and speed (fast M=277, SD= 22; slow M=273, SD=19; standard M=283, SD=22), F(2,52)=3.55, p=0.0358, ε=1.0. Further analyses showed N300 latency for slow speed was faster than standard speed, t(27)=-2.5, p=.02. And N300 latency for fast speed was also faster, but not significantly, than standard speed, t(27)=-1.5, p=0.15. For N300 amplitude, there were significant main effects of Group (schizophrenia M=-2.2, SD=0.7; healthy M=-1.6, SD=0.6), F(1,26)=6.1, p=0.0205, and presentation order (first grating M=-2.0, SD=0.8; second grating M=-1.8, SD=0.7), F(1,26)=5.5, p=0.0267. Inspection of the N300 topographies and minimum norm solutions (see Figure 12) indicate that the between-groups difference on N300 difference amplitude was accounted for by

greater right inferior parietal cortex activity among the schizophrenia subjects.

Second, latency and amplitude differences of three VERP components (N1, P2 and N300) identified at four types of averaged trial based on the velocity difference between target speed and standard speed (0%, ±10%, ±20%, ±30%) were tested with Group (schizophrenia, healthy) by trial type (0%, ±10%, ±20%, ±30% difference) repeated-measures ANOVA (with Huyhn-Feldt adjusted degrees of freedom). There were no group by velocity difference interactions found for all three VERP components.

Relationships Between Behavior and Brain Activity

Pearson correlations were used to investigate relationships between behavioral responses (threshold) and brain activity measures that differentiated the groups (FFT power of late FFT component, P2 amplitude of second stimulus, N300 latency and amplitude; see Figure 13). For schizophrenia patients, there were only significant correlation between behavior and P2 amplitude of second stimulus ($r(14)=-0.48, p=0.043$). The same correlation was marginally statistically significant for the healthy subjects ($r(14)=-0.43, p=0.06$). The magnitude of this relationship did not differ between the groups, $Z=-0.15$, $p > .05$. This similar negative correlation between behavior threshold and P2 amplitude at second stimulus between groups indicated both healthy subjects and schizophrenia patients were better at identifying the motion speed difference as P2 amplitude of second stimulus increased. For healthy subjects, there were additional significant associations between behavior and late FFT power component ($r(14)=-0.53, p=0.026$), N300 amplitude ($r(14)=0.54, p=0.023$), N300 latency ($r(14)=-0.57, p=0.017$).

Discussion

In STUDY 2, consistent with the first hypothesis and previous studies (Chen et al., 1999a; Clementz, McDowell & Dobkins, 2007), schizophrenia patients showed higher velocity discrimination thresholds compared to healthy subjects. And consistent with the second and third hypotheses, schizophrenia patients showed normal early VERP (N1) for both the first and second presented moving stimuli but abnormal late VERP (P2) for the second presented moving stimulus, with neural sources for this component in inferior parietal cortex beyond MT (V5). In addition, strong associations between this abnormal P2 and higher velocity discrimination threshold indicated that impaired performance among schizophrenia patients was a consequence of late stage dysfunction. Again, this finding can't be attributed to early magnocellular pathway processing deficits (Kim et al., 2006) and supports the late stage deficit hypothesis (Chen et al., 2004).

The inferior parietal cortex is reportedly activated during higher level motion processing of salient stimuli (Claeys et al., 2003). Claeys et al. (2003) compared fMRI responses when subjects were instructed to detect motion from three types of stimuli: high salience moving gratings (high green/red saturation ratio with equal luminance), iso-salience moving gratings (equal green/red saturation ratio with equal luminance) and a control luminance-modulated archromatic moving grating. Results indicated MT was activated in all tasks, but only high relative salient gratings generated activation at bilateral inferior parietal lobule (IPL). Based on this finding, they suggested there were two motion systems in the human brain: a low-level 'energy-driven' system involved MT and a 'salience-driven' high-level system involved inferior parietal lobule (Claeys

et al., 2003). This specific high-level motion processing-related IPL activation was also seen in other tasks requiring high-level motion processing; for example, apparent motion (Claeys et al., 2003) and "motion standstill" stimuli (Federspiel et al., 2006). Relative salience of a stimulus can be modulated by exogenous factors (e.g. color saturation, Claeys et al., 2003) or endogenous factors (e.g. attention, Lu et al., 1999a). In the current study, the second moving stimulus during the velocity discrimination task drew more attention since the discrimination decision was made immediately after presentation of second grating. Enhanced attention in relation to the second stimulus relative to the first stimulus was evidenced by enhanced N1 amplitude to the second stimulus which was found for both schizophrenia patients and normal subjects. Therefore, reduced inferior parietal activity to the second stimulus at the time of P2 among schizophrenia patients may reflect abnormal processing of the salience (second) stimulus at high-level motion processing stage.

In addition to a lower IPL response at the time of P2, however, schizophrenia patients had a stronger N300 with a similar inferior parietal source. Although not previously reported in schizophrenia literature, this enhanced N300 has been observed during visual motion awareness (Haarmeier & Thier, 1998). For example, Haarmeier and colleagues instructed subjects to perform smooth pursuit eye movements to a moving target across a background image and report the moving direction of background image during pursuit. The moving speed and direction of background image was manipulated to generate two subjective motion perceptions: motion stationary and motion opposite the direction of the eye movement. Concurrently recorded VERP results showed significant N300 difference (with parieto-occipital negativity) between the two

subjective motion perceptions and suggested the N300 component was involving in visual motion awareness (Haarmeier & Thier, 1998). On the basis of this finding, the observed increased N300 (at inferior parietal cortex) among schizophrenia subjects in STUDY 2 may be a motion-related component that may play a complimentary role in velocity discrimination. On the one hand, the combination of reduced P2 and increase N300 in schizophrenia suggests that, in order to make reasonably accurate velocity discrimination decisions, schizophrenia patients might need to generate a late motion response in inferior parietal cortex to compensate for their reduced inferior parietal cortex response at the preceding (P2) stage. On the other hand, the fact that normal subjects showed much smaller N300 activity suggested they were able to make accurate velocity discrimination decisions by relying solely on stronger inferior parietal cortex activities during the P2 time period. Moreover, it seems unlikely that task difficulty is a parsimonious explanation for this difference between patients and controls because we didn't find group by task difficulty (different speed deviation from standard grating).

Another important finding in STUDY 2 was the habituation effect for both healthy subjects and schizophrenia patients indicated by smaller N1 amplitudes in relation to the standard speed for both healthy and schizophrenia subjects. This similarly reduced N1 across groups suggested all subjects were aware of the standard speed although we only explicitly required subjects to do velocity discrimination instead of memorizing the standard speed. Thus, this habituation effect could be a reflection of intact implicit memory for the frequent moving stimulus (standard speed) among the schizophrenia patients. Intact implicit memory in schizophrenia has been widely reported in various implicit memory tasks (e.g. word stem completion task, Kazes et al., 1999;

word priming task, Sponheim, Steele & McGuire, 2004), and is related to intact implicit learning in schizophrenia (Danion et al., 2001).

