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Published in:
Neuroscience Letters

DOI:
[10.1016/j.neulet.2016.08.041](https://doi.org/10.1016/j.neulet.2016.08.041)

2016

Document Version:
Peer reviewed version (aka post-print)

[Link to publication](#)

Citation for published version (APA):

Nielzén, S., Holmberg, J., Sköld, M., & Nehlstedt, S. (2016). Brain stem audiometry may supply markers for diagnostic and therapeutic control in psychiatry. *Neuroscience Letters*, 632, 163-168.
<https://doi.org/10.1016/j.neulet.2016.08.041>

Total number of authors:
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Brain Stem Audiometry may supply Markers for Diagnostic and Therapeutic Control in Psychiatry

Short title: Some biological markers in psychiatry

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Key words: ADHD, schizophrenia, auditory brainstem response, brainstem, biomarker

Abstract

The purpose of the present study is to try an alternative way of analyzing the ABR (Auditory Brainstem Response). The stimuli were complex sounds (c-ABR) as used in earlier studies. It was further aimed at corroborating earlier findings that this method can discriminate several neuropsychiatric states. Forty healthy control subjects, 26 subjects with the diagnosis schizophrenia (Sz) and 33 with ADHD (Attention deficit hyperactivity disorder) were recruited for the study. The ABRs were recorded. The analysis was based on calculation of areas of significantly group different time spans in the waves. Both latency and amplitude were thereby influential. The spans of differences were quantified for each subject in relation to the total area of the curve which made comparisons balanced. The results showed highly significant differences between the study groups. The results are important for future work on identifying markers for neuropsychiatric clinical use. To reach that goal calls for more extensive studies than this preliminary one.

Introduction

Neuropsychiatric diseases are mostly diagnosed and therapy controlled by clinical observation and rating procedures. More objective methods such as EEG [1], brain imaging [2], psychological testing etc. support decisions, but they often lack sufficient sensitivity and/or specificity for psychiatric states. In psychiatric clinical practice it would be valuable to be able to assess or discard neuropsychiatric states by means of some easy to use experimental measuring instrument. This would avoid confounding, costly and time consuming considerations and discussions. Thus, there is an obvious need for experimental documentation of biological traits which can increase the validity of diagnostic and therapeutic processes. This study deals with a method based on operational theory, meaning that an investigative method showing high reproducibility and differentiation can be used as a definition (diagnosis) of a phenomenon (disease).

In the 1990^{ths}, our studies on automatic grouping of complex sound stimuli [3] showed that individuals with the diagnosis of schizophrenia reported aberrant perception of complex psychoacoustic test sounds (auditory illusions) such as discontinuous streaming of tones [4], continuity illusion [5], and contralateral induction [6]. The aberrances indicate a disturbance of automatic sorting in the midbrain of schizophrenics. In order to objectify this, we employed a variant of brain stem audiometry using complex sounds as stimuli (c-ABR) as previously reported [7].

ABR (Auditory Brain stem Response) was first described in 1971. ABR is a diagnostic tool used primarily to detect conductive or sensorineural hearing loss. It registers evoked potentials, generated by subcortical neuronal activity in the auditory pathway in the brainstem, within the first 10 msec following acoustic stimulation (Fig 1). The ABR consists of a sequence of seven positive peaks following the onset of a stimulus. Waves I and II are produced by the Auditory Nerve, whereas the subsequent peaks are due to the combined electrical activity of

nuclei at gradually higher levels of the ascending auditory pathway in the brainstem. Waves III and IV are believed to be generated in the Cochlear Nucleus and Superior Olivary Complex (SOC), respectively, whereas wave V is thought to represent activity at the levels of Lateral Lemniscuses and Inferior Colliculus (IC). Generators for VI and VII are situated at the level of Medial Geniculate Body (MGB) and in thalamocortical neurons [8, 9].

FIG 1 in here

Analysis of the ABR wave patterns normally comprises measurements of inter-peak latencies as well as peak amplitude ratios [10]. The use of complex sounds as acoustic stimuli increases the variability of responses which becomes exposed by more sophisticated analyses. They may reveal aberrations, which may not be assessed by standard audiological ABR procedures. The method does not require active patient participation and is said to be an objective approach to investigate brainstem function.

