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Auditory Brainstem Response Abnormalities in Schizophrenic Patients with Auditory Hallucinations

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Abstract: *Background: although the exact pathogenesis of auditory hallucinations is not yet known, some suggested the impairment of perception and processing of auditory information as a possible explanation. So, the aim of this study is to evaluate auditory pathways of schizophrenic patients using auditory brainstem responses (ABR).*
Methods: schizophrenic patients with auditory hallucinations and age and sex matched healthy non-relative controls were recruited in this case-control study. Scale for assessment of positive symptoms (SAPS) was used for rating the severity of hallucinations. Then, ABR recorded from all participants and the latencies of waves I, II, III, IV, V and inter-peak latencies (IPL) of waves I-III, III-V were analyzed on both sides. Chi squire and independent t tests were applied for statistical analysis. P-value≤0.05 was considered significant.
Results: 39 patients and 35 controls were included. Latencies of waves III and V and IPL of III-V were significantly prolonged on the left side. Disease duration had no influence on the results.
Conclusion: there is a link between abnormal ABRs and auditory hallucinations in schizophrenic patients that indicates dysfunction and abnormal asymmetry of auditory pathways in these patients.

Keywords: *schizophrenia; auditory brainstem response; auditory hallucination.*

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1. Introduction

Schizophrenia is a chronic mental illness that affects about 1% of the population (Patel et al., 2014). Signs and symptoms of this disease are classified into three major categories of positive, negative, and cognitive signs. Abnormal sensory experiences such as hallucinations are among the most common positive signs of the disease with 70% of schizophrenic patients experiencing auditory hallucinations (Waters et al., 2012). The exact mechanism of auditory hallucination in schizophrenic patients is still not well understood. However, recent studies have revealed certain aspects of it (Kumar et al., 2009; Tracy and Shergill, 2013), some of the most important of which focused on changes in brain lateralization of these patients. Reduction of right ear processing ability in the dichotic listening test (Hugdahl et al., 2008), decreased right-handedness (Hirnstein and Hugdahl, 2014), and changes in language lateralization (Ocklenburg et al., 2013) are among the findings of studies conducted on schizophrenic patients. Meanwhile, the decreased volume of Heschl's gyri, especially in the left hemisphere and smaller size of right inferior colliculus are recent findings in the brain of schizophrenic patients that can be associated with auditory hallucinations (Kasai et al., 2003; Kang et al., 2008). Interestingly, this decrease in the nervous system volume occurs mainly in areas related to the central auditory system. Therefore, it seems that the prevalence of auditory hallucinations in schizophrenia is associated with structural changes in the brain.

Some researchers investigating the mechanisms of auditory hallucinations have studied central auditory pathways through electrophysiological recording methods, and since the brainstem is the main transmission route of auditory information, recording of auditory evoked potentials (AEP) in the brainstem is considered an optimal electrophysiological method for studying this sign (Wahlstrom et al., 2015).

Auditory brainstem response (ABR) is an exogenous response that is recorded in the first 10 milliseconds (ms) of an auditory stimulation in the auditory pathways and is a sign of simultaneous neuronal activity from the auditory nerve through the brainstem (Wahlstrom et al., 2015). Few studies evaluating ABR in schizophrenic patients with or without auditory hallucinations yielded inconsistent results; the abnormal findings of these studies included the absence of one or more waves, an increase in the waves' latency, and a decrease in waves' amplitude (Harrel et al., 1986; Hayashida et al., 1986; Igata et al., 1994; Lindstrom et al., 1987; Siegel et al., 1984).

Although there is no agreement on abnormal ABR findings in schizophrenic patients, these changes indicate a brainstem dysfunction and possibly a defect in the processing of auditory perceptions in its early stages. This means that auditory signals undergo abnormal changes before they reach the auditory cortex.

Therefore, we designed a case-control study to investigate changes in the brain AEPs in schizophrenic patients with auditory hallucinations to help better understand the abnormalities of the central auditory pathways of these patients.