In summary, STUDY 2 indicates that schizophrenia patients have high-level motion processing deficits for high salience speed information that accounts for their elevated velocity discrimination thresholds. More specifically, motion processing was abnormal at the time of evaluation of motion information at second presented stimulus. The reduced inferior parietal cortex activity in schizophrenia suggested the deficits during velocity discrimination task were not due to the impaired low-level motion information processing (e.g. luminance) since MT itself may only involve processing of motion (Orban et al., 1998; Sunaert et al. 2000). Alternatively, this deficit may be related to a special kind of impaired arousal and orienting reaction to stimuli with high relative salience in schizophrenia (Federspiel et al., 2006). Additional studies will be needed to evaluate these possibilities.

Chapter 4 General Discussion

The experiments reported here show that schizophrenia patients have motion deficits indicated by impaired target detection in STUDY 1 and raised velocity discrimination thresholds in STUDY 2. These results extend the results of previous studies (Chen et al., 1999a; Clementz, McDowell, Dobkins, 2007) on motion deficits in schizophrenia by provide unique temporal information about brain activity associated with motion processing. In general, both studies showed late stage motion processing deficits in schizophrenia. However, with respect to the different tasks required in the two studies, schizophrenia patients showed different patterns of abnormal processing. In STUDY 1, schizophrenia patients showed impaired target detection performance related to abnormal late superior parietal cortex activity. In STUDY 2, schizophrenia patients showed impaired velocity discrimination performance related to reduced late inferior parietal cortex activity. The two impaired performance-related neural activity differences indicated that motion processing deficits in schizophrenia occurs at late stage, which is inconsistent with theory of early magnocellular pathway processing deficits (Kim et al., 2006).

The inconsistency between studies could be explained by a combination of different stimuli properties and task requirements. Firstly, steady-state flickering stimuli were used in Kim's study (Kim et al., 2006). Previous studies have shown steady-state flicker maximally activates low-level visual cortex with two major neural sources on primary visual cortex (V1) and motion sensitive area (MT/V5) (Di Russo et al., 2007). Activation beyond sensory cortex areas associated with visual flicker were much smaller or absent (Claeys et al., 2003; Sunaert et al., 1999), especially with regard to IPL activity found in current study which was not observed in

flicker-generated brain activity (Claeys et al., 2003). Secondly, during Kim's study, they only required subjects to passively look at the flickering stimuli without requiring any response while our studies required responses: target detection in STUDY 1 and velocity discrimination in STUDY 2. Therefore, combining these differences, our studies may tap the different, perhaps more elaborate, stages of motion processing compared to Kim's study (Kim et al., 2006).

Implications for smooth pursuit eye movements

Schizophrenia patients, when presented with unexpected moving targets, can have normal initial eye movement responses (Avila et al., 2006). Our brain activity data are consistent with such results because patients had at least normal-level VERPs in both STUDY 1 and STUDY 2. Taken together, these data suggest early sensory motion areas (including MT) are not likely to be involved in pursuit initiation deficits in schizophrenia. In addition, previous research has indicated that inappropriate expectation may play an important role in the abnormal pursuit performance among schizophrenia patients as evidenced by the results of "remembered pursuit tasks" (Avila et al., 2006). The inappropriately large amplification of initial motion signals observed in STUDY 1 provides a possible explanation for these expectation effects. During the smooth pursuit eye movement task, target information must be continually updated. Inappropriate amplification of current target motion signals may lead to incorrect anticipation/predication of subsequent target motion, and may cause the abnormal pursuit gain reported in schizophrenia (Ross et al., 1996). Moreover, the delayed neural response in inferior parietal cortex (N300) in schizophrenia observed in STUDY 2 may underlie the higher frequency 'catch-up' saccades reported schizophrenia (Radant & Hommer, 1992).

Potential limitations and future directions

In the present study, Electroencephalography was an appropriate tool for examining dynamic motion processing in schizophrenia. In order to complement and strengthen the research investigating motion deficits in schizophrenia, however, several issues merit further investigation and additional and alternative strategies could be used.

First, future studies should further evaluate neural correlates of motion processing during velocity discrimination tasks in first-degree relatives of schizophrenia patients. This would allow for a determination of whether the impaired late VERPs reported in present the studies could sever as either biological markers for schizophrenia risk or as co-familial traits for both schizophrenia patients and their first-degree relatives. Previous studies have shown both schizophrenia patients and their first-order relatives to have elevated velocity discrimination thresholds (Chen et al., 1999a).

Second, complimentary EEG investigations should be done among schizophrenia patients during the detection of the motion direction of random dot patterns, which requires global motion processing (Chen et al., 2003). In STUDY 1, we did not find reduced activities at the cortical level at the initial motion registration stage. This pattern could be different when we utilize the random dot design as opposed to using grating stimuli. Based on the impaired global motion processing deficits reported in Chen's study (Chen et al., 2003), we predict there would be abnormal late VERPs (decreased amplitudes) observed for simple random dot motion patterns. Again, accompanying EEG studies of first-degree relatives could also be important since Chen et al. (2005) reported impaired global motion integration only occurred in schizophrenia but not in

their first-degree relatives. Therefore, the accompanying EEG studies of first-degree relatives could identify the specific neural deficits in schizophrenia.

Third, comparing data acquired during similar tasks should be done for both medicated and unmediated schizophrenia patients to provide information about effects of antipsychotics on behavior and its mediating neural substrates. Finally, additional neuroimaging techniques (e.g. Diffusion Tensor Imaging) providing information about structural connectivity between regions assessing early and late stages of motion processing input would be useful are necessary to provide a better understanding of the nature of neural network dysfunctions underling the motion processing deficits observed in schizophrenia.

Conclusions and summary

By using behavioral measurements together with high time resolution EEG techniques, this study provided evidence that motion deficits in schizophrenia occurs at late stage in the processing stream (at or beyond V5). As a result, they significantly enhanced our understanding of the underlying neurophysiological mechanisms of motion deficits in schizophrenia. The pattern of motion dysfunction varied with tasks. In STUDY 1, schizophrenia patients showed impaired target detection associated with the late N400 component (at superior parietal cortex) and this deficit was significantly associated with behavioral performance. In STUDY 2, schizophrenia patients showed impaired velocity discrimination which was related to the abnormal processing of high salience stimuli (reduced P2 component at inferior parietal cortex in response to the second stimulus). These findings enrich the schizophrenia literature on motion dysfunction and clarify the ambiguity of previous studies.

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Figure 1. Example of motion grating used in STUDY 1 and schematic of the experimental procedure.

