Electrophysiological Assessment of Auditory Stimulus-Specific Plasticity in Schizophrenia

Ryan P. Mears and Kevin M. Spencer

Background: Disrupted neuroplasticity may be an important aspect of the neural basis of schizophrenia. We used event-related brain potentials (ERPs) to assay neuroplasticity after auditory conditioning in chronic schizophrenia patients (SZ) and matched healthy control subjects (HC).

Methods: Subjects (15 HC, 14 SZ) performed an auditory oddball task during electroencephalogram recording before and after auditory tetanic stimulation (Pre/Post Blocks). Each oddball block consisted of 1000-Hz and 1500-Hz standards and 400-Hz targets. During tetanic conditioning, 1000-Hz tones were presented at 11 Hz for 2.4 min. We analyzed the standard trials, comparing the ERPs evoked by the tetanized stimuli (1000 Hz tones: TS+) and untetanized stimuli (1500 Hz tones: TS–) in the Post Blocks with ERPs from the Pre Blocks (averaged into Baseline ERPs).

Results: In Post Block 1 in HC, TS+ tones evoked a negative shift (60–350 msec) at right temporal electrodes relative to Baseline. No pre-/post-tetanus effects were found in SZ. In Post Block 2 in HC, TS+ tones evoked a positive shift (200–300 msec) at bilateral frontal electrodes. In SZ, TS+ tones evoked a positive shift (100–400 msec) at right frontotemporal electrodes. No pre-/post-tetanus effects were found in either subject group for the TS– tones. The right temporal Post Block 1 and 2 effects were correlated in SZ, suggesting a trade-off in the expression of these effects.

Conclusions: These results suggest that stimulus-specific auditory neuroplasticity is abnormal in schizophrenia. The electrophysiologic assessment of stimulus-specific plasticity may yield novel targets for drug treatment in schizophrenia.

Key Words: Auditory processing, ERP, event-related brain potential, NMDA receptor, plasticity, schizophrenia

Abnormalities in the structure and function of the auditory cortex figure prominently in schizophrenia. The volume of gray matter in primary and secondary auditory cortical areas is reduced (1,2), and neuropathologic studies have documented abnormalities in the microcircuitry of auditory cortex (3,4). Functionally, the amplitudes of auditory event-related brain potentials (ERPs) are reduced (5,6), schizophrenia patients have deficits in auditory perception (7), and auditory hallucinations are a hallmark symptom of this disorder (8). However, to our knowledge, the plasticity of auditory cortical circuits has not yet been examined in schizophrenia.

Plasticity is a fundamental property of neural systems that enables them to alter their structure and dynamics in response to changes in their inputs and hence underlies learning and memory (9). Disturbances of plasticity-related mechanisms could thus underlie the abnormal development, structure, and function of neural circuits in neuropsychiatric disorders such as schizophrenia (10,11). For example, the induction of cortical plasticity through long-term potentiation (LTP) is dependent on the integrity of *N*-methyl-D-aspartate receptors (12), which are also implicated in the pathophysiology of schizophrenia (13–15). Consistent with this hypothesis, reduced motor cortex plasticity in schizophrenia patients has been found using transcranial magnetic stimulation (16,17).

We examined the plasticity of auditory cortex in schizophrenia by measuring event-related brain potentials (ERPs) in a stimulus-specific plasticity (SSP) paradigm based on the study of Clapp and colleagues (18). Investigations of SSP in mouse visual cortex (19) have demonstrated that this phenomenon shares the same cellular and molecular substrates as LTP, so SSP may serve as a noninvasive measure of LTP-associated plasticity mechanisms in humans. In our SSP paradigm subjects performed an oddball task with two standard tones of different frequencies presented in each block. One of these tones (the tetanized stimulus or TS+) was also presented during a tetanic stimulation block. Tetanic stimulation is the presentation of a train of stimuli at a high rate (typically ≥10 Hz) and is used to induce LTP. For example, in classical studies of LTP in the hippocampus, tetanic stimulation consists of a train of electrical pulses and results in increased neuronal responses to a test stimulus. In SSP studies, tetanic stimulation consists of a train of brief sensory stimuli (e.g., tones or visual stimuli) that results in response enhancements that are specific to the TS+ compared with an untetanized stimulus (TS–). In this study, we assessed the ERPs to an auditory TS+ and TS– before and after tetanic stimulation in healthy control subjects (HC) and chronic schizophrenia patients (SZ). We report evidence that the plasticity of auditory processing mechanisms is abnormal in schizophrenia.

Methods and Materials

Subjects

This study was approved by the Institutional Review Boards of the Veterans Affairs Boston Healthcare System and Harvard Medical School. After a complete description of the study to the subjects, written informed consent was obtained. All subjects were paid for their participation.

Seventeen chronic SZ (aged 21–54 years; mean age = 42) and 15 HC (aged 21–54 years; mean age = 42) participated in the study. The SZ subjects were diagnosed according to DSM-IV criteria. Subjects were selected without regard for ethnicity and met our standard inclusion criteria: 1) aged between 18 and 55 years; 2) right-handed (so that possible hemispheric lateralization effects would not be obscured by left-handers with reduced or reversed functional laterality); 3) no history of electroconvulsive treatment; 4) no

From the Research Service, VA Boston Healthcare System, Department of Psychiatry, Harvard Medical School, Boston, Massachusetts.

Address correspondence to Kevin M. Spencer, Ph.D., VA Boston Healthcare System/Harvard Medical School, Research 151C, 150 S. Huntington Avenue, Boston, MA 02130; E-mail: kevin_spencer@hms.harvard.edu.

Received Jun 20, 2011; revised Nov 21, 2011; accepted Dec 20, 2011.

