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Research report

Stimulus sequence affects schizophrenia–normal differences in event processing during an auditory oddball task

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Abstract

Schizophrenia patients have difficulty distinguishing relevant from irrelevant auditory information. Auditory oddball paradigms are commonly used to investigate the processing of stimulus relevance. The present study used dense-array EEG and distributed source reconstructions to examine schizophrenia–normal differences in the processing of targets and standards as a function of the temporal sequence of stimuli. Brain responses were evaluated separately for early and late standards (standards 1–3 and 4–6 following a target, respectively) and early and late targets (those following 2–3 standards and 4–6 standards, respectively). The latencies of peaks (N1, P2, P3) in the event-related potential (ERP) waveforms did not differ between schizophrenia and normal subjects. However, schizophrenia–normal differences in neural activity, derived from minimum norm estimation, occurred at specific times during stimulus processing as a function of stimulus sequence. Schizophrenia patients displayed smaller activity than normals in early ERPs (left hemispheric N1, right frontal P2) to late targets, and they produced P3-like responses to late standards. Furthermore, during the P2/N2 time interval, opposite patterns of brain activity were elicited in schizophrenia and normal subjects in response to standards, indicating different neural responses to the same stimulus events. These results suggest attention allocation to task-irrelevant stimuli in schizophrenia, consequent upon insufficient representation of stimulus significance and context. Thus, schizophrenia compromises the ability to properly use context to solve even simple cognitive problems.

Theme: Disorders of the nervous system
Topic: Neuropsychiatric disorders

Keywords: Schizophrenia; Auditory; Event-related potentials; P300; Sequence effects; Minimum norm

1. Introduction

A characteristic of impaired cognitive functioning in schizophrenia is difficulty distinguishing relevant from irrelevant information in the auditory environment [5,19,31]. A common method used to investigate the processing of stimulus relevance is the auditory oddball paradigm [14]. In the simplest version of this paradigm, two tones that differ on some physical characteristic (pitch, volume, etc.) are presented with differing probabilities, one occurring more frequently than the other. Subjects are required to attend to the infrequent tones (targets), which are considered relevant in this task. The neural correlates of processing abnormalities observed during auditory oddball tasks are associated with auditory hallucinations, thought disorder, and other characteristic symptoms of schizophrenia [26,27,35,38].

Performance on the oddball task is ostensibly mediated by both perceptual capacity and working memory ability [28,55,58]. During the auditory oddball task, subjects must maintain a representation of the physical characteristics of each stimulus (auditory sensory, or 'echoic,' memory) as well as the context in which the stimulus occurs (the stimulus was a standard or a target). Each stimulus must be

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evaluated and compared to its mental representation in order to determine whether a target stimulus has occurred. Additionally, as the task progresses, subjective expectancies of upcoming stimuli are formed based on the structure of previously presented stimuli [16,56]. Not only is it the case that targets are rare compared to standards, but the sequential structure of the stimulus series may affect the processing of subsequent stimuli.

Schizophrenia patients' performance is impaired on auditory tasks, as well as on tasks that require more complex working memory ability [24,30,31,32,57]. Furthermore, studies evaluating event-related potentials (ERPs), particularly the P300 (P3), elicited by the auditory oddball task have demonstrated that abnormal neural functioning underlies the stimulus evaluation, working memory, context updating, and expectancy generation deficiencies in schizophrenia (see [19] for a review). Examination of the auditory P3, as well as earlier, more sensory-related ERPs such as the N100 (N1), may shed light on the relationship between relevant versus irrelevant stimulus processing, and the concomitant perceptual and cognitive deficiencies, in schizophrenia.

The N1, which is evoked by relatively abrupt changes in sensory energy [42], represents an early stage of stimulus processing. The N1 reflects sensory registration of a stimulus, as well as the formation of a sensory ('echoic') memory of the stimulus within auditory cortex [36,42,54]. This echoic memory formation may play a role in the comparison of targets and standards during the auditory oddball task. Thus, the N1 is a potentially important index of the processing of stimulus relevance. Smaller N1 amplitude in schizophrenia patients, compared to normal subjects, is a consistent finding in the literature [4,8,20,52,54]. Recent findings suggest that reduced N1 in schizophrenia may be specifically associated with dysfunction of left hemisphere processing in schizophrenia [10,48,49,50].

While N1 represents sensory registration of a stimulus and is elicited across paradigms, a later component of the ERP elicited primarily by the oddball paradigm is the P3 (see [55] for a review). The P3 reflects both voluntary and involuntary detection of novel stimuli. A component of the P3, the P3b, which is evoked by novel stimuli that are task-relevant (attended to voluntarily), is theorized to reflect allocation of attentional resources, generation of expectancies, processing termination, and context updating within working memory [15,16,55,56]. Cortical generators of the P3b ostensibly reside in temporoparietal junction, anterior cingulate, and prefrontal cortex [2,41,55].

Schizophrenia patients tend to have P3b responses to target stimuli that are of smaller amplitude compared to normal subjects [19,33]. Furthermore, these smaller P3s in schizophrenia take place on individual trials, indicating that they are not a function of signal averaging and may index a critical feature of patients' auditory processing abnormalities [21,51]. Recent studies have shown, however, that these P3b differences are sensitive to the parameters of the auditory oddball task and that schizophrenia and normal subjects differentially process both the target and standard stimuli in these tasks [6,7,25,37].

Traditionally, only the ERPs to targets were examined for schizophrenia–normal P3 differences. However, a complete understanding of the cognitive and neural dysfunction underlying the relationship between relevant and irrelevant stimulus processing necessarily demands examination of ERPs elicited by standards as well. Recent studies have evaluated ERPs to standard stimuli in the auditory oddball task, but in these studies either all standards have been treated as homogenous or only standards immediately preceding or following the target have been analyzed [6,7].