There were some early attempts in the 1980s to study neuropsychiatry and brainstem functions. For schizophrenia, evoked response abnormality was 1977 reported by Shagass [11]. Evoked Response (ER) showed greater amplitudes and shorter latencies in schizophrenia. Hayashida et al found irregularities of the ABR, such as low amplitudes, an absence of waves, and low amplitudes which correlated with the clinically rated degree of deterioration in schizophrenia [12].

Lindström et al [13, 14] demonstrated aberrations in individuals with the diagnosis of schizophrenia by means of standard ABR. Later they showed that these aberrations were associated with low levels of homovanillic acid (HVA) and 5-hydroxyindoleacetic acid (5-HIAA) in CSF (Cerebral Spinal Fluid). The findings were suggested to indicate a dysfunction in the brain stem in schizophrenia.

The influence of mental states on the ABR was shown by Grillon et al [15], who demonstrated differences between healthy subjects and schizophrenic patients. A method similar to the one applied in this study using complex sound stimuli (c-ABR) was recently employed for investigating Schizophrenic responses [16]. The authors found stimulus-related variability before and after treatment in schizophrenia and conclude that the method c-ABR is “an objective, multidimensional measure of sound encoding that is abnormal in some neurodevelopmental disorders...” and that “it may serve as a sensitive biomarker that predicts and corresponds to therapeutic response....”

Källstrand et al [17] investigated forward masking in subjects with schizophrenia versus healthy subjects by means of a rating method. Schizophrenics displayed rigidity at a certain level of the stimulus-noise configuration, indicating a deficiency in the changing of one of the midbrain's use of its detection mechanisms into another. This finding led to the inclusion of e.g. masking tests in the collection of stimuli into the present ABR method. In preliminary studies of our group important differences between schizophrenia and healthy

states were assessed [18, 19]. Further, these differences raised questions whether other neuropsychiatric states would show differences between study groups as well. Therefore, a control group of individuals with the diagnosis of ADHD (Attention Deficit Hyperactivity Disorder) was included here.

ADHD has been seen to affect the standard ABR. Porrás et al [20] found possible ABR desynchronization in the auditory pathway. Jafari et al [21] found significant differences between children with and without ADHD on ABR following click stimulation and still greater when spoken sounds were used as stimulus. In a study of children 7-10 years of age by Schochat et al, no differences from healthy subjects occurred in the ABRs of ADHD cases. No ABR studies on grown up cases of ADHD seem to have been published as yet [22].

Aims of the study

The aim is to assess divergent mesencephalic pathology between schizophrenia and ADHD versus healthy controls by means of a further developed variant of ABR. This method is based on complex sounds as stimuli and is sometimes called c-ABR. Another objective was to test an alternate new approach to analyze the ABR responses from stimulation with complex sound samples.

Method

Subjects

Study subjects were chosen from a data base that had been collected for about 5 years, containing subjects from Lund University Hospital. They were chosen in the frames of description in Källstrand et al 2012 [23] to represent as clinically significant type cases as possible. The number and ages of the subjects were: Schizophrenia; n=26, age m=38.9, SD=9.1, ADHD; n=33, m=37.4, SD=10.9 and healthy controls n=40, age m=38.4, SD=10.8. Their diagnoses had been set by senior psychiatrists according to DSM-IV. All of the schizophrenics but two were medicated with neuroleptics and 11 ADHD-patients were medicated with methylphenidate. Approval for the study was granted from the ethical committee of the Lund University: LU-353/2006.