2. Materials and methods

2.1. Participants

This is a cross-sectional descriptive-analytic study that was conducted from August to December 2017 at Razi Psychiatric Center (Tehran, Iran). Patients aged 18 to 60 years admitted to this center with a diagnosis of schizophrenia were considered to be included in the study. Inclusion criteria were schizophrenia confirmed by a psychiatrist (OR) according to DSM-5 criteria and presence of active auditory hallucinations. Patients with hearing impairment, known central nervous system (CNS) diseases (history of stroke, head trauma in the last 3 months, history of epilepsy or seizure in the last 6 months, multiple sclerosis or other CNS inflammatory diseases and history of brain tumors) and systemic diseases (such as diabetes) that affect the auditory pathways were excluded. Healthy ones, non-relatives of patients with no history of psychotic disorders in their first degree relatives, were selected as controls.

2.2. Ethical considerations

The study was approved by the Ethical Review Board, University of Social Welfare and Rehabilitation Sciences (1395.158). Informed consent was obtained from all participants or their first degree relatives; they were able to withdraw the study at any time.

2.3. Data collection

Demographic data including age, gender, duration of illness, and drug use were recorded. The Scale for the Assessment of Positive Symptoms (SAPS) was used to record and determine the intensity of hallucinations. This scoring system provided by Andreasen in 1984 evaluates four domains of schizophrenia, including hallucination, delusion, bizarre behavior, and positive formal thought disorder. The hallucination domain consists of

seven items, including auditory hallucinations, voices commenting, voices conversing, somatic or tactile hallucinations, olfactory hallucinations, visual hallucinations, and global rating of hallucinations, ranging from zero to five in severity. This test has good validity and inter-rater reliability for the screening of positive signs (Andreasen, 1984). Then, ABR of all participants was recorded with an EMG/NC/EP device (Negarandishegan Co., model 5000Q). This test, which lasts about 20 minutes, is non-invasive and does not require active collaboration of the patient. The patient sits in a relaxed position on a chair in a dimly lit room. Two active electrodes are placed on both mastoids, a reference electrode on the vertex, and an earth electrode on the forehead using a special gel, and then a headphone is placed on the participant's ears. Before starting the test, the impedance of the electrodes is measured to ensure their proper connection. First, the test method is fully explained to the participant and a short-sequence click is sent to the patient's ears to become familiar with the test. The device then sends 1000 audio clicks (not more than 80 dB) separately to each ear. The duration and frequency of each click are 1 ms and 5 Hz, respectively. The device records the signals of neuronal activity in the auditory nerve and brainstem 10 ms after each click. These potentials include five waveforms named I to V, and the five-wave latency and the inter-peak latency (IPL) of the I-III, III-V waves are determined individually for each ear and recorded in ms. The results of ABR are analyzed by a neurologist (MS) who is blind to the participants.

2.4. Statistical analysis

Data were analyzed in SPSS 20 through chi-square and independent *t*-test for single-variable data. *P*-values of 0.05 or less were considered significant.

3. Results

A total of 39 schizophrenic patients (20 male) and 35 healthy controls (20 male) were recruited for the study. The median age was 37.5 years for the patients and 34.5 years for the controls. Twenty-three patients (59%) had disease duration more than 2 years.

In the hallucinations domain of SAPS, the mean severity of auditory hallucinations, voices commenting, voices conversing, and global rating of hallucinations were 3.8±0.02, 3.7±0.04, 2.2±0.02, and 3.9±0.03, respectively.