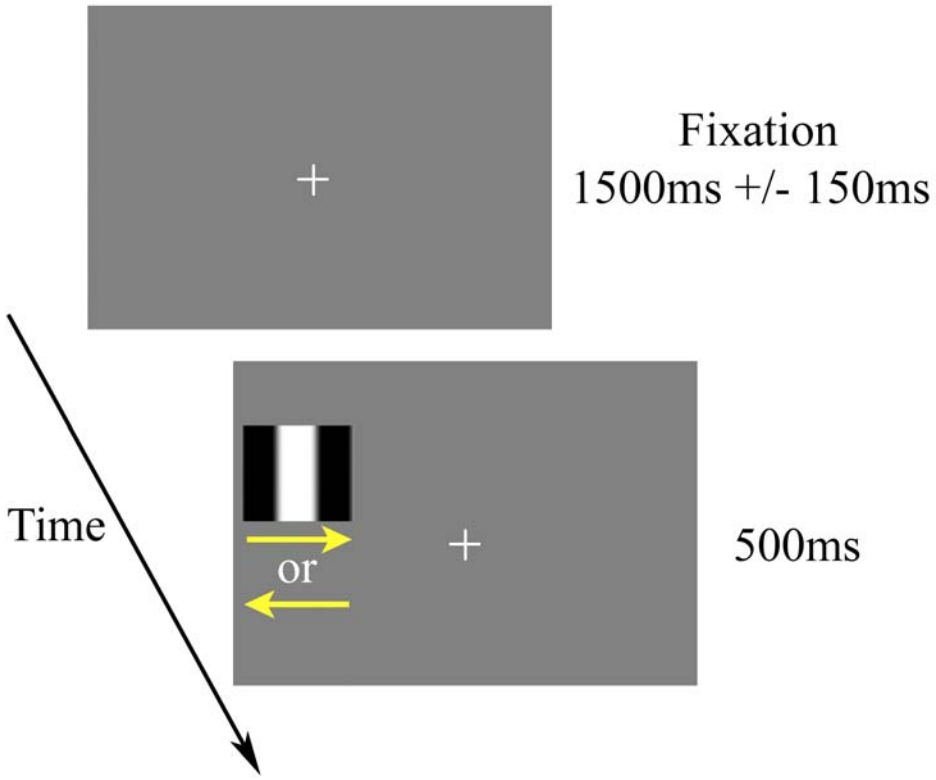

Fixation
1500ms +/- 150ms
Time
or
500ms

Figure 2. Time-frequency results of STUDY 1.

The top row of the figure shows time-frequency results for schizophrenia subjects (left) and healthy subjects (right). The bottom of the figure shows time-frequency results for the group difference.

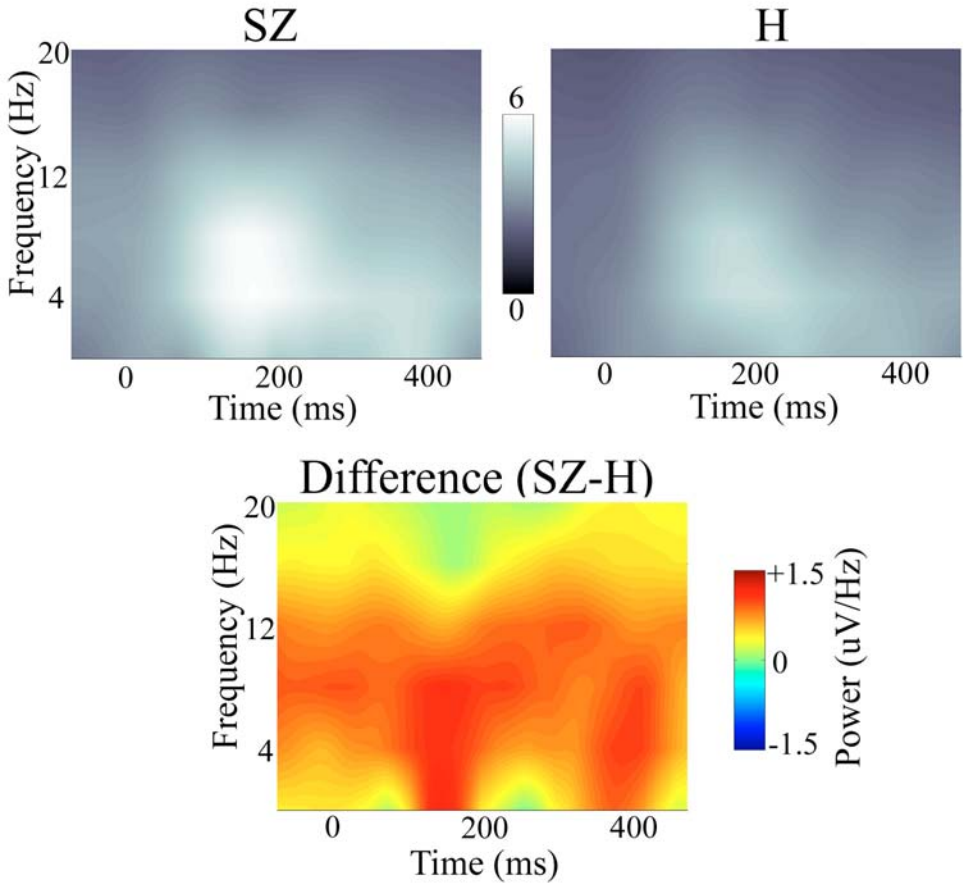

SZ
H
20
12
4
Frequency (Hz)
6
0
0
200
400
Time (ms)
Difference (SZ-H)
+1.5
0
-1.5
Power (uV/Hz)

Figure 3. The group-averaged voltage waveforms and eye movement waveforms for healthy subjects and schizophrenia subjects in study1.

Figures in the top panel demonstrate the group-averaged voltage waveforms for healthy subjects (black line) and schizophrenia subjects (red line). Waveforms are the mean of the response at ten electrode sites used for P1/N1/P2/N400. A red disc indicates the location of the ten electrode sites in the left hemisphere used for P1/N1/P2 to the stimulus presented in the right visual field. A blue disc indicates the location of the ten electrode sites in the right hemisphere used for P1/N1/P2 to the stimulus presented in the right visual field. A green disc indicates the location of the ten central electrodes used for the N400 difference between target and non-target stimuli. Figures in the bottom panel demonstrate horizontal eye movements and vertical eye movements in healthy subjects (black solid and dashed lines) and schizophrenia subjects (red solid and dashed lines) for stimuli presented to the left and right.