Stimuli and apparatus

A square-shaped click pulse was used as a starting stimulus. The click pulse had a duration time of 0.000136 seconds and a rise and fall time of 0.000023 seconds. There was an inter-stimulus interval (ISI) from onset to onset in trains of pulses of 0.192 seconds. Thirteen trains of stimuli were used in the experiment. In train 2 SPL (Sound Pressure Level) was changed to get a weak sound. In 4-7 high pass, and in train 8 low pass pulses were

used. A forward and backward paradigm was used in 9-13. The stimuli trains are patented. The square-shaped click pulses were presented to the subjects with an intensity level of 80 dB SPL. The evoked potentials were recorded with a standard equipment (GN Otometrics, Taastrup, Denmark). TTL trigger pulses coordinated the sweeps with the auditory stimuli. In each condition the stimuli were repeated until a total of 1024 accepted trains for each ear had been collected. Each ABR waveform represents an average of the responses to 1024 stimulus presentations. Aberrant activity, such as extremely high amplitudes due to extraordinary movements, was rejected using the standard setup GN Otometrics' Chartr software. Sound levels were calibrated using a Bruel and Kjaer 2203 sound level meter and Type 4152 artificial ear (Bruel and Kjaer S&V Measurement, Naerum, Denmark). All stimuli were constructed using MATLAB Signal Processing Toolbox (The MathWorks, Inc., Natick, MA, USA) and presented using a Denon DCD-685 compact disc player (Denon Electronics, Mahwah, NJ, USA). The output of the CD player was connected to TDH-50P headphones with Model 51 cushions (Telephonics, Farmingdale, NY, USA). Presentations were made binaurally with the stimuli in phase over headphones.

Testing procedure

All tests were performed in a quiet darkened room. Participants were comfortably seated in an armchair in a resting position. Electrodes were attached to the skin over the mastoid bones behind the left and right ear, with a ground electrode and a reference electrode placed on the vertex and forehead, respectively. Before the test session, the procedure was fully explained to the test subject and the click sounds were presented beforehand to make him/her acquainted with the stimuli. Absolute impedances and inter-electrode impedance were measured before and after the experiments to verify that electrode contact was maintained (below 5000 Ω). The subjects were instructed to relax with their eyes closed and were permitted to fall asleep. The test required no active participation other than being subjected to sound stimulation. The subjects were tested one at a time and the duration of the testing procedure was 40 minutes.

Analysis of data

The individual auditory brain stem curves from the raw data of the GN Otometrics' Charter EP ABR recordings were listed. The curves were united into median curves for the ADHD, Schizophrenic (Sz) and Healthy controls' (Hc) groups respectively. Amplitude differences between the study groups of these median curves were measured at all consecutive 1760 points on the time axis (abscissa). Time spans of the curves where significant higher or lower amplitude from the Hc median curve occurred (Mann Whitney $p < 0, 5$ and higher levels) were cut. The areas under the curve during the spans of varying length were divided with the total area under the subjects' ABR curve, multiplied with a fixed constant (1000) and the exact level of significance between groups was calculated. The calculation of relative span areas instead of point calculation includes latency differences at the same time, and as relative values they are possible to compare. If a significant deviation was specific for one

of the groups (ADHD, Sz) and not for the other it was labelled a “trait” for that diagnostic group. The deviations of the pathological groups had to be significantly different from the Hc group in the first hand.

Then all individuals’ position relative to all significant traits of the median curves’ of the two genders was calculated. The Mann-Whitney significances of n.s., < .05, < .01 and < .001 for a trait of the ADHD and Sz in relation to the Hc median trait rendered the individual trait a value of 0, 1, 2, or 3. The numerals (0, 1, 2, 3) were summed to a total for each subject and divided with the total possible sum of the diagnostic group in question. This proportion (sum ratio) is displayed in percent for the subjects of the study in Fig 2 and 3. When comparing the degree of match between the samples a cut off at 60 percent was chosen, i.e. the sum ratio of trait values over 60 percent was set as indicating pertinence to the diagnostic group and a value under 60 percent as not reflecting the particular diagnosis (see Fig 2, 3).

Results

From visual inspection of the curves presented in Fig.1 it may be observed that the curves of the Sz are different in early midbrain (0-590 data points) and late midbrain (1100-1760 data points). It can also be seen that the whole lines differ in that among Sz the left side curve lags less behind the right side curve than among Hc. This regards again early and late midbrain. The great differences between genders are conspicuous Tables (1a,b). The levels of each individual’s sum ratio of traits expressed as percent for the diagnostic groups are presented in Fig. 2, 3. The results obtained show a high degree of discrimination between the study groups as seen from Table 2. There are few outliers. The Fischer’s exact test for the concordance versus non-concordance with the subjects’ clinical diagnoses and the ABR diagnoses (ADHD / Hc and Sz / Hc) both yield $p < 0.0001$.