There are suggestions that schizophrenia and normal subjects differentially process targets and standards as a function of when in the sequence of stimuli they occur. Mathalon and Ford [37] demonstrated that increasing the ISI (from 1.5 s to 8 s) resulted in attenuation of the P3b amplitude to targets in normal subjects, while schizophrenia patients showed no appreciable change in P3b amplitude to targets. P3 amplitude, therefore, was smaller among schizophrenia patients compared to normal subjects at the short ISI, but this difference was essentially eliminated at the long ISI. Gonsalvez et al. [25] demonstrated that schizophrenia subjects' P3b amplitudes to targets were not reduced, compared to normals, when targets were preceded by either shorter (<3) or longer (>9) series of standard tones. Schizophrenia patients also appear to produce more P3bs to standards than do normal subjects [51]. Finally, Brown et al. [6,7] examined the difference between ERPs to targets and standards immediately preceding and/or following the targets. N1 and P3 were generally lower in amplitude among schizophrenia subjects. Normal subjects, however, had smaller amplitude and earlier latency P2s to targets and larger amplitude and later latency P2s to standards. P2 was not different between standards and targets, however, among chronic schizophrenia patients [7]. Furthermore, the larger N1 amplitude to the standard preceding the target relative to the standard following the target exhibited by normal subjects was not found in the schizophrenia patients [7].

These findings suggest that schizophrenia and normal subjects may differentially process relevant and irrelevant auditory stimuli as a function of when in the stimulus sequence they occur. Expectancy and/or stimulus context effects (e.g., [9]) may critically determine schizophrenia–normal differences on the auditory P3. The present study, therefore, sought to systematically examine differential processing of irrelevant and relevant stimuli as a function of stimulus sequence. The relationship between standards and targets was evaluated based on when the stimulus occurred in the series: (1) standards occurring early (standards 1–3 following a target) or late (standards 4–6 following a target) in the series and (2) targets occurring early (after 2–3 standards) or late (after 4–6 standards) in the series. Dense-array EEG and distributed source reconstructions were used to study schizophrenia–normal similarities and

differences in the unfolding of neural activity associated with context updating, expectancy, and target identification during the auditory oddball task.

2. Materials and methods

2.1. Subjects

Fifteen DSM-IV [1] schizophrenia patients and 15 normal subjects participated in this study. Two subjects, one schizophrenia and one normal, were excluded due to having less than 50% usable trials after data pre-processing, resulting in a total sample of 14 patients (mean age = 41.6 years, SD = 8.8; 5 females) and 14 normals (mean age = 43.6 years, SD = 8.4; 10 females). Patients were recruited through advertisements placed in the community, as well as through outpatient services of the Medical College of Georgia in Augusta, GA and Advantage Behavioral Health Systems in Athens, GA. Schizophrenia patients were diagnosed by a psychologist using the Structured Clinical Interview for DSM-IV [17]. Normal subjects were recruited through advertisements placed in the community. All subjects provided informed consent and were paid for their participation. This study was approved by the UGA Institutional Review Board.

2.2. Stimuli and procedure

Stimuli were sine wave tones of 1000 Hz and 2000 Hz (100 ms duration, 5 ms rise/fall) created using NCH tone generator software (Version 2.0; NCH Swift Sound, Bruce, Australia). Tones were delivered binaurally through Etymotic insert earphones (Etymotic Research, Elk Grove Village, IL) at 76 dB SPL.

An oddball paradigm was used, in which the standard (1000 Hz) tones and target (2000 Hz) tones were presented with .80 and .20 probabilities, respectively. Tones were quasi-randomly presented, with a 1 s ISI, such that two to six standard tones occurred between targets. There were 604 total trials presented in six blocks: two blocks of 100 trials (20 targets), two blocks of 82 trials (16 targets), and two blocks of 120 trials (24 targets), presented randomly and counter-balanced between subjects within a group. During stimulus presentation, subjects were instructed to focus on a fixation cross presented on a computer screen 80 cm in front of them and to keep a silent count of the number of target tones they heard, restarting their count after each break between blocks. Subjects' counts were recorded after each block.

2.3. Magnetic resonance images

For a subset of subjects (8 normal and 8 schizophrenia), high-resolution (1 mm × 1 mm × 1.3 mm) anatomical magnetic resonance images (MRIs) were acquired on a GE Signa Horizon LX GE 1.5 T system located at HealthSouth Diagnostic Center (Athens, GA). For each subject, automatic shimming reduced inhomogeneities of the basic magnetic field. Mid-sagittal localizer images were obtained to determine the parameters necessary to image the whole head with 124 slices. Images were obtained using a standard spoiled gradient recall protocol (TE = 2.8 ms, TR = 10.8 ms, flip angle = 20deg, FOV = 24 × 24cm, matrix = 256 × 256 pixels, NEX = 2).

2.4. EEG recording

Electroencephalographic (EEG) data were recorded vertex-referenced using a 256 channel Geodesic Sensor Net and two linked 128 channel NetAmps 200 amplifiers (Electrical Geodesics; EGI, Eugene, OR). Electrode impedances were kept below 50 kΩ, as is standard when using high input impedance amplifiers like those from EGI. Data were sampled at 500 Hz with an analog filter bandpass of 0.1–200 Hz.

Head and face surface geometry, sensor locations, and fiducial markings were digitized using EGI's photogrammetry method. Subjects wearing the sensor net were placed under an open geodesic frame equipped with 11 cameras. Photos were taken in rapid succession, after which image recognition software identified corresponding points among multiple frames in order to construct a 3D image of the sensor locations. Sensor locations were then used to fit the ellipsoidal head model to head shape and size prior to source analysis.

2.5. ERP data screening

Raw data were visually inspected offline for bad channels and individual trials containing eye blink or cardiac artifacts. Bad channels were interpolated (no more than 5% of channels for any subject) using a spherical spline interpolation method (as implemented in BESA 5.0; MEGIS Software, Gräfelfing, Germany). Trials containing blink or cardiac artifact were automatically corrected using a spatial filtering algorithm in BESA [3,29]. Trials with activity greater than 100 μV were automatically eliminated from further processing. The data were transformed to an average reference and digitally bandpass filtered from 1–30 Hz (6 dB/octave rolloff). Trials consisted of 1000 ms epochs, beginning 250 ms prior to stimulus presentation, averaged according to the position of the stimulus in the series: early or late standards and early or late targets. The data were baseline corrected using the −200 to 0 ms prestimulus period. Fig. 1 shows the grand averaged data, by condition, for a subset of 27 channels.

2.6. Data analysis

2.6.1. Component latency quantification

To measure component latencies, global field power (GFP) plots were derived for every subject and condition.