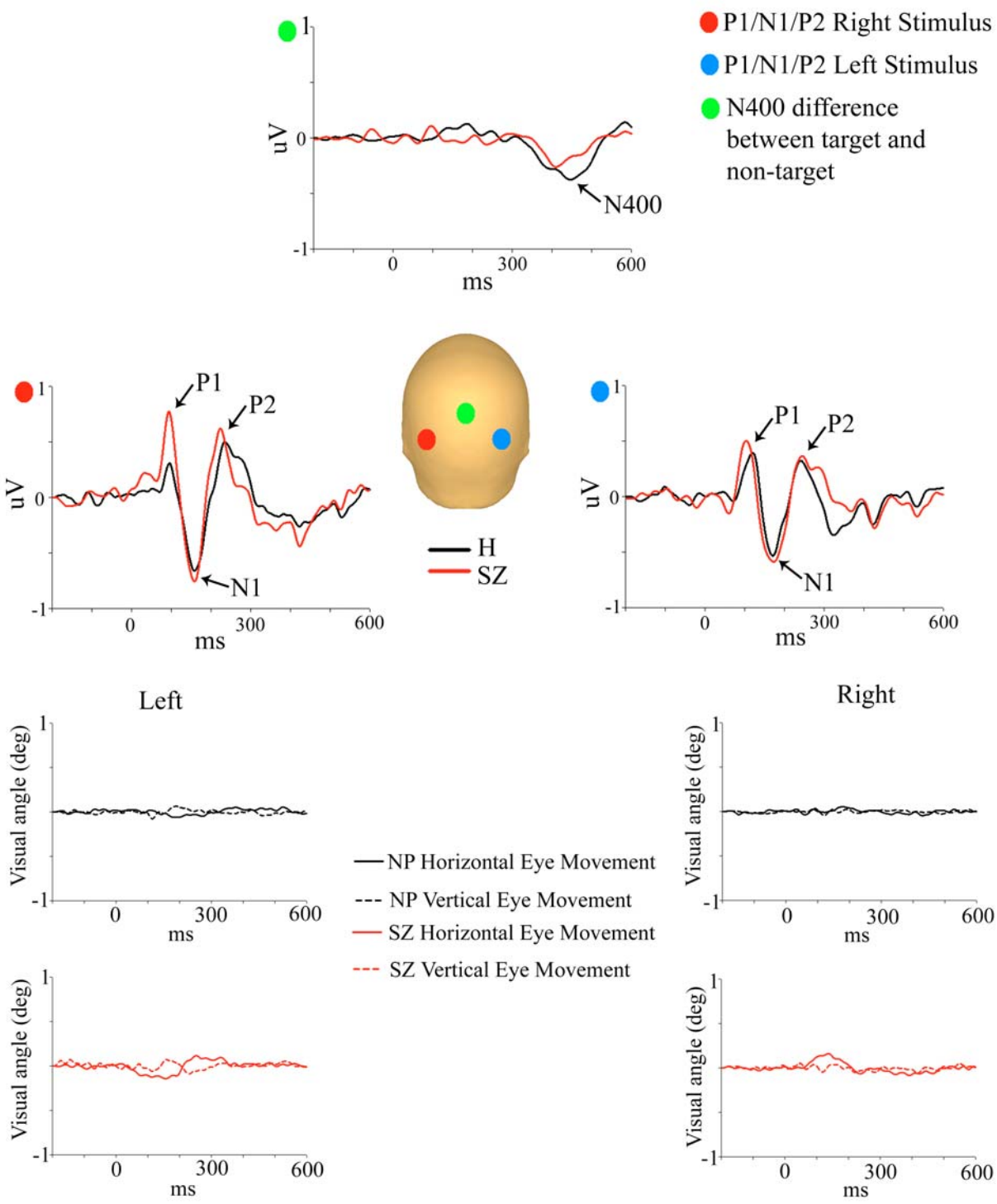

P1/N1/P2 Right Stimulus
P1/N1/P2 Left Stimulus
N400 difference between target and non-target
uV
ms
N400
P1
P2
N1
H
SZ
Left
Right
Visual angle (deg)
NP Horizontal Eye Movement
NP Vertical Eye Movement
SZ Horizontal Eye Movement
SZ Vertical Eye Movement

Figure 4. The voltage maps and minimum-norm solutions for group-averaged VEPs in STUDY 1.

The first two columns of the figure shows the head surface maps and minimum-norm solutions for grand average VEPs (P1/N1/P2) in schizophrenia subjects. The second two columns of the figure show the head surface maps and minimum-norm solutions for grand average VEPs (P1/N1/P2) in healthy subjects.

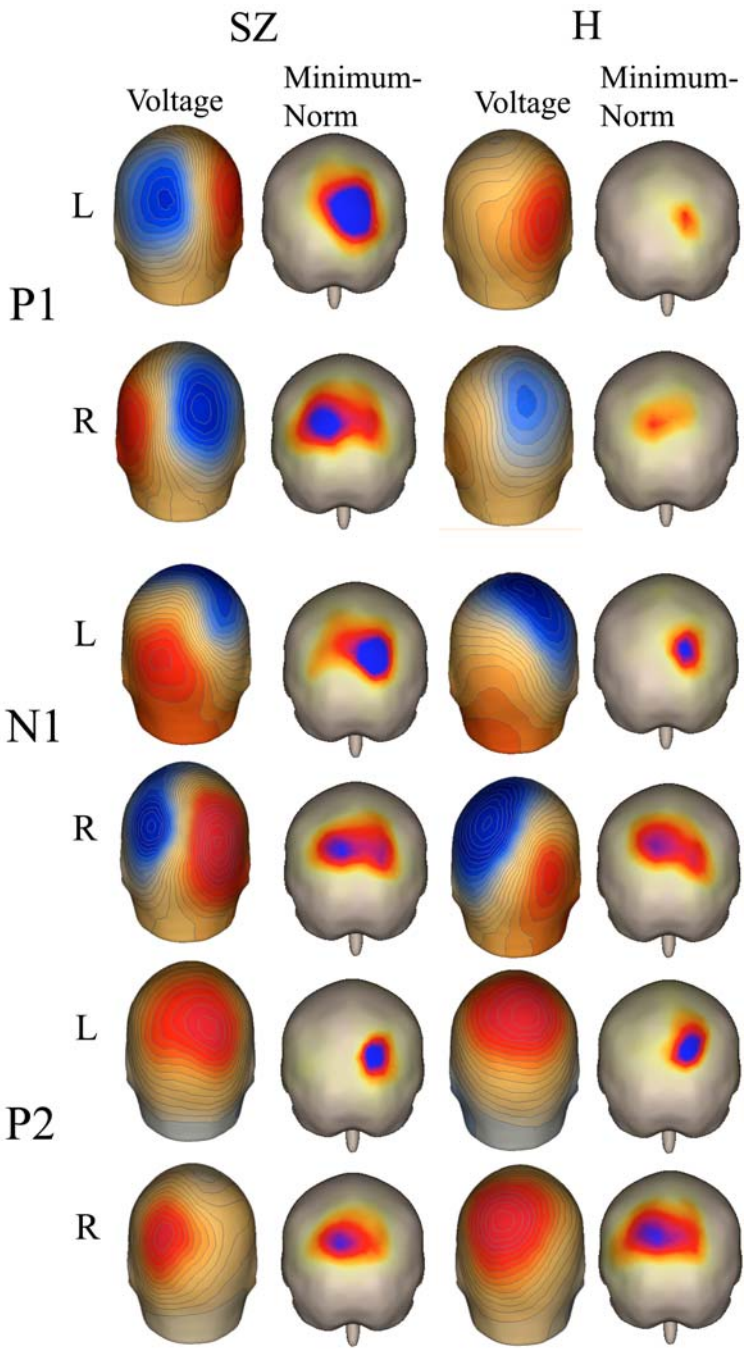

SZ
H
Voltage
Minimum-Norm
Voltage
Minimum-Norm
P1
L
R
N1
L
R
P2
L
R

Figure 5. The voltage maps and minimum-norm solutions for the N400 difference for each group in STUDY 1.