Table 1 a and b in here

Figure 2 and 3 in here

Discussion

This study was undertaken to get a preliminary cue of the possibility to assess discrimination between diagnostic groups of clinical neuropsychiatric states. It was one in a row of experiments performed since the 1990s which took its start with schizophrenia on the assumption that this disease must be influenced by pathology in the brain stem. The symptoms of this disease are, namely, not regular or focalized as e.g. in dementia, and they may include sensory, motoric, olfactory, visual and most importantly auditory dysfunctions in random and unforeseeable combinations.

It had earlier been discovered that schizophrenics perceived psychoacoustic test sounds in grossly erratic ways. Therefore, we introduced complex sound stimulation, as psychoacoustic complex processing (automatic sorting) takes place in the brain stem. This process was suspected to have a prominent role in schizophrenia. Especially sequential testing, as in ABR measurements, is important because the discontinuity of perceptual and other brain processes is core symptom in this illness. Further, the present way of analyzing the curve was used as the mere estimation of amplitude and latencies commonly used is less informative. It was supposed that a complex approach targeting amplitude and latency at the same time and reflecting the dynamic pattern of the whole curve would be more sensitive to subtle differences of activity.

Even with an unarm'd eye one can see that there are several irregularities in the Sz curve-compared with the one from the Hc group (Fig 1). They most importantly concern early and late midbrain processes (see also Table 1 b). The diminished priority of normal right ear dominance within these areas in Sz, not seen in ADHD (not shown), tells about lateralization differences also in the midbrain (cf 23). They are earlier known from cortical areas [24]. The same early and late areas likewise dominate the ADHD significances but the two samples are different in the whole curve aspect. The great differences of the sexes are interesting and reflecting similar ones in clinical practice. In fact, only one significant area in each of the study groups is common for the two genders.

Medication can influence the results. This could not specifically be considered here, but earlier studies have indicated that in schizophrenia the effect of psychotic symptoms strongly overrides that of medications [25]. Consequently, the possible influence on these pathological markers was supposed to be of minor importance in this context. Regarding ADHD, a pilot study showed reduction of pathology of the markers in 10 of 11 patients after Methylphenidate medication [26].

The frequency distributions of individual sum ratios in percent values discriminate the three diagnostic groups at a high level of significance. The pathological study groups showed one false positive value as well as some false negative ones. The causes of these may be related to background factors. Sampling, imprecise diagnostics, machine failure at some point, age, sex, medication and much more plays roles here. When investigating other samples such as groups of personalities, drug abuse samples, autism spectrum disorders etc., the significant areas occur more evenly distributed than in the present two groups. With regard to e.g. autism a significant difference around wave III was shown [27]. Evidently, there are organic and/or physiological disturbances in the brain stem of many psychiatric diagnostic groups. The disturbances may be explained either by original developmental lesions [28, 29, 30, 31] and/or plasticity changes provoked by influences from structures near or in the auditory pathway [32].

According to the present findings, schizophrenic brain stems have their weakness already in the acoustic nerve, cochlear nucleus (CN) and at a later stage in the thalamo-cortical region where comprehensive acoustical features are composed and sorted [33, 34, 35, 36]. A dysfunctional generation of genuine (primary, basic) sorting

(correlative activity with inhibition and facilitation) in CN may build up difficulties for the MGB to create meaningful combined neuronal response (features, schema-based sorting). The disarray at this point may later hamper the cortex to make correct interpretations. Hallucinations and cognitive dysfunctions may be partially caused by such changes.

ADHD brain stems show affection in the late midbrain as well as a few significant aberrations in the medial brainstem. In inferior colliculus (wave IV, V) all codes have been translated into place codes for frequency, sound pressure and phase [37]. No wonder that a dysfunction here - meaning diminished precision of perception of spectrum, direction and loudness - would contribute to causing uncertainty and attentional problems. In passing, it may be mentioned that we found aberrances in early structures in autism spectrum disorder (lateral lemniscus, superior olivary complex and the trapezoid nucleus), possibly contributing to the changes of hearing, well-known in that disorder.