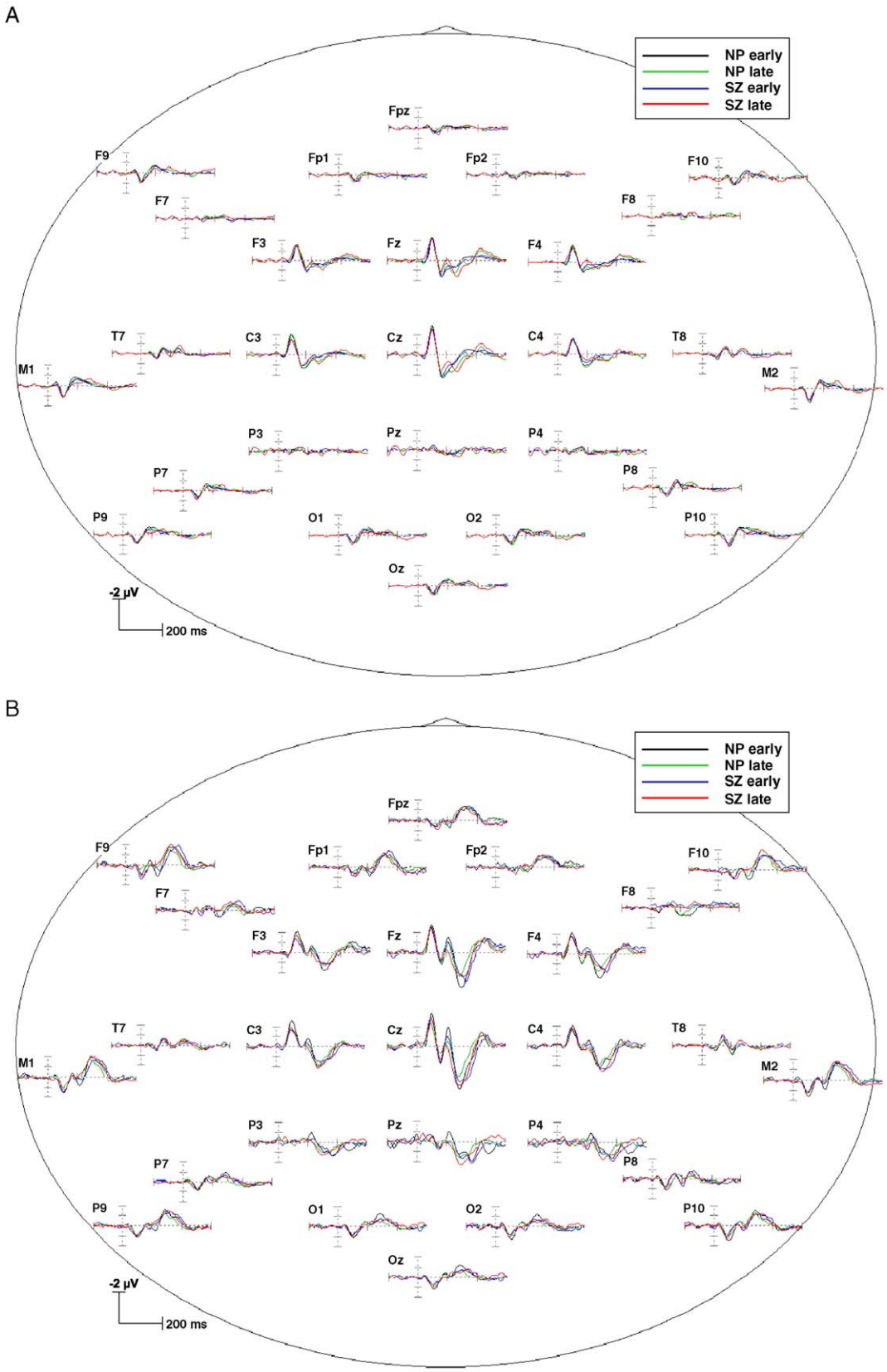

Fig. 1. Grand averaged data, by condition, for a subset of 27 channels: (A) standards, (B) targets. Negative is up. NP = normal subjects, SZ = schizophrenia subjects.

Peaks in the GFP were defined as the largest amplitude deviations of the N1, P2, and P3, corresponding to the proper polarity of the component at Cz (N2 was measured as well but could not be reliably identified in most subjects, so N2 latency data were not subjected to data analysis).

2.6.2. Brain activity quantification

Averaged "normal" and "schizophrenia" MRIs were constructed by averaging whole-head MRIs from 22 normal subjects (8 of whom participated in the present study) and 24 schizophrenia patients (8 of whom participated in the present study), respectively, using BrainVoyager 2000 (Version 4.4; Brain Innovation B.V., Maastricht, The Netherlands). The skin and cortical gray matter were segmented using Curry (Version 4.6, Neuroscan, El Paso, TX). The digitized head shape and fiducial markings (formed by the EEG sensors obtained from the photogrammetry data) were co-registered to the averaged segmented skin surface of their respective group prior to projection of the EEG activity on the skin surface (see Figs. 3 and 4). The averaged segmented cortical surface was used for displaying minimum norm source reconstruction results (see Figs. 3 and 4).

Statistical comparisons of scalp potential amplitudes were conducted for the 0–400 ms time period. First, at each time point, channel-by-channel (257 total channels, including the reference), *t* tests were conducted between-groups (normal vs. schizophrenia subjects), separately for each condition: early and late standards and early and late targets. Then, during time windows in which between-group differences were found, within *t* tests were conducted (early vs. late standards and early vs. late targets, separately for normal and schizophrenia subjects). Traditional Bonferroni correction for multichannel and/or multisource data leads to prohibitively low alpha levels that seriously reduce the ability to detect real brain activations. A more applicable technique used in the fMRI literature [13,22] that can be adapted for present purposes integrates the probability of significance for an individual channel with a cluster threshold technique. Cluster thresholding was done because multichannel EEG data result in significant activations of multiple channels that are in close spatial proximity. The following statistical significance rules were determined based on Monte Carlo simulations calculated using AlphaSim in AFNI [11]. To maintain the familywise alpha at no higher than 0.05 within a comparison, the following conditions needed to be met: (1) an individual *t* test at a single time point for a given channel was significant at $P < 0.02$; (2) at least two other neighboring channels were statistically significant at $P < 0.02$; and (3) the first two conditions were true for at least 6 ms (three consecutive data points). Maps of significant differences were then projected onto the skin surface obtained after averaging MR images.