The top row of the figure shows the head surface map of the grand average N400 difference (target minus nontarget) for both healthy (left) and schizophrenia subjects (right). The bottom row of the figure shows the minimum-norm solution of the N400 difference in both groups (healthy: left; schizophrenia: right).

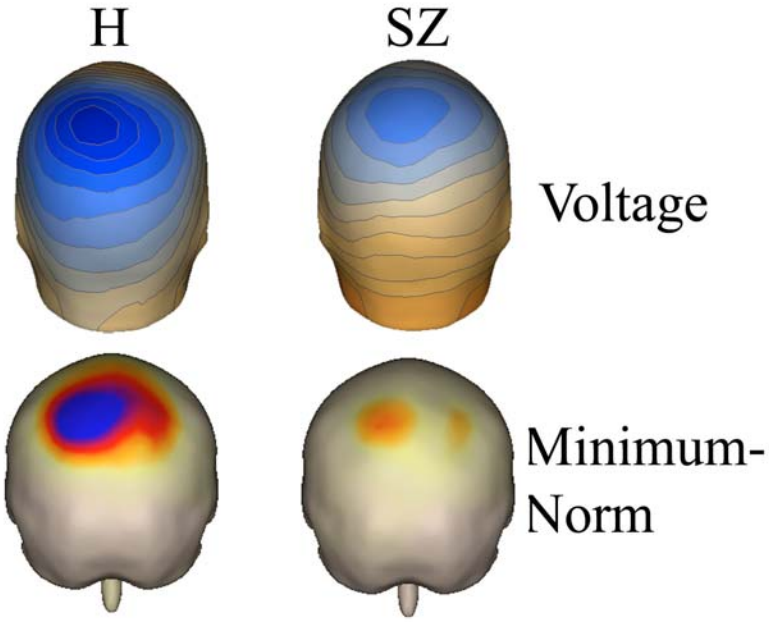

H
SZ
Voltage
Minimum-
Norm

Figure 6. Bivariate scatter plot of relationships between behavioral responses and brain activities in STUDY 1.

The plot shows the relationship between d-prime and VERP (N400) amplitudes for healthy (black dots) and schizophrenia (red dots) subjects. The best fitting regression lines are also included for both groups.

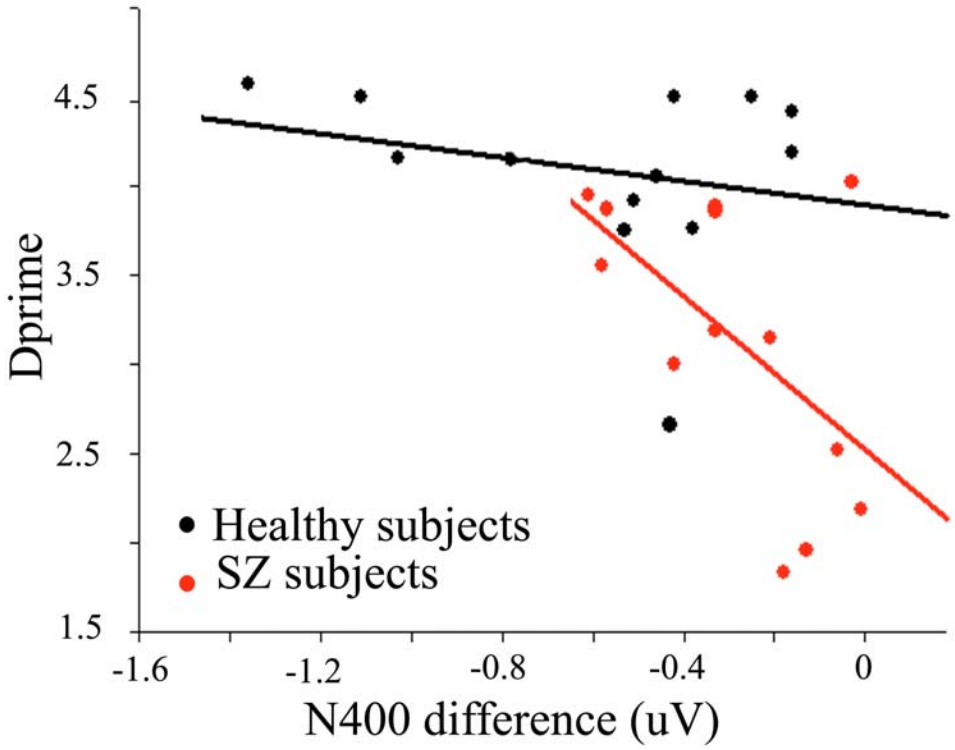

4.5
3.5
2.5
1.5
Dprime
Healthy subjects
SZ subjects
-1.6
-1.2
-0.8
-0.4
0
N400 difference (uV)

Figure 7. Example of motion grating used in STUDY 2 and schematic of the experimental procedure.