Although this study has a value in pointing at the existence of neurophysiological bases for neuropsychiatric disorders in the brain stem, it has to be regarded as preliminary. Carefully designed controlled studies must follow. The ultimate immediate task will be to further search for still better analyzing algorithms, to enhance the dissolution of the ABR machine, and to get corroboration of the results from independent researchers. Our expectation is to finally get reliable validations in order to offer the technique as a means for supporting diagnostics and therapy control in psychiatric clinical settings.

Conclusion

The present investigation has demonstrated characteristic and intergroup mutually exclusive activity of auditory brain stem nuclei between diagnostic groups of schizophrenia and ADHD and a group with no such diagnosis. There is an increasing growth of interest in psychoacoustics and neurophysiology of hearing which by new methods of tracing and imaging has shown details of organic and biochemical impairments in the studied disorders. The study therefore contributes to the knowledge of biological bases of them, and might be useful for different research. It certainly seems encouraging in the search for an objective measuring instrument supporting clinical decisions in the future.

Conflict of interest

Author Sören Nielzén holds stock in SensoDetect AB. Authors Mia Sköld, Jens Holmberg and Sara Nehlstedt are employees of, and hold stock in SensoDetect AB.

Acknowledgements

We are grateful for the support given by the Psychiatric clinic, Lund University Hospital, especially Professors Åsa Westrin and Anders Tingström. We also appreciate the willingness of SensoDetect AB® for putting its resources at our disposal.

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Table 1**a)**

Traits of the diagnostic group ADHD. I: Ordinal number of the 13 complex sound stimuli. II: . L=electrode on the left side, R= electrode on the right side of the head, L/R electrodes from both sides. III: Area borders= time limits of the significant spans.

b)

Traits of the diagnostic group schizophrenia (Sz). I: Ordinal number of the 13 complex sound stimuli. II: . L=electrode on the left side, R= electrode on the right side of the head, L/R electrodes from both sides. III: Area borders= time limits of the significant spans.

Table 2

Shows the study-groups, Hc; healthy subjects, Sz; subjects with schizophrenia and ADHD; subjects with Attentional Deficit Hyperactivity Disorder. Sex ratios. Ratios of trait values as an expression of sensitivity.

Table 1

a)

Spans of significant ADHD traits of the median curves

Female group,		
I	II	III
1	R	1435-1454
1	R	783-816
2	R	1266-1286
5	L/R	185-190
5	L/R	783-792
8	R	1577-1592
9	R	1450-1468
9	R	687-717
10	L/R	388-399
10	R	1335-1347
11	L	1014-1037
13	L	1228-1260
13	L/R	1289-1303
13	R	1383-1413

Male group		
I	II	III
5	L/R	504-528
5	L/R	1242-1264
6	L/R	16-29
6	L/R	236-245
6	L/R	298-303
7	L/R	177-187
7	L/R	335/367
7	R	1410-1424
8	L/R	346-359
8	L/R	572-582
11	L	1014-1037

Table 1

b)

Spans of significant schizophrenia traits of the median curves

Female group		
I	II	III
4	L/R	546-566
4	L/R	712-737
6	R	1433-1443
7	L	1038-1068
8	L/R	142-146
8	L/R	302-307
8	R	692-717
8	R	837-846
8	L/R	1240-1250
8	L	1344-1355
8	R	1437-1446
9	L	136-153
13	L	1634-1643

Male group		
I	II	III
1	L	1168-1179
1	R	1346-1392
1	R	1430-1443
2	L/R	596-607
4	R	1089-1113
4	L	1220-1239
5	R	1342-1359
6	L	1128-1147
8	L/R	244-258
8	L/R	446-463
8	L/R	1304-1312
9	L/R	550-573
9	L	1117-1143
11	R	1454-1467
12	L/R	589-601

Table 2

Display of study-groups, number and gender distribution and proportion of concordance with the clinical diagnosis (sensitivity)

