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EC NEUROLOGY
Research Article

Identification of Brainstem Biomarkers Supporting Clinical Diagnoses of ADHD and Schizophrenia Using Noninvasive ABR Technique

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Received: February 09, 2016; **Published:** April 07, 2016

Abstract

The auditory brainstem response (ABR) waveform comprises a set of waves (labeled I – VII) recorded with scalp electrodes over 10 milliseconds after an auditory stimulation with a brief click sound. Quite often the waves are confluent and baseline irregular and sloped making wave latencies and wave amplitudes difficult to establish. In this paper we describe how disease-specific biomarkers are found using measurements of data from ABR recordings. We also describe how these biomarkers can be used to build up a trait match for groups of patients with ADHD and schizophrenia, respectively, both of which showing high prediction values.

Keywords: *Auditory Brainstem Response; Schizophrenia; ADHD; Biomarker*

Abbreviations: ABR: Auditory Brainstem Response; ADHD: Attention Deficit Hyperactivity Disorder; HC: Healthy Control; SZ: Schizophrenia; PCR: Patient´s Cutoff Response; PTV: Patient's Trait Value; TRC: Trait Constant; SOC: superior olivary complex; qEEG: Quantitative Electroencephalogram; dB: decibel; Hz: hertz; ms: milliseconds; W68: Width 68 data points; W136: Width 136 data points; TTL: Transistor – Transistor Logic; SPL: Sound Pressure Level; SCP: Standard Click Pulse; LA: Low Amplitude; HP1-4: High Pass sounds1 to 4; LP: Low Pass; FM1-3: Forward Masking sounds 1 to 3; BM1-3: Backward Masking sounds 1 to 3; PDM: Patient's Disease Match; N.A.: Not Applicable

Introduction

A detailed understanding of auditory processing was described by Jewitt and Williston back in 1971. The auditory brainstem response (i.e. ABR) is built up by wave patterns following click stimulation and is a result from evoked electrical potentials measured in microvolts, recorded from surface electrodes attached to the vertex and the mastoid bones [1]. ABR is an objective method that does not require active subject participation. The subsequent ABR comprises seven waves, denoted I – VII, that occur within 10 milliseconds after peak in wave I. The first two waves originate from the cochlear nerve [2,3]. The subsequent waves III and IV emanate from the cochlear nucleus and the superior olivary complex (SOC), respectively. Wave V represents electrical activity from both the lateral lemniscus and inferior colliculus [4]. Waves VI and VII are believed to have thalamic (medial geniculate body) origin [2]. The ABR waves are traditionally analyzed in terms of latencies and amplitudes of these seven peaks [3,5]. This include measurements of inter-peak latencies as well as peak amplitude ratios [6,7].

Various audiological and neurological abnormalities can be detected by examining the waveform, albeit with the inherent disadvantage of displaying high inter- and intra-individual variability [3,5,8]. We have included quantitative measures for norm curve similarities, in line with quantification of data following qEEG measurements [9]. An analogue approach to this procedure that quantitatively cor-

related individual measures towards norm curves was included in this ABR analysis. We have previously reported bilateral similarity by correlating left-right hemisphere activity [10]. In this study, we employ a similar procedure, but choose to correlate individual patient data with norm curves from disease-groups, as well as with healthy control groups.

As sex differences have been reported in human ABRs, the present study separated diagnostic groups by gender for statistical analyses [11,12].

Previously, quantification of ABR measurements has revealed novel biomarkers for several neuropsychiatric conditions like schizophrenia [10]. bipolar disorder [13]. Asperger's syndrome [14,15]. In the present paper we describe how disease-specific biomarkers are found using measurements of data from ABR recordings. We also describe how these biomarkers can be used to build up a trait match for groups of clinically diagnosed ADHD and schizophrenia patients, respectively, both of which showing high prediction values.

Due to the fact that our previous research within psychoacoustics has been set around stimulation with complex sounds [14,16,17]. This study also employed click-stimuli with reduced amplitude, processed by filters and in connection with preceding or subsequent masking noises.

Material and Methods

Subjects

This study included 29 patients with ADHD (14 males between 22-45 years, median 32.5 years; 15 females between 22-67 years, median 29 years), 33 patients with schizophrenia (17 males between 20-53 years, median 38 years; 16 females between 26-58 years, median 39 years) and 39 control subjects (19 males between 22-54 years, median 28 years; 20 females between 20-60 years, median 40 years) as depicted in Table I below. A formal consent was ascertained in accordance with the requirements of the ethical committee at the University of Lund, Sweden (document number 353/2006).