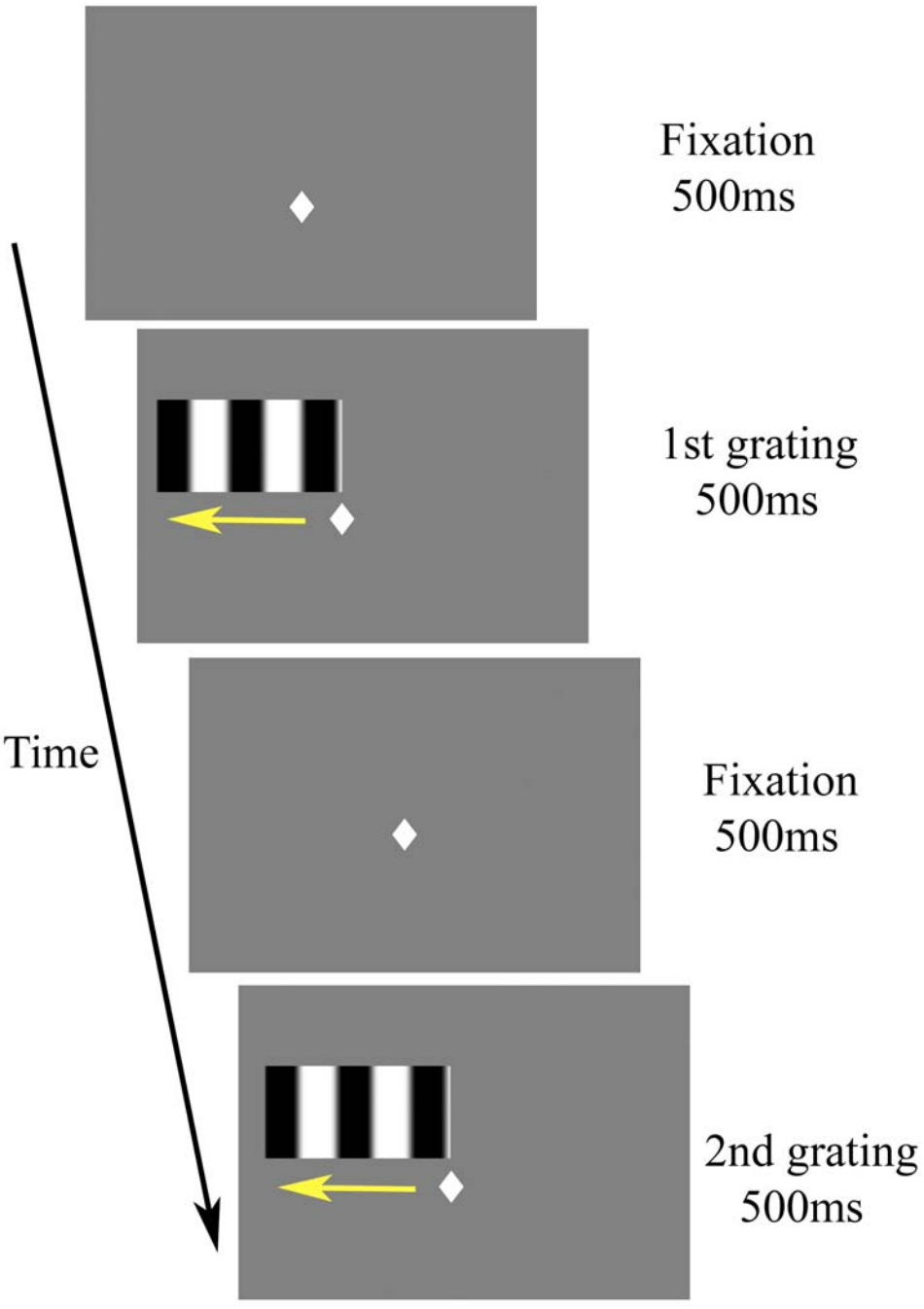

Fixation
500ms
1st grating
500ms
Time
Fixation
500ms
2nd grating
500ms

Figure 8. Time-frequency results of STUDY 2.

The top row of the figure shows time-frequency results for schizophrenia subjects (left) and healthy subjects (right). The bottom of the figure shows time-frequency results for the group difference.

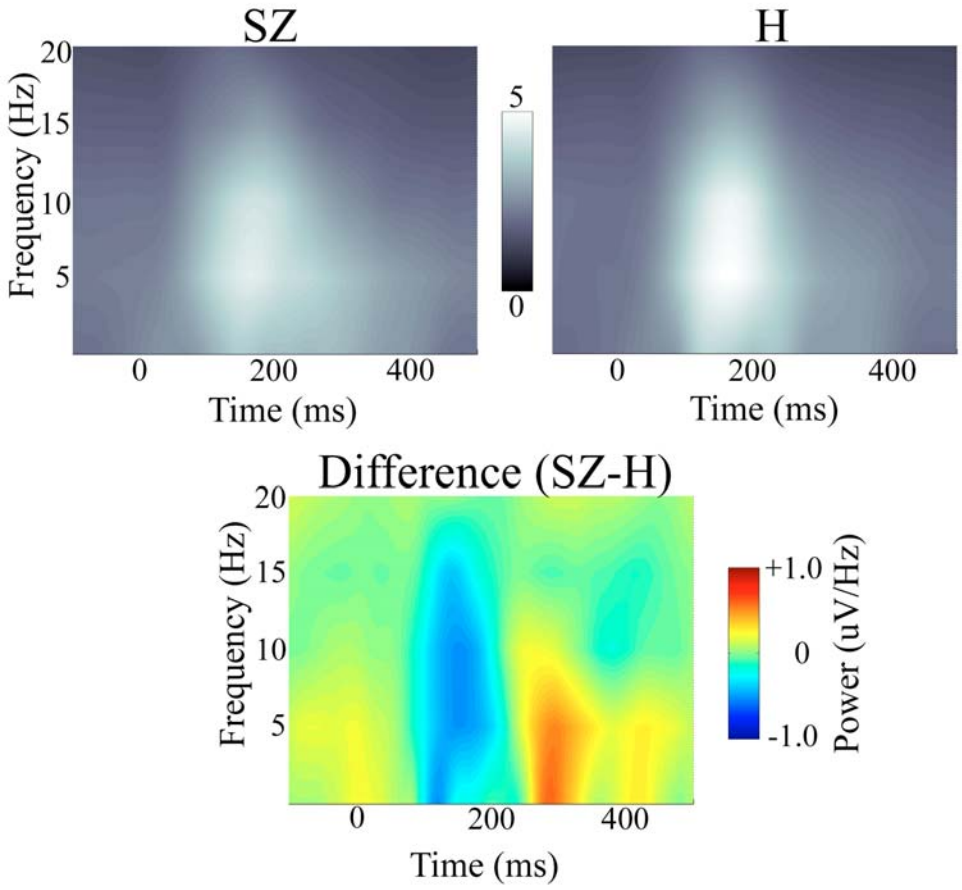

SZ
H
Frequency (Hz)
20
15
10
5
0
200
400
Time (ms)
5
0
Difference (SZ-H)
+1.0
0
-1.0
Power (uV/Hz)

Figure 9. The group-averaged voltage waveforms for healthy subjects (black line) and schizophrenia subjects (red line) in STUDY 2.

Waveforms represent the mean of the response at ten electrode sites used for N1/P2/N300. A green disc indicates the location of the ten central electrodes used for N1/P2/N300.