Group	n (male/female)	Sensitivity
ADHD	33 (16/17)	29/33 (88%) 4 false negative
Hc	40 (15/25)	36/40 (90%) 4 false positive for ADHD
Sz	26 (18/8)	22/26 (85%) 4 false negative, 1 false positive for ADHD

Legends

Fig 1

Illustration of wave patterns of the median ABR within the 10msec recording. Upper two wave forms are from the schizophrenic sample, lower two from the healthy controls. Whole lines are from the left side electrodes and dotted/dashed from the right. Roman numerals refer to the conventional peaks of ABR. Arabic numerals indicate the time data points.

Fig 2, Fig 3

Individual percentual values (round points, sum ratios) for each of the subjects. ADHD; Attention Deficit Hyperactivity Disorder, Hc; Healthy Controls, Sz; Subjects diagnosed with schizophrenia. Short horizontal lines indicate medians.

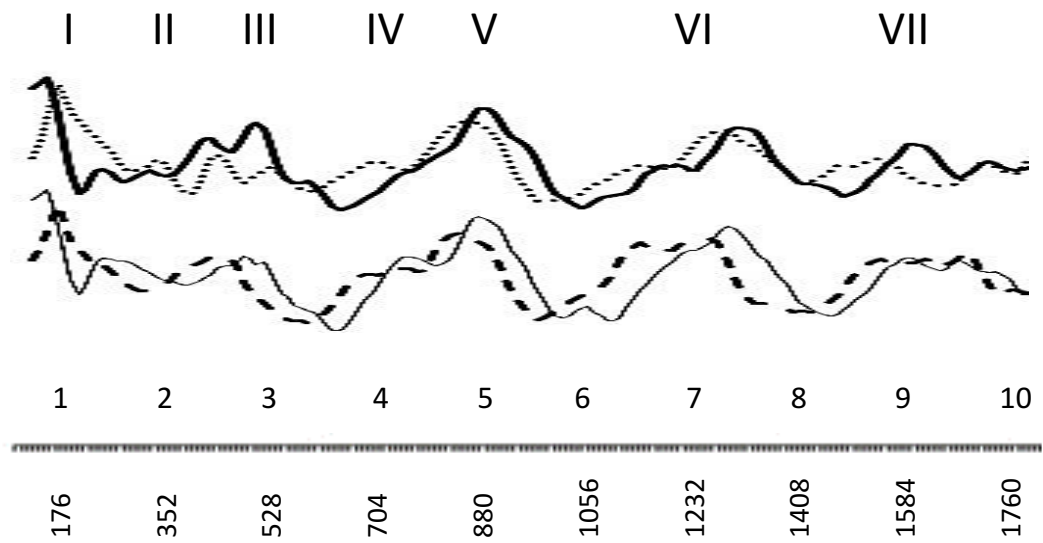


Fig 2

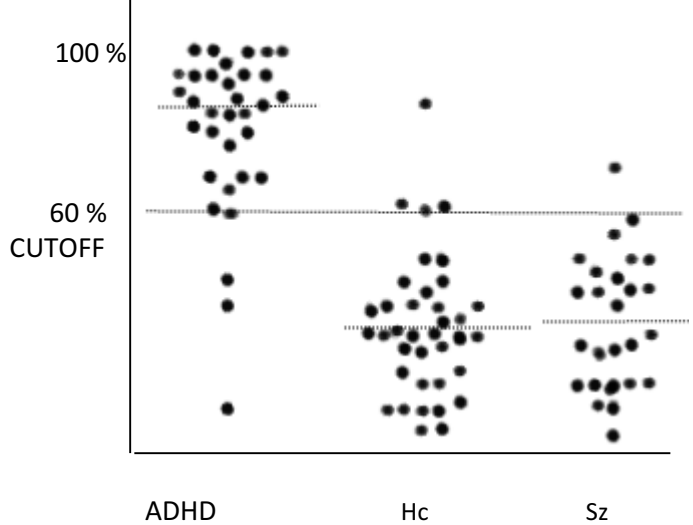


Fig 3