Finally, at times of significant differences between-groups, distributed source reconstructions were calculated using least-squares minimum norm estimation (MNE) as implemented in BESA. Using a four-shell ellipsoidal head model (shells represented the brain, CSF, skull, and skin with conductivities of .33, 1.0, .0042, and .33, respectively), activations were estimated for 162 fixed source locations at each time point using the method of Dale and Sereno [12] that employs a reciprocal correlation measure to produce focal minimum norm reconstructions. Noise estimates were obtained by taking 15% of the sample vectors with the smallest magnitude. Channels were weighted by individually-determined noise levels. Areas of activity difference between groups were then projected onto the cortical reconstructions obtained after averaging the MR images as described above. These MNE difference maps were obtained by subtracting schizophrenia subjects' MNE results from those of normal subjects (for the between-groups analysis) and by subtracting MNE results in response to late standards/targets from that of early standards/targets (for the within-group analysis).

3. Results

3.1. Number of usable trials and percentage of correct target identification

There were no significant between-group differences in the number of usable trials for the remaining 14 normal (standards: $M = 384$, SD = 46.5; targets: $M = 101$, SD = 10.1) and 14 schizophrenia (standards: $M = 365$, SD = 64.3; targets: $M = 95$, SD = 16.3) subjects ($F(1,26) = 0.90$, $P = 0.35$) nor in the percentage of targets correctly identified by the normal ($M = 99.3\%$, SD = 0.64%) and schizophrenia ($M = 98.7\%$, SD = 0.96%) subjects ($t(26) = 1.91$, $P = 0.07$).

3.2. Component latency differences

Differences in component latency were evaluated separately for standards and targets using repeated measures ANOVAs with the between-subjects factor of Group (normals, patients) and the within-subjects factors of Condition (early, late) and Peak (N1 and P2 for standards; N1, P2, and P3 for targets). There was no significant main effect of Group on component latencies for the standards ($F(1,26) = 0.608$, $P = 0.44$) or targets ($F(1,26) = 0.398$, $P = 0.54$) nor were there any significant interactions involving Group membership for component latencies. Table 1 shows

Table 1
Component latencies in ms (Mean ± SD), grand averaged across conditions

Component	Standards		Targets	
	NP	SZ	NP	SZ
N1	104.0 ± 5.0	104.7 ± 8.8	102.0 ± 12.5	101.2 ± 13.9
P2	188.3 ± 22.2	181.1 ± 27.1	167.6 ± 15.5	164.6 ± 21.5
P3			304.0 ± 27.3	315.6 ± 27.7

component latencies of standards and targets for each group grand averaged across conditions.

3.3. Between-group brain activity differences

While Fig. 2 shows potential maps for each condition at peak times of the N1, P2, and P3, Fig. 3 shows data in time windows where there were significant between-groups effects. Grand average potential maps are shown for normal and schizophrenia subjects. *t* test maps were projected onto the averaged segmented skin surface, and minimum norm (MNE) difference maps were projected onto the cortical surface of the averaged MRI. Table 2 summarizes the significant between-groups brain activity differences.

3.3.1. Early standards

There were two time windows during which significant effects occurred when comparing normal and schizophrenia subjects on responses to early standards (see Fig. 3A). From 144–160 ms post-stimulus, schizophrenia subjects had greater negative potentials over left hemisphere posterior parietal regions. MNE results indicated that normals had greater activity in right hemisphere auditory cortex and in superior mesial parietal cortex during this time window. From 242–258 ms, schizophrenia subjects had greater negative potentials over the right inferior frontal and over left frontal–parietal regions. MNE results indicated greater activity in right lateral frontal cortex among normal subjects and greater activity in left temporal–parietal cortex among schizophrenia subjects in the neighborhood of supramarginal gyrus.