	Control males	Control females	ADHD males	ADHD females	SZ males	*SZ females*
N	19	20	14	15	17	*16*
***Age at test (m/f)**	28 (22 - 54)	40 (20 - 60)	32,5(22 -45)	39(22-67)	38 (20-53)	*39 (26-58)*
Psychiatric medication	*0 med n = 14,* *no data n = 4, sertralin n = 1*	*0 med n = 16,* *no data n = 3,* *citalopram n = 1*			*0 antipsychotic med n = 1,* *no data n = 4,* *antipsychotic med not spec n = 5,* *quetiapine n = 1,* *clozapine+ zuklopentixol dep n = 1,* *aripiprazole 1,* *zuklopentixol dep n = 1,* *olanzapine n = 1,* *olanzapine+ aripiprazole n = 1, clozapine n = 1*	*no data n = 4,* *antipsychotic med not spec n = 8,* *clozapine + ziprasidone n = 1,* *olanzapine injectable n = 1, aripiprazole n = 1,* *clozapine n = 1*

Table 1: *Study Subjects.*

**Age median (range).*

Click stimuli modifications

One complete test comprised a standard square-shaped click SCP followed by 12 modified stimulations. Firstly, a standard click ABR was conducted. After this, mentioned click pulse was amplified -3dB, thus having a LA. Thereafter, the original click pulse was high pass filtered with a Butterworth filter and repeated three times HP1-4. Stimulation number seven used a LP filtered version of the click pulse. The last six stimulations all used the standard click, with a preceding grey noise (i.e. FM1-3) for sessions eight to ten, and a subsequent noise (i.e. BM1-3) for sessions eleven to thirteen. The noise amplitude differed for the three forward masking sessions, with a low level of noise initially and the highest last (starting at 54dB and increased in steps of +3dB). This was applied to backward masking accordingly. Curves were processed as previously described [18].

Stimuli descriptions

The click pulses were repeated until a total of 1024 accepted evoked potentials had been collected for each sound stimulus. Thus, each ABR waveform represents an average of the responses to 1024 stimulus presentations. TTL (transistor logic) trigger pulses coordinated the sweeps with the auditory stimuli. A TTL pulse is the signal which tells the ABR system to measure. With a correctly timed TTL pulse, all ABR representations will be synchronized. Aberrant activity, such as extremely high amplitudes due to extraordinary movements was rejected. Sound levels were calibrated using a Bruel and Kjaer 2203 sound level meter and Type 4152 artificial ear (Bruel & Kjaer S&V Measurement, Naerum, Denmark). The acoustic output from the earphones corresponds to sound pressure level (SPL): 80 dB hearing level HL or 109 pe SPL (peak equivalence). A square-shaped click pulse was used as probe in the auditory masking stimuli [14]. The sound stimuli included square-shaped click pulses (0.136 ms duration including 0.023 ms rise and fall; 192 ms inter stimulus interval), high pass filtered pulses (a Butterworth high-pass filtered square shaped click pulse with a cutoff of 3000Hz), forward masking (12.3 ms gap from masker to click pulse) and backward masking (12.3 ms from click pulse to the masker) stimuli as previously described [14]. A 1500 Hz Butterworth low-pass filtered noise with 15 ms duration including 0.4 ms rise and fall time was used as masker for both forward and backward masking stimuli. All stimuli were constructed using MATLAB Signal Processing Toolbox (The Math Works, Inc., Natick, Massachusetts, USA) and stored in a flash memory in the ABR. The stimuli were presented via TDH-50P headphones with Model 51 cushions (Telephonics, Farmingdale, New York, USA). Presentations were made binaurally with the stimuli in phase over headphones.

Data Analysis

Trait identification

ABRs were scrutinized to unfold potential trait regions with respect to stimuli used for left/right ear. Three types of filter processing (i.e. designated “Unprocessed, W68 or W136”) were employed as shown for the identified traits in Tables II-V, as previously described [18].