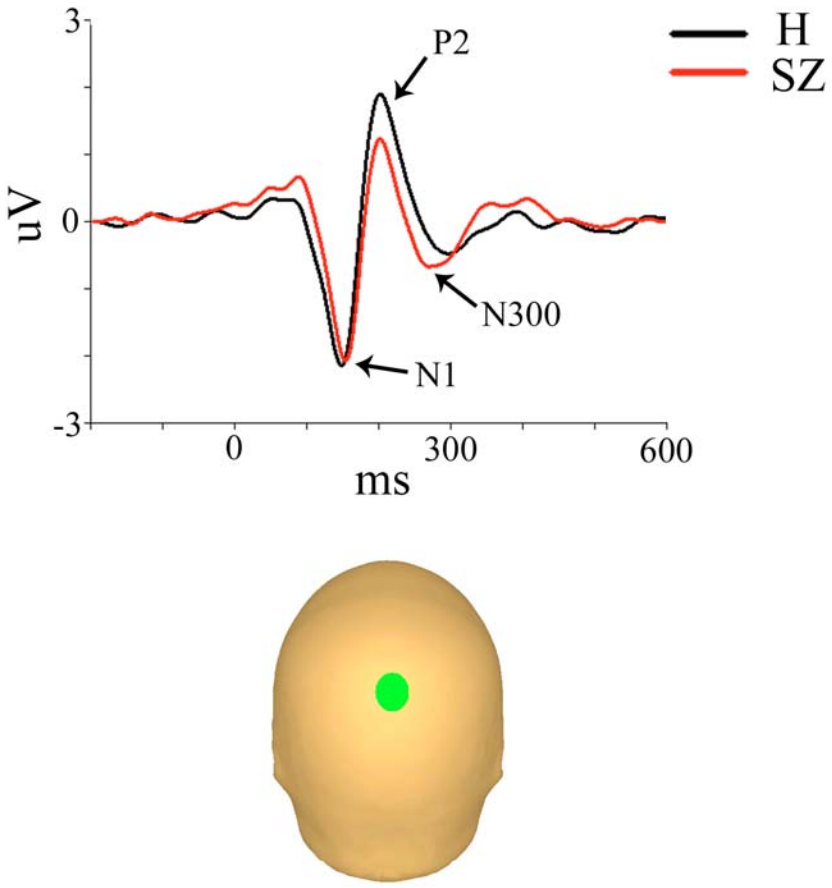

3
0
-3
uV
0
300
600
ms
P2
N1
N300
H
SZ

Figure 10. The voltage maps of group-averaged VEPs to left and right presented stimulus in STUDY 2.

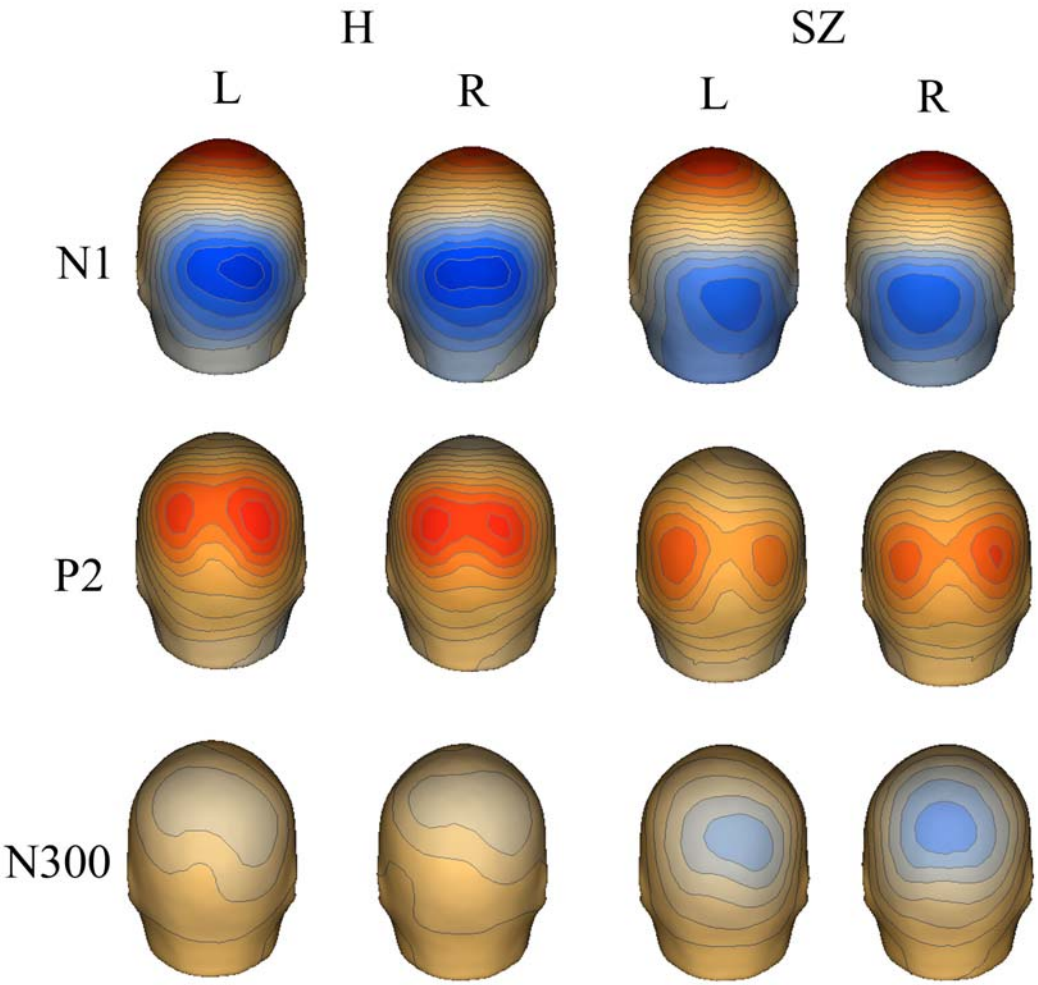

H
SZ
L
R
L
R
N1
P2
N300

Figure 11. Plot of the psychometric function for schizophrenia (red) and healthy (black) subjects for speed discrimination.

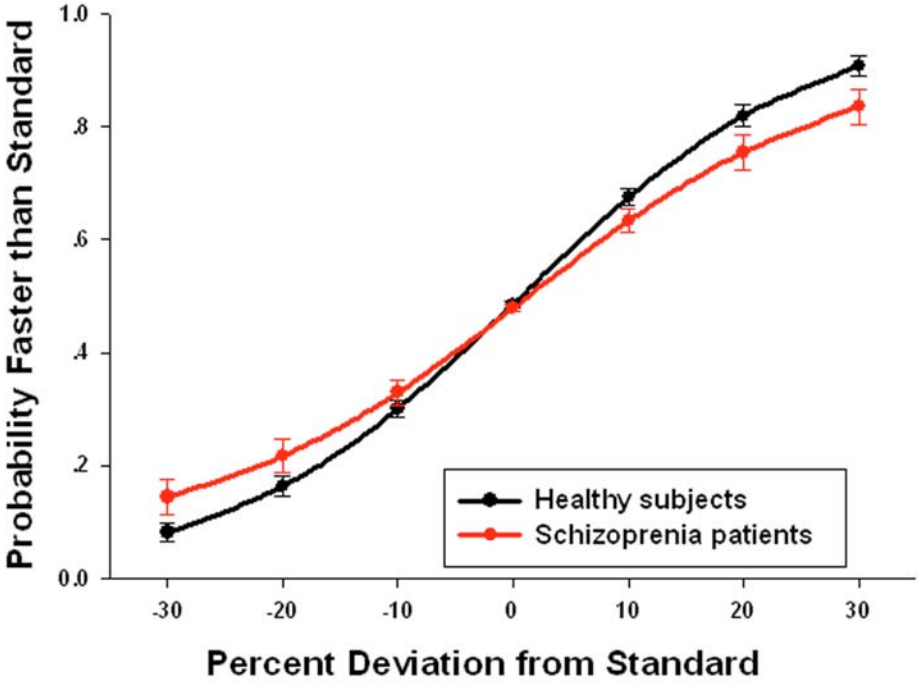

Probability Faster than Standard
1.0
.8
.6
.4
.2
0.0
-30
-20
-10
0
10
20
30
Percent Deviation from Standard
Healthy subjects
Schizoprenia patients

Figure 12. The voltage maps and minimum-norm solutions for group-averaged VEPs in STUDY 2.