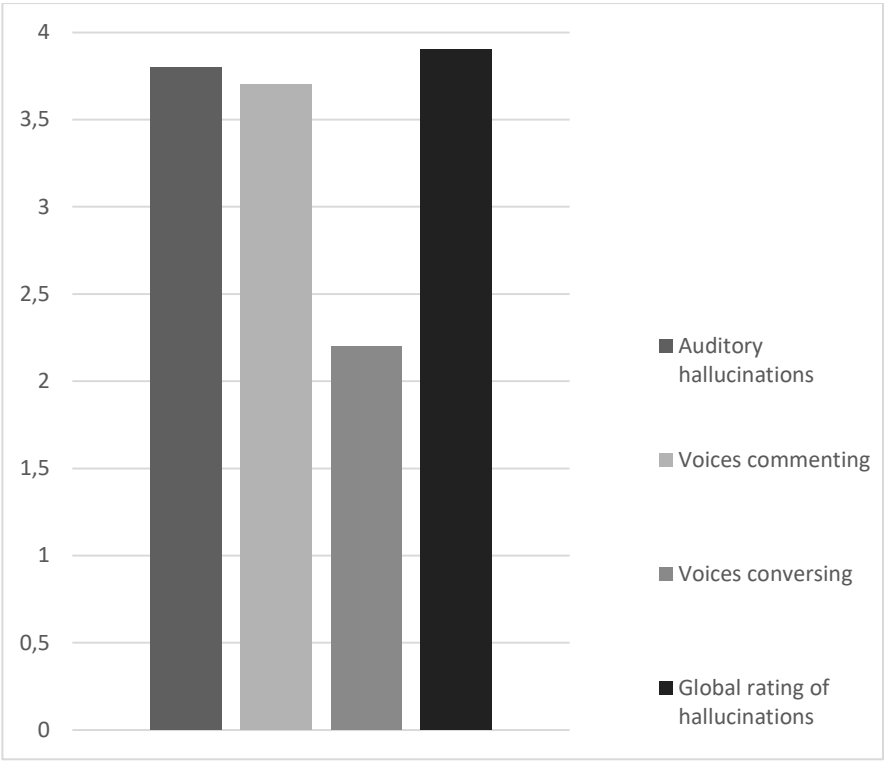


Figure 1. Severity of auditory hallucinations according to the Scale for the Assessment of Positive Symptoms.

Comparison of latencies of ABR waves recorded from the right ear showed no significant changes between patients and controls (Table 1).

Table 1. Comparison of right sided ABR waveform latencies between patient and control groups.

	Latency (±SD)		
Waves	Patients (n=39)	Controls (n=35)	P value
I	1.78±0.02	1.77±0.02	0.27
II	2.87±0.04	2.87±0.04	0.53
III	3.95±0.02	2.96±0.02	0.06
IV	5.25±0.02	5.25±0.03	0.74
V	5.80±0.01	5.80±0.03	0.35
I-III	2.24±0.02	2.21±0.19	0.34
III-V	1.85±0.01	1.83±0.04	0.13

Table 2. Comparison of left sided ABR waveform latencies between patient and control groups.

	Latency (±SD)		
Waves	Patients (n=39)	Controls (n=35)	P value
I	1.78±0.02	1.77±0.02	0.52
II	2.85±0.03	2.86±0.04	0.30
III	3.95±0.03	2.97±0.04	**0.03**
IV	5.24±0.03	5.23±0.05	0.47
V	5.81±0.02	5.77±0.08	**0.03**
I-III	2.23±0.02	2.25±0.04	0.23
III-V	1.86±0.01	1.82±0.03	**0.001**

Table 3. Comparison of right sided ABR waveform latencies between patients with different disease duration. (DD: disease duration)

	Latency (±SD)		
Waves	DD<2 yr (n=16)	DD>2yr (n=23)	P value
I	1.78±0.02	1.78±0.02	0.34
II	2.87±0.04	2.87±0.03	0.47
III	3.95±0.02	3.94±0.04	0.62
IV	5.25±0.02	5.25±0.03	0.24
V	5.80±0.01	5.81±0.03	0.32
I-III	2.24±0.02	2.23±0.03	0.51
III-V	1.85±0.02	1.83±0.04	0.27

Table 4. Comparison of left sided ABR waveform latencies between patients with different disease duration. (DD: disease duration)

	Latency (±SD)		
Waves	DD<2 yr (n=16)	DD>2yr (n=23)	P value
I	1.78±0.02	1.78±0.01	0.54
II	2.85±0.02	2.85±0.04	0.37
III	3.95±0.03	2.97±0.04	0.33
IV	5.24±0.03	5.23±0.05	0.47
V	5.81±0.02	5.77±0.08	0.64
I-III	2.23±0.02	2.25±0.04	0.23
III-V	1.86±0.01	1.82±0.03	0.45

Comparison of latency of ABR waves recorded from left ear between patients and controls showed a significant difference in the waves III, V, and III-V, so that the latency was longer in the patient group (Table 2).