Total stimuli traits were put forth to establish stable measures and were constructed as a median value from traits of 26 ABRs (ie both left and right sides for all 13 variations of stimulus). Hence, total stimuli for each ear comprised 13 stimuli variations from each side ABRs, respectively. For correlation traits, the r-value for a specific time window from each ear and sound stimulus was listed to depict the median value. Sometimes, this procedure was applied specifically for masking sounds (i.e. FM1,2,3 and BM1,2,3).

In addition, each studied group was randomly split in half, to unbias training data, thus. Ocular investigations as well as group statistics further revealed that disease characteristics were identified in time windows, rather than in specific peaks. Thus, the majority of traits were of either correlation or distance types as described below.

Principles of the trait descriptions

As shown in figures 1A and 1B below, five different trait types were used in the study, denoted A to E. The gender-specific correlations (A and B) were calculated with respect to time windows, stimulus, and ear, between the measured patient and a specified norm curve (i.e.from SZ, ADHD or Control). An identical approach was applied regarding the gender-specific distance-to-norm ABR calculations (C and D). For these calculations, the accumulated absolute distance within a specific time window for the measured patient's ABR was calculated. In addition, time-specific amplitudes of interest (E) were also analyzed, See figure 1A.

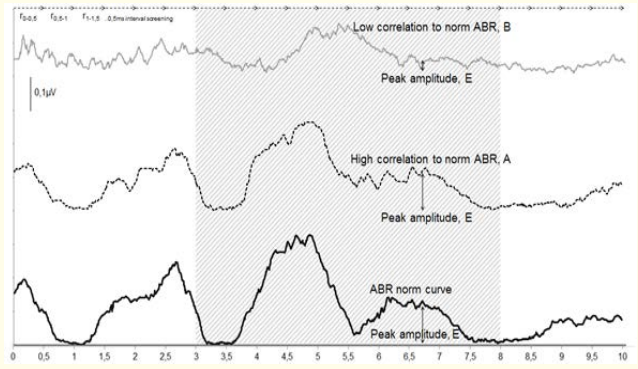

Figure 1A: *Graph representationof how calculations were performed using gender-specific correlations (i.e. > 0.5 ms interval screening) with respect to time windows, stimulus, and ear, between the measured patient and a specified norm curve.In this figure W136 processed curves are used as previously described (Källstrand J, 2014). A) Example of high correlation for a patient´s ABR curve (time window 3-8 ms) towards the ABR norm curve; B) Example of low correlation for a patient´s ABR curve (time window 3-8 ms) towards the ABR norm curve; E) Example of how time-specific amplitude was measured.*

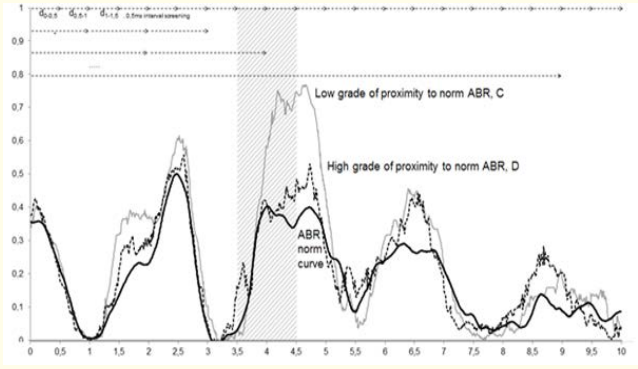

Figure 1B: *Graph representation of how calculations were performed using gender-specific distance values (i.e. > 0.5ms interval screening). C) Example of high distance to norm ABR for a patient´s ABR curve (time window 3.5-4.5 ms) towards the ABR norm curve; D) Example of low distance to norm ABR for a patient´s ABR curve (time window 3.5-4.5 ms) towards the ABR norm curve. Y: Relative amplitude; X: Time (ms).*

Calculation of diagnostic trait match

In this study, a categorical cutoff approach (i.e. Boolean statistics) for each trait was chosen. Trait cutoffs were first set as the average between the median of the healthy control training group and the median of the specific disease training group. If a patient´s trait value (PTV) was above or below the cutoff level, depending on the direction of the disease training group, he or she received the value of 0 or 1, hence labelled the patient´s cutoff response (PCR). A patient's disease match (PDM) index for ADHD and schizophrenia, respectively, was represented by the patient's sum of the PCRs, each multiplied by a trait constant (TRC; weight) and divided by the maximum number of traits for the disease group times 100. The index values for the PDMs ranged from 0 – 100%. Trait constants were applied in order to obtain highest possible sensitivities and specificities.