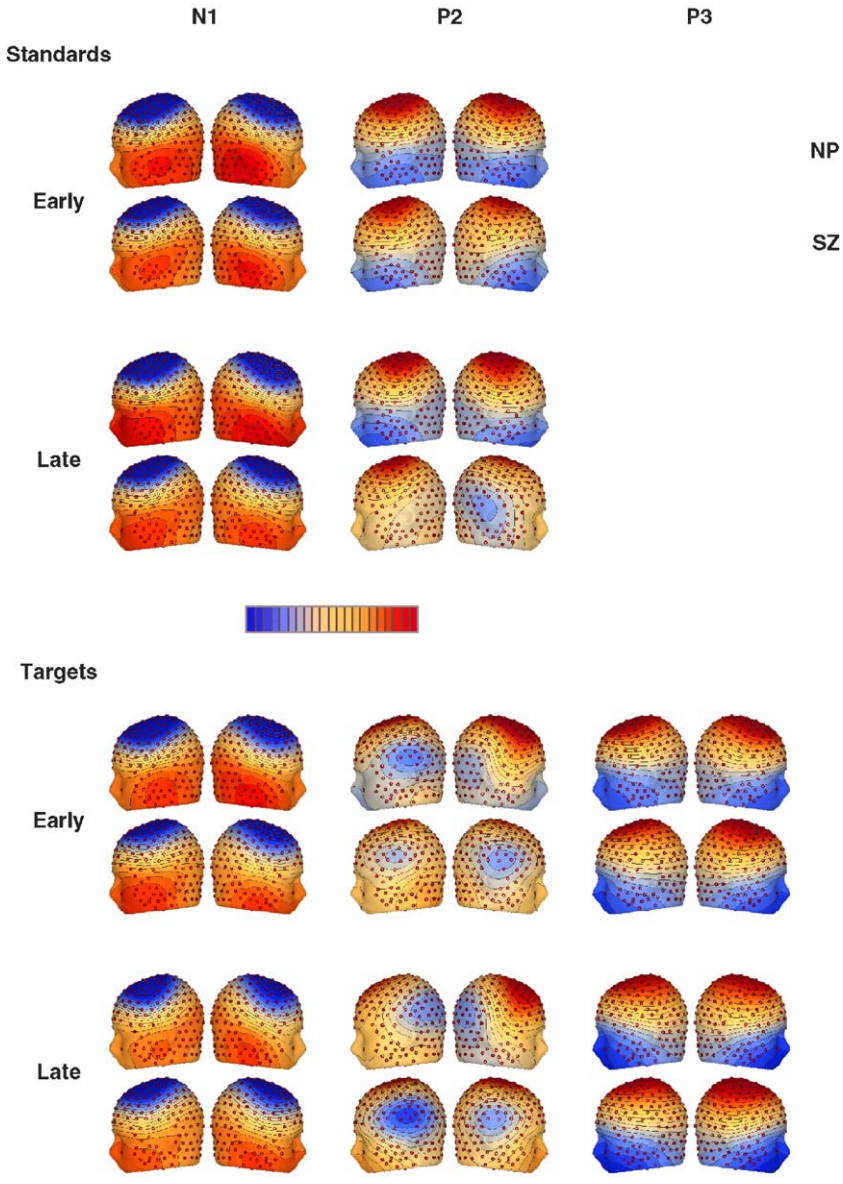

Fig. 2. Scalp potential maps for each condition at peak times of the N1, P2, and P3. NP = normal subjects, SZ = schizophrenia subjects. Scale is shown in the middle. For both Standards conditions, scale is 0.16 μV/step for all maps. For both Target conditions, scale is 0.22 μV/step for N1 maps, 0.11 μV/step for P2 maps, and 0.31 μV/step for P3 maps.

3.3.2. Late standards

There was one time window during which significant effects occurred when comparing normal and schizophrenia subjects on responses to late standards (see Fig. 3A). From 170–182 ms, normal subjects showed greater positive potentials over the right hemisphere anterior parietal–posterior frontal region. MNE results indicated greater superior bilateral and mesial parietal activity among normal subjects during this time range.

3.3.3. Early targets

There were three time windows during which significant effects occurred when comparing normal and schizophrenia subjects on responses to early targets (see Fig. 3B). From 162–184 ms, normal subjects had greater positive potentials over the anterior right superior and inferior frontal regions. MNE maps indicated that normal subjects had greater activity than schizophrenia patients in right anterior frontal cortex and in the neighborhood of supramarginal gyrus bilaterally during this time range.

From 186–216 ms, normal subjects continued to have greater positive potentials over right frontal regions, but this difference shifted to a more posterior and inferior position compared to the previous time range. In addition, schizophrenia subjects had greater positive potentials than normal subjects over right occipital brain regions during this time range. MNE maps indicated that normal subjects had more activity in superior mesial frontal regions and bilateral middle and posterior temporal regions, while schizophrenia patients had greater activity specifically in the right posterior temporal–occipital region during this time range.

In the 320–374 ms time range, schizophrenia subjects had greater positive potentials over the mesial superior parietal region. MNE difference results showed widespread areas of activity differences. Normal subjects had greater activity in superior mesial frontal and parietal regions, while schizophrenia patients had greater activity principally in right temporal–occipital and inferior parietal regions.

3.3.4. Late targets

There were five time windows during which significant differences occurred when comparing normal and schizophrenia subjects on responses to late targets (see Fig. 3B). From 118–136 ms, normal subjects had greater positive potentials over the right hemisphere parietal region. MNE results showed a widespread area of greater brain activity in normal subjects, with foci in left anterior frontal cortex and right auditory cortex.

From 162–184 ms, normal subjects had significantly greater positive potentials in the same regions as seen in response to early targets during this time range, right anterior frontal cortex. MNE results indicated greater right middle temporal lobe activity among normal subjects during this time window.

From 216–230 ms, schizophrenia subjects had an area of significantly greater positive potentials over the anterior frontal region. MNE results, however, indicated that normal subjects had greater superior and lateral right frontal cortex activity than schizophrenia patients during this time range. Schizophrenia subjects also had significantly greater positive potentials from 310–320 ms over the right hemisphere superior parietal region. MNE results indicated that normal subjects had greater activity over lateral frontal cortex bilaterally (much stronger on the right), while schizophrenia subjects had greater activity in right superior parietal lobe.

From 320–374 ms, the activity differences between-groups expanded to include a widespread region over anterior parietal–superior frontal cortex, during which schizophrenia subjects had greater positive potentials. In addition, normal subjects had greater positive potentials over bilateral inferior parietal regions during this time range. MNE results from this time range indicated a continuation of accentuated activity (although less dramatic than in the 310–320 ms time range) among normal subjects over lateral prefrontal and superior parietal regions. The area of greater brain activity found in schizophrenia subjects from 310–320 ms moved from superior parietal to the posterior temporal–occipital region during the 320–374 ms time range.

3.4. Within-group brain activity differences

Fig. 4 shows significant within-group effects during time windows in which between-group differences were found. Grand average potential maps are shown for each condition. *t* test maps were projected onto the averaged segmented skin surface, and MNE difference maps were projected onto the cortical surface of the averaged MRI of the respective group. Table 3 summarizes the significant within-group brain activity differences.

3.4.1. Early versus late standards

There were 2 time windows during which significant effects occurred when comparing responses to early and late standards (see Fig. 4A). In the 160–220 ms range, the differences between scalp potentials were similar for normal and schizophrenia subjects. From 160–220 ms, both groups' area of greater positive potentials to early standards was over superior mesial frontal regions, with schizophrenia subjects also showing an area of greater negative potentials to early standards over posterior temporal regions. MNE difference maps illustrate important between-groups differences during this time range. Both groups showed greater brain activity to early standards throughout the 160–220 ms time range. Normal subjects' increased activity was in bilateral prefrontal regions, slightly stronger in left hemisphere. Schizophrenia subjects' greater activity to early standards, however, was located in superior mesial parietal regions throughout this time range.

In the 240–274 ms time range, normal subjects had greater negative potentials to late standards over the right posterior temporal region and greater positive potentials to late standards over mesial frontal regions. In contrast, schizophrenia subjects had greater negative potentials over left anterior temporal regions in response to late standards.