To evaluate the effect of the duration of the disease on the ABR findings, patients were divided into two groups of disease duration of less than two years and more than two years, and the latency of their waves was compared, showing no significant difference (Tables 3 and 4).

4. Discussion

Our study showed that the presence of auditory hallucinations in schizophrenic patients was associated with changes in AEPs; *i.e.*, the prolonged latencies of the waves III, V and III-V IPL on the left side was significantly correlated with auditory hallucinations.

Study of auditory, visual, and somatosensory evoked potentials in schizophrenia has been of interest to researchers since the 1980s, although it has not yet found its place as a biomarker in the diagnosis of these patients. Kubiszewski et al. (1993) reviewed the findings of evoked potentials in schizophrenic patients and presented the most common changes as 1) higher sensory evoked potentials (SEP) amplitude during first 0.1 seconds in chronic schizophrenic patients with severe psychotic signs, 2) reduced amplitude and latency of ABR waves and increased waveform variability of visual evoked potentials (VEP) in schizophrenic patients with active hallucinations, 3) N2 latency prolongation in motor responses to simple and complex stimuli, 4) abnormal P300 and 5) increased waveforms variability in all modalities in chronic schizophrenics (Kubiszewski et al., 1993).

Although attempts to record changes in the evoked potentials in schizophrenic patients have contributed to the understanding of structural abnormalities in the central and peripheral nervous system of these patients, there are still contradictions in these findings. According to researchers, impaired ABR indicates abnormal processing of auditory information and impairment in sensory inhibitory gating in schizophrenic patients, which can lead to auditory hallucinations (Freedman et al., 1996; Siegel et al., 1984).

Siegel et al. (1984) evaluated sensory gating in schizophrenic patients by recording ABR and found that, compared to normal subjects, schizophrenic patients (and some of their first-degree relatives) had deficits in inhibition of second auditory stimuli. The researchers interpreted these findings in favor of gating impairment or the inability to filter auditory stimuli, meaning that the influx of sensory information into the brain of

these patients (in the absence of appropriate and effective filtering) leads to misinterpretation and the occurrence of psychotic signs (Siegel et al., 1984).

In one of the first studies in this regard, Lindstrom et al. (1987) reviewed changes in ABR waves in patients with auditory hallucinations and recorded abnormal ABR waves in half of the 20 patients. These abnormal changes did not correlate with severity of signs, age, and gender, but the association of abnormal ABR with auditory hallucinations was statistically significant; so that 9 out of 11 patients reporting auditory hallucinations had abnormal ABR. The researchers concluded that the brainstem dysfunction was involved in the psychopathology of schizophrenia, and impaired auditory pathways in the brainstem could lead to hallucinations in these patients (Lindstrom et al., 1987). In our study, as in the above research, abnormal changes were recorded in ABR, which could be in favor of an organic basis for the production of auditory hallucinations in schizophrenic patients. These researchers suggested mechanisms, such as denervation hypersensitivity for auditory hallucinations which can result in spontaneous impulse generation in the presence of neuronal injury (Lindstrom et al., 1987).

Lindstrom et al. (1990) investigated the relationship between impaired ABR and monoamine metabolites (HVA, 5-HIVV) in the cerebrospinal fluid of schizophrenic patients. Patients with abnormal ABR had a lower level of HVA. These findings suggest that brainstem dysfunction is associated with decreased levels of dopaminergic and possibly serotonergic activity in schizophrenia (Lindstrom et al., 1990).

In another study, Igata et al. (1994) recorded ABR in 30 schizophrenic patients. In 27% of patients, at least one of the waves I, II or III was missed on either side. The authors interpreted these changes in favor of impaired auditory transmission in the inferior brainstem. In this study, ABR changes were associated with negative signs of patients (not hallucinations) (Igata et al., 1994). In our study, the pattern of ABR involvement was in favor of auditory pathways impairment in the superior brainstem, and these contradictions indicate that impaired ABR in schizophrenia is not specific and fixed, especially with regard to patient's symptoms.