0006-3223/$36.00
doi:10.1016/j.biopsych.2011.12.016

Table 1. Demographic, Clinical, and Task Performance Data and Between-Group Comparisons for the Healthy Control (HC) and Schizophrenia Patient (SZ) Groups

	HC (n = 15)	SZ (n = 14)	Statistic	p
Age (Years)	42.1 ± 9.7	42.6 ± 10.6	$t[27] = -.14$	.89
Parental Socioeconomic Status	2.1 ± 1.2	2.9 ± 1.1	$t[25] = -1.6$	.13
Age of Onset (Years)		23.7 ± 5.7		
Positive Symptom Total (SAPS)		9.5 ± 3.7		
Negative Symptom Total (SANS)		10.9 ± 7.2		
Medication Dosage		257 ± 184		
(Chlorpromazine Equivalents)		Range: 50–650		
% Error				
Pre Block 1	3.9 ± 4.9	17.0 ± 25.3		
Pre Block 2	5.0 ± 5.9	21.4 ± 24.0		
Baseline	4.4 ± 4.9	19.2 ± 23.3		
Post Block 1	3.3 ± 4.2	22.0 ± 28.4		
Post Block 2	4.4 ± 10.0	16.1 ± 20.1		
Reaction Time (ms)				
Pre Block 1	372 ± 61	397 ± 69		
Pre Block 2	374 ± 64	423 ± 93		
Baseline	373 ± 61	410 ± 76		
Post Block 1	381 ± 59	412 ± 83		
Post Block 2	381 ± 70	419 ± 67		

Mean ± SD are given for each variable.

SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms.

history of neurologic illness, including epilepsy; 5) no history of alcohol or drug dependence or abuse within the past year, nor long duration (>1 year) of past abuse (DSM-IV criteria); 6) no present medication for medical disorders that would have deleterious electroencephalogram (EEG), neurological, or cognitive functioning consequences; 7) verbal IQ above 75; 8) no alcohol use in the 24 hours before testing; and 9) English as a first language.

The data from 3 SZ were excluded because of technical problems, bad channels, or excessive artifacts, resulting in a final sample of 14 SZ and 15 HC. Demographic and clinical data are presented in Table 1. Schizophrenic symptoms were assessed using the Scale for the Assessment of Positive Symptoms (SAPS) (20) and the Scale for the Assessment of Negative Symptoms (21). The final SZ and HC groups did not differ in gender (all male), age, parental socioeconomic status (22), nor handedness (all right-handed) (23). The diagnostic composition of the SZ group was 7 paranoid, 4 undifferentiated, 2 schizoaffective, and 1 disorganized. Information on antipsychotic medication at the time of the experiment was available for 11 of the 14 SZ. Of these 11 patients, all were receiving atypical antipsychotics, and 1 patient was also receiving a typical antipsychotic. Antipsychotic medication dosages were converted to chlorpromazine equivalents using the values from Stoll (24) for typical and Woods (25) for atypical antipsychotics.

Stimuli and Experimental Design

The structure of the SSP paradigm is diagrammed in Figure 1. Subjects performed an auditory oddball task while seated in a quiet room in a comfortable chair in front of a computer monitor. Stimuli were presented binaurally through headphones (50-msec duration, 70-dB sound pressure level, 800-msec stimulus onset asynchrony [SOA]). In the oddball task, subjects were instructed to look at the fixation cross on the monitor and to press a button with their right hand to target tones (440 Hz, 24 trials per block), which were embedded in a sequence with 1000 Hz (TS+) and 1500 Hz (TS–) standard tones (120 trials each per block). Subjects performed 2 pretetanus oddball blocks (Pre Blocks 1 and 2) before the tetanic stimulation block. During tetanic stimulation, 1000-Hz tones were presented at 11 Hz (91 msec SOA) for 2.4 min (1560 stimuli total) while subjects looked at the fixation cross on the monitor. Subjects then performed an oddball block immediately after the tetanic stimulation block (Post Block 1). After performing a visual discrimination task for ~20 min, subjects performed a final oddball block (Post Block 2).

Electrophysiologic Recording and Processing

The EEG was recorded (.01−100 Hz, 500-Hz digitization) with a Neuroscan Synamp amplifier using sintered Ag/Ag-Cl electrodes in an electrode cap at 64 standard scalp sites (26), nosetip, and left mastoid, referenced to the right mastoid, and grounded at AFz. Electrode impedances were <10 kΩ. Bipolar vertical and horizontal electro-oculograms were recorded from electrodes above and below the right eye and at the left and right outer canthi, respectively. Because of electrode problems, 11 channels were excluded from further processing (F7/8, FT9/10, T9/T10, CP5/6, P9/10, and nosetip), leaving 54 scalp channels. Single-trial epochs were extracted from −250 to +772 msec relative to stimulus onset and corrected for ocular artifacts with independent component analysis (27). Next, epochs containing other artifacts were removed. The artifact criteria were as follows: 1) greater than ± 90 μV change in one time point and 2) amplitude range within an epoch exceeding

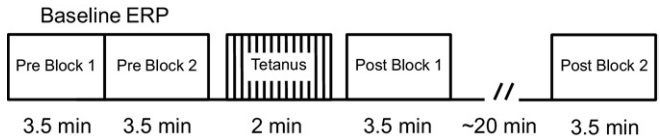

Figure 1. Experimental paradigm. In each block, an auditory oddball task was performed in which the standard stimuli consisted of tetanized (1000 Hz, TS+) and untetanized (1500 Hz, TS–) stimulus tones. Two blocks were performed both before and after the tetanus block. During the tetanus block, TS+ tones were presented at a rapid rate. Subjects performed an irrelevant visual discrimination task during the period between Post Blocks 1 and 2. The event-related potentials (ERPs) from Pre Blocks 1 and 2 were averaged into Baseline ERPs.