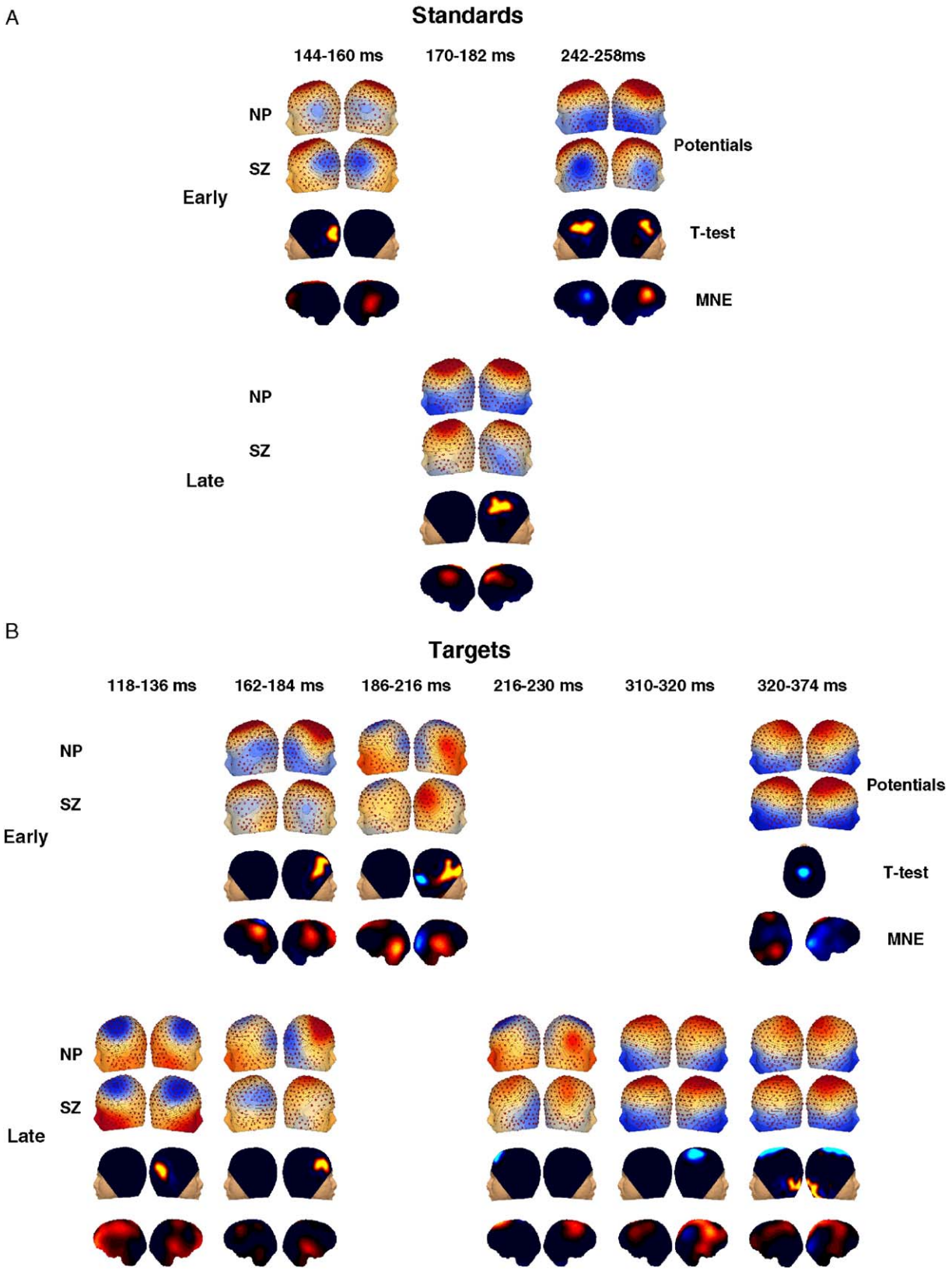

Table 2
Summary of significant between-groups brain activity differences

Latency	Standards		Targets	
	Early	Late	Early	Late
118–136				NP Lt Frnt; NP Rt Inf Temp
144–160	NP Sup Par; NP Rt Temp			
162–184		NP Bi Sup Par	NP Bi Temp–Par; NP Rt Frnt	NP Rt Temp
186–216			NP Bi Inf Temp; NP Sup Frnt; SZ Rt Temp-Occ	
216–230				NP Rt Sup Frnt
242–258	NP Rt Frnt; SZ Lt Temp–Par			
310–320				NP Bi Sup Frnt; SZ Rt Sup Par
320–374			NP Sup Par–Frnt; SZ Rt Temp–Occ	NP Bi Frnt; NP Sup Par; SZ Rt Inf Par

NP = normals had significantly higher brain activity, SZ = schizophrenia subjects had higher activity.
Rt = Right, Lt = Left, Bi = Bilateral.
Inf = Inferior, Sup = Superior.
Frnt = Frontal Cortex, Occ = Occipital, Par = Parietal, Temp = Temporal.

MNE maps illustrate a continuation of between-groups processing differences to early and late standards. Normal subjects had increased activity to late standards in mesial and lateral parietal regions while schizophrenia subjects had greater frontal activity bilaterally in response to late standards during this same time window.

3.4.2. Early versus late targets

There were 3 time windows during which significant effects occurred when comparing responses to early and late targets (see Fig. 4B). From 172–182 ms, schizophrenia subjects had greater negative potentials to early targets over the right temporal–parietal region. MNE results indicated greater activity in right anterior frontal cortex in response to late targets among schizophrenia patients during this time window.

In the 205–250 ms time range, both groups showed increased positive potentials to late targets over widespread superior frontal and parietal regions. Normal subjects also had increased negative potentials to late targets over inferior temporal–occipital regions bilaterally. The normal and schizophrenia subjects' MNE results were similar in that there was an area of greater mesial activity in response to the early targets located more frontally and increased activity to late targets located in parietal lobe. Additionally, schizophrenia subjects had an area near right auditory cortex that showed greater activity in response to early targets.

Finally, from 320–360 ms, normal subjects had increased positive potentials to early targets over mesial frontal regions. The MNE difference map indicated that this same area, mesial superior frontal cortex, was more active in response to the early targets and that a region of right superior parietal cortex was more active in response to the late targets.