Various neurophysiologic hypotheses have been proposed for the occurrence of hallucinations in schizophrenia including auditory hallucinations (Chen et al., 2019; Cho and Wu, 2013; Kumar et al., 2009; Tracy and Shergill, 2013; Zhang et al., 2018). In the neurophysiologic dissociation theory, the occurrence of hallucination arises from dissociation of the primary sensory cortex from the cortical association areas (Kumar et

al., 2009). In the present study, prolonged latency of the recorded waves can lead to dissociation of the auditory cortex from the pathways ending to it, indicating the reduced regulatory effect of cortical areas on lower pathways, which can lead to hallucinations. Another theory in this approach is the perceptual release, based on which a censorship mechanism in the brain can actively keep away most of the sensory information that continually reaches the brain from the conscious level (Aleman & Laroi, 2008; Kumar et al., 2009). However, the censorship mechanism has the best performance when there is a continuous flow of sensory inputs. Impairment in recorded ABRs in the present study will also lead to disintegration of the auditory information input to the brain; so, this impaired censorship mechanism is another mechanism that is suggested for the auditory hallucinations in the patients of this study. However, it should be emphasized that none of the above mechanisms alone can justify hallucinations in these patients (Aleman & Laroi, 2008). For example, impaired ABR waves can be secondary to a defect in the superior brainstem that can simultaneously cause neurotransmitter disorders which role in the occurrence of auditory hallucinations has been proven (Jardri et al., 2016).

Asymmetry of abnormal ABR changes with a leftward focus was another remarkable point in this study. Although the auditory pathways in the brainstem can establish bilateral hemispheric connections, these findings reconfirm the abnormal asymmetry of brain connectivity in schizophrenic patients (Ribolsi et al., 2014). In recent years, several pieces of evidence have been obtained regarding the decrease in normal asymmetry and the occurrence of both structural and functional abnormal asymmetry in schizophrenic patients (Ribolsi et al., 2014; Sun et al., 2017). For example, patients with significant positive signs have shown leftward asymmetry in the brain functional connectivity confirmed by fMRI (Andreou et al., 2015; Ke et al., 2010; Xie et al., 2018). In contrast, patients with more severe negative signs showed a rise in rightward asymmetry of functional connectivity (Ke et al., 2010). This asymmetry in the central pathways (including the brainstem auditory pathways in our study) can be of a developmental nature and confirm the neurodevelopmental hypothesis in schizophrenic patients. The ineffectiveness of the disease duration on the findings of ABR also suggests that these changes are likely to occur before the onset of clinical disease.

The present study had some limitations. In this study, the traditional method for recording auditory-evoked activity was employed which detects mainly the subcortical (brainstem) auditory pathways. So, this method would not completely elucidate the cortical contribution of auditory processing and

for this reason, limits our study. New methods for concurrent brainstem and cortical AEP measurements may be more useful to analyze disturbed neural pathways of hallucinating patients (Slugocki et al., 2017). In addition, our findings were based on monaural stimulation but some studies emphasizes on the binaural testing in evaluation of central auditory pathways which represents signal detection in a noisy environment. Assessment of binaural interaction may reveal additional abnormalities in patients with auditory hallucinations. For this assessment, some studies used artificial intelligence such as a hybrid machine learning approach for the objective detection of the central auditory pathway disorders and showed promising results (Strauss et al., 2004).

For further research, evaluation of AEPs of healthy first degree relatives of the patients, applying new methods of AEP recording and simultaneous study of AEP-functional brain imaging would be practically useful for elucidating the neural dynamics involved in auditory hallucinations. Also, repeating ABR after attenuation of hallucinations can help evaluate the relationship between ABR impairment and auditory hallucinations more accurately.

5. Conclusion

The present study showed a relationship between the impaired ABR in schizophrenic patients and their auditory hallucinations. This relationship, which was mainly observed in the left side waves III, V and III-V IPL, indicates that this dysfunction was in the superior half of the brainstem (pons and above). So, disturbance in the auditory input processing in cortical areas contribute to the occurrence of hallucinations. These findings demonstrate the organic basis of auditory hallucinations in this disease and may confirm the neurodevelopmental theory of schizophrenia.

Author's contribution:

OR: design of the study, interpretation of data and revision of the article critically
MS: the conception and design of the study, interpretation of data, drafting and final approval of the article
RK: acquisition and analysis of data
Conflict of interest: none

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