The top portion of the figure shows the head surface maps of grand average VEPs (N1/P2) at first and second stimulus for schizophrenia subjects (left) and healthy subjects (right). For the above components, minimum-norm solutions were provided for only the P2 at second stimulus because it was the only VERP component having a group difference. The bottom portion of the figure shows the head surface maps and minimum-norm solutions of the grand average VERP (N300) across first and second stimulus for schizophrenia subjects (left) and healthy subjects (right).

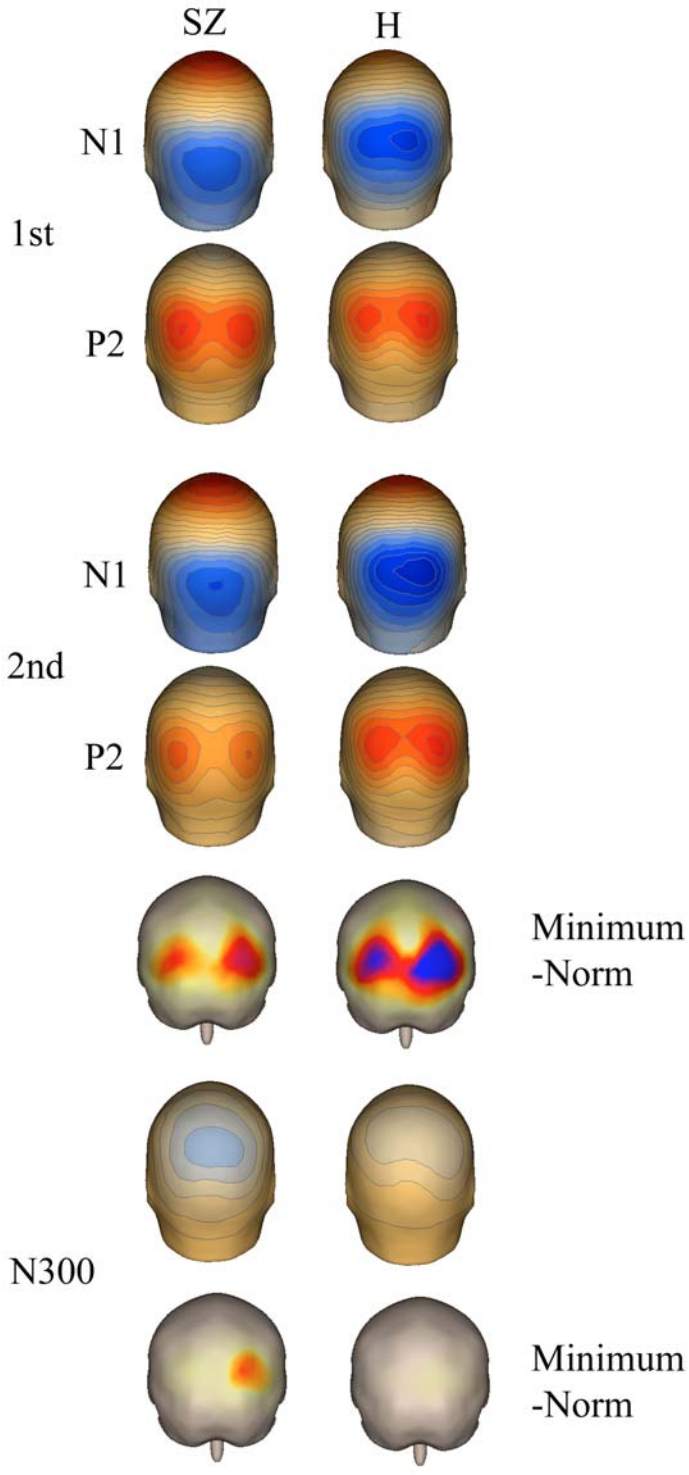
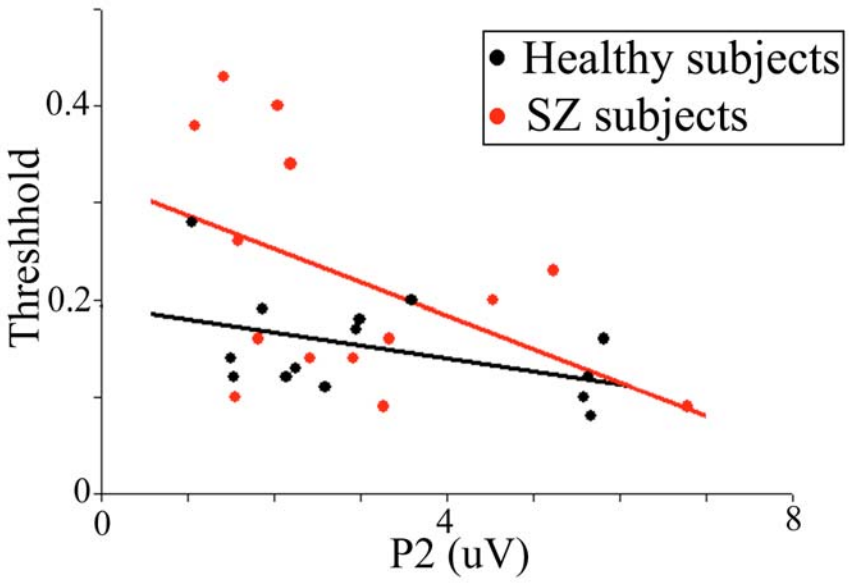

SZ
H
N1
1st
P2
N1
2nd
P2
Minimum
-Norm
N300
Minimum
-Norm

Figure 13. Bivariate scatter plot of relationships between threshold and P2 amplitude in STUDY 2.

Healthy subjects are represented by black dots and schizophrenia subjects are represented by red dots. The best fitting regression lines are also included for both groups.


Healthy subjects
SZ subjects
Threshhold
0.4
0.2
0
0
4
8
P2 (uV)