4. Discussion

The present study revealed differences between schizophrenia and normal subjects in the development of neural activity associated with the processing of relevant and irrelevant stimuli during an auditory oddball task. As hypothesized, results indicated that these differences were a function of when the stimulus occurred in the sequence of stimuli. Furthermore, these sequence effects did not simply occur at latencies of peaks in the ERP waveform, illustrating that interesting and important neural processes are occurring throughout stimulus processing (see [46]).

Despite the between-groups differences, there was remarkable similarity in the dynamic pattern of brain activity between normal and schizophrenia subjects associated with stimulus processing during the auditory oddball task. Considering the relatively few time windows during which significant between-group differences occurred, there were, in fact, more similarities than differences. Throughout stimulus processing, schizophrenia subjects' pattern of neural activity seemed to deviate from, then re-synchronize with, that of normal subjects. Thus, it does not appear to be the case that schizophrenia subjects' neural activity becomes abnormal and remains abnormal but that it is different from normal during specific types of stimulus processing.

To assess schizophrenia–normal differences and similarities in neural activity in response to auditory stimuli, the present study used a multistage approach. First, data were evaluated in sensor space. Accurate assessment of the recorded potentials, whose pattern changes over time as a

Fig. 3. Between-groups comparisons: Grand average potential maps for early and late standards (A) and early and late targets (B) for normal (NP) and schizophrenia (SZ) subjects, *t* test result maps projected onto the averaged skin surface, and minimum norm (MNE) difference maps projected onto the cortical surface of the averaged MRI. On the *t* test maps, warmer colors (reds, yellows) represent either stronger positive potentials in normal subjects or stronger negative potentials in schizophrenia subjects (depending on polarity of the response), while cooler colors (blues) represent either stronger negative potentials in normal subjects or stronger positive potentials in schizophrenia subjects (depending on polarity of the response). On the MNE maps, warmer colors represent areas of greater brain activity in normal subjects, while cooler colors represent areas of greater brain activity in schizophrenia subjects.

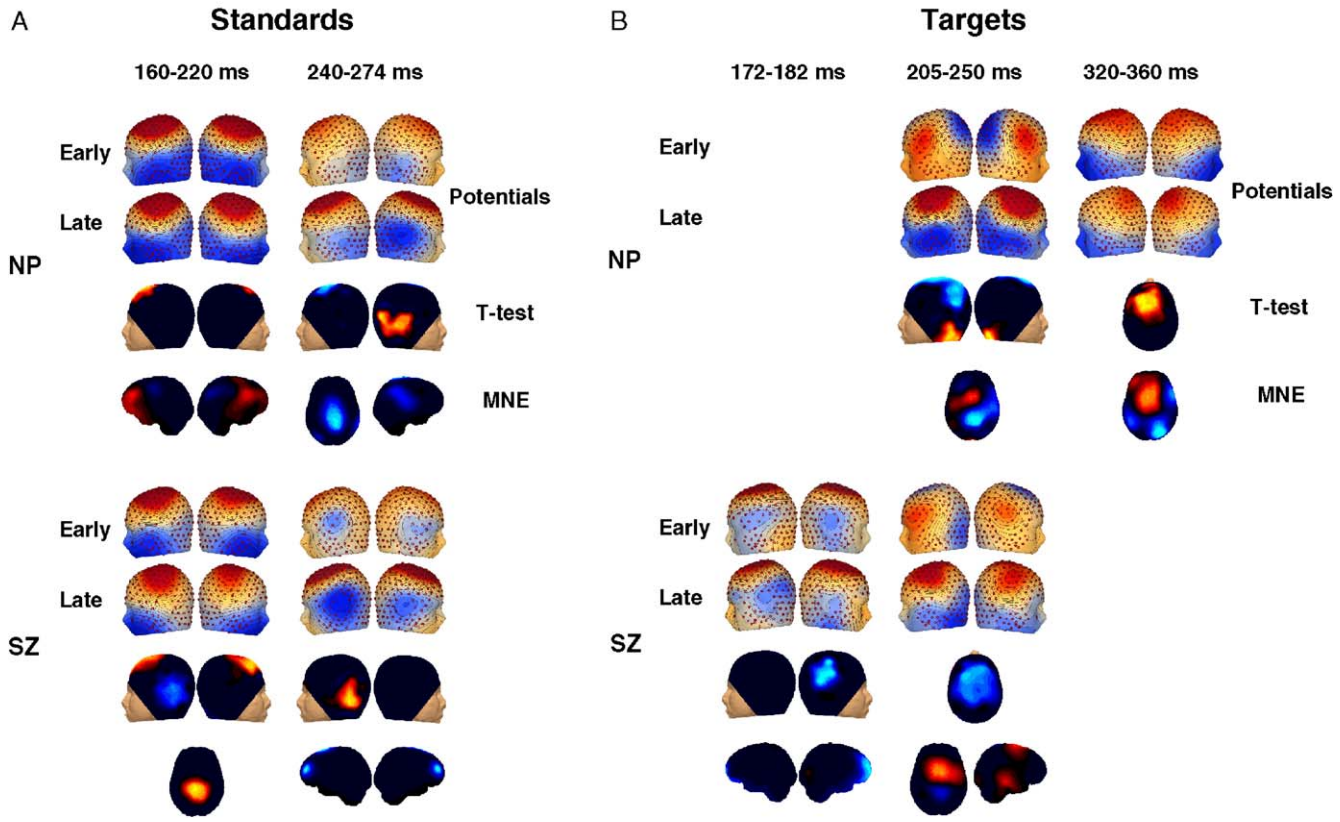

Fig. 4. Within-group comparisons: Normal (NP) and schizophrenia (SZ) subjects' grand average potential maps for early and late standards (A) and early and late targets (B), *t* test result maps projected onto the averaged skin surface, and minimum norm (MNE) difference maps projected onto the cortical surface of the averaged MRI of the respective group. On the *t* test maps, warmer colors (reds, yellows) represent either stronger positive potentials to early standards/targets or stronger negative potentials to late standards/targets (depending on polarity of the response), while cooler colors (blues) represent either stronger negative potentials to early standards/targets or stronger positive potentials to late standards/targets (depending on polarity of the response). On the MNE maps, warmer colors represent areas of greater brain activity in response to early standards/targets, while cooler colors represent areas of greater brain activity in response to late standards/targets.

function of the orientation and location of multiple brain sources, was facilitated by the use of dense-array EEG (with multiple sensors located across the head, including a sufficient number below the canthomeatal line), and average referencing, which is unbiased by any particular reference sensor [46]. However, while comparing potentials recorded at the sensors may reveal important between-group differences, the locations of the neural generators of these potentials cannot be precisely determined by analyzing data in sensor space alone. Thus, data collected in sensor space were transformed to source space via least squares MNE in order to provide information concerning the cortical sources of the potentials recorded at the sensors. The present study illustrated the effectiveness of dense-array EEG, average referencing, and source space analysis for evaluation of normal and schizophrenia subjects' stimulus processing during the auditory oddball task.

Table 3
Summary of significant within-group brain activity differences

Latency	Standards		Targets	
	NP	SZ	NP	SZ
160–220	Early Bi Frnt	Early Sup Par		
172–182				Late Rt Frnt
205–250			Early Sup Frnt; Late Sup Par	Early Sup Frnt; Early Rt Inf Temp; Late Sup Par
240–274	Late Rt/Sup Par	Late Bi Frnt		
320–360			Early Sup Frnt; Late Rt Sup Par	

NP = Normal subjects, SZ = schizophrenia subjects.
Early = greater activity in Early standards/targets, Late = greater activity in Late standards/targets.
Rt = Right, Lt = Left, Bi = Bilateral.
Inf = Inferior, Sup = Superior.
Frnt = Frontal Cortex, Occ = Occipital, Par = Parietal, Temp = Temporal.

Early in the course of stimulus processing, through the time of the N1, brain activity is remarkably similar between groups. This similarity was expected based on the results of previous studies [52,54]. The only indication of an early difference between groups occurred in response to late targets. MNE results from this time show a widespread area in left hemisphere in which normal subjects have significantly greater neural activity, which is absent among schizophrenia patients. These results are consistent with

reports of left hemisphere dysfunction in schizophrenia around the time of the N1 [10,48,49].

Across conditions, at times surrounding the P2, normal subjects had more activity in auditory cortex than did schizophrenia subjects. Additionally, an interesting pattern was evident in the P2/N2 time window for the early vs. late standards within-group comparisons. Normal subjects had greater frontal activity to early standards around the time of P2, which moved over parietal cortex in response to late standards around the time of N2. In contrast, schizophrenia subjects started with greater parietal activity to early standards followed by increased bilateral frontal activity to late standards during the same time range. Normal and schizophrenia subjects, therefore, showed exactly opposite patterns of brain activation over this time range in response to the same stimulus events.

The P2 is theorized to index stimulus evaluation, stimulus encoding, decision-making, and stimulus comparison operations [7,39,43]. The N2 is thought to index attention and stimulus classification [47,53]. Increased auditory cortex activity in normal subjects around P2 suggests they were performing verification or validation processes, possibly comparing the stimulus to the echoic memory representation formed at the time of the N1. As the task progresses, normal subjects may form a representation of the stimulus sequence that includes the condition that a target will not be followed by another target. While the occurrence of a target signals to normal subjects that close attention need not be paid to immediately succeeding stimuli (as another target is unlikely to occur), encountering a target may actually increase schizophrenia subjects' attention and vigilance to the stimuli in general. Thus, greater frontal activity among normal subjects to early standards around the time of P2 may reflect working memory processes, while increased parietal activity may index the increased vigilance to stimulus evaluation by schizophrenia subjects. As the number of standards following the target increases, normal subjects attend more closely to the stimuli, vigilant for the next target appearance, as indexed by greater parietal activity around 250 ms. However, with an increasing number of standards, schizophrenia subjects may depend more on working memory processes, mediated largely by frontal cortex, to evaluate and compare stimuli in expectation of an upcoming target.

The P3 was also affected by the position of the target in the stimulus sequence. Around the peak of the P3, schizophrenia subjects showed the typical lower amplitude P3 compared to normal subjects. This greater activity in normal subjects occurred over right frontal, temporal, and parietal lobes, with foci over anterior cingulate bilaterally [41,59]. The smaller P3 response in these areas among schizophrenia subjects, however, occurred primarily in response to late targets. Schizophrenia subjects' P3 to late targets was enhanced compared to that of normals in right temporal–parietal cortex. Just following the P3, these areas of activity difference persisted and were also evident in response to early targets. The observed pattern of activity differences is consistent with previous schizophrenia research [18,34,40,44,45]. In the present study, however, these differences were present earlier and persisted longer in response to the late targets. These results suggest that stimulus context effects, such as expectancy for a target following a long string of standards, play an important role in determining schizophrenia–normal differences on auditory P3 responses.

The present study also revealed that schizophrenia subjects produced some P3-like responses to the late standards (cf. [51]). As the number of standards increases, schizophrenia subjects may expend more attentional resources in anticipation of a target. This increased expectancy and attention, then, produces the P3-like response to the late standards. Upon the occurrence of a target following a long series of standards, schizophrenia subjects' expectancy generation seems to operate more normally, producing the parietal P3b reflective of voluntary detection of a relevant stimulus.

The present study demonstrated that stimulus sequence is a critical factor in the processing of relevant and irrelevant auditory information in both normal and schizophrenia subjects. Schizophrenia patients exhibit abnormal attentional allocation, stimulus evaluation, and context-updating processes when faced with the demands of the oddball task, as indexed by brain activity differences elicited by both standard and target stimuli. The findings of increased P2 to late targets, dependence on working memory processes with increasing number of standards, more attention unnecessarily paid to irrelevant stimuli immediately following a target, and P3-like responses to late standards suggest that schizophrenia patients may rely more on the temporal sequence of the stimuli than on stimulus properties for identification of relevant stimuli. However, even though patients rely on temporal context, results of this study further suggest that their ability to effectively utilize context is compromised. This reliance on temporal sequence may be related to a signal-to-noise ratio problem in schizophrenia patients' auditory registration system [8,23] which does not allow clear identification of stimuli based solely on physical properties. In turn, the inability to properly identify stimuli based on physical properties could lead to higher-level cognitive abnormalities as a result of starting with inadequate information. Thus, schizophrenia patients' neuronal ensembles may lack the flexibility to meet the changing demands of the stimulus context.

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