Statistical analysis

For group comparisons during identification of significant traits to be used, Student t-test was used (*p < 0.1; **p < 0.01; ***p < 0.001). Pearson correlation was used to depict the degree of linear dependence between any two ABR curves. Sensitivity and specificity was also calculated using either Graph PAD PRISM.

Results and Discussion

Results

Tables 2 to 5 below show identified traits, used for ADHD and Schizophrenia trait matching towards clinical diagnoses.

Trait Id	Stimulus	Time	processing	L/R	Trait Type	Norm Curve	Cut off for disease	P-value (t-test)
AF 1	FM 1, 2, 3	6-7 ms	W 136	Bilateral	B	Healthy	< -0.3	< 0.001
AF 2	BM 1	6-7 ms	W 136	Bilateral	A	ADHD	> 0.46	< 0.1
AF 3	Total Stimuli	4-9 ms	W 136	Bilateral	A	ADHD	> 0.7	< 0.001
AF 4	Total Stimuli	2-9, 5 ms	W 68	Bilateral	A	ADHD	> 0.4	< 0.001
AF 5	BM 1	2,5-3,5 ms	W 68	Bilateral	A	ADHD	> 0.44	< 0.1
AF 6	Total Stimuli	7, 5-9,5 ms	W 68	Left	A	ADHD	> 0.37	< 0.01
AF 7	Total Stimuli	7, 5-9,5 ms	W 68	Right	A	ADHD	> 0.46	< 0.1
AF 8	BM 1	2-9, 5 ms	Unprocessed	Bilateral	B	Healthy	< 0	< 0.001
AF 9	Total Stimuli	6-9, 5 ms	Unprocessed	Left	A	ADHD	> 0.2	< 0.01
AF 10	Total Stimuli	6-9, 5 ms	Unprocessed	Right	A	ADHD	> 0.46	< 0.001
AF 11	Total Stimuli	2-9, 5 ms	Unprocessed	Bilateral	A	ADHD	> 0.5	< 0.001
AF 12	Total Stimuli	7-9,5	Unprocessed	Bilateral	A	ADHD	> 0.56	< 0.001
AF 13	Total Stimuli	5-7 ms	Unprocessed	Left	A	ADHD	> 0.4	< 0.001
AF 14	Total Stimuli	5-7 ms	Unprocessed	Right	A	ADHD	> 0.6	< 0.001
AF 15	Total Stimuli	2-9, 5 ms	W 136	Bilateral	C	ADHD	< 1	< 0.01
AF 16	Total Stimuli	2-9, 5 ms	W 68	Bilateral	C	ADHD	< 1	< 0.001
AF 17	HP 1	5, 5-6, 5 ms	W 68	Left	C	ADHD	< 1	< 0.001

Table 2: *Identified ADHD Traits for females.*

Table 2 depicts 17 significant female ADHD traits that were extracted following data scrutinization, most of which were found using Trait Type A (i.e. high correlation to norm ADHD curve). Some traits were specifically identified using masking click-stimuli (i.e. AF1, 2, 5, 8) or high pass click-stimuli (i.e. AF17). The majority of identified traits could be observed in the 6-9 ms ABR region, peaking at 6-7 ms in the first half of wave VI region representing thalamus.

Trait Id	Stimulus	Time	Processing	L/R	Trait Type	Norm Curve	Cutoff for disease	P-value (t-test)
AM 1	SCP	6,5-7,5 ms	W136	Bilateral	B	Healthy	< -0.1	< 0.1
AM 2	Total Stimuli	2-9,5 ms	W136	Bilateral	A	ADHD	> 0.41	< 0.001
AM 3	FM1,2,3 & BM1,2,3	7-9, 5 ms	W68	Bilateral	A	ADHD	> 0.4	< 0.001
AM 4	Total Stimuli	2-9,5 ms	Unprocessed	Bilateral	A	ADHD	> 0.39	< 0.001
AM 5	Total Stimuli	2-5 ms	W136	Bilateral	C	ADHD	< 1	< 0.001
AM 6	BM1	3, 5-4, 5 ms	Unprocessed	Left	A	ADHD	> 0.35	< 0.1
AM 7	BM1	3, 5-4, 5 ms	Unprocessed	Right	A	ADHD	> 0.25	< 0.01
AM 8	Total Stimuli	6-9, 5 ms	W136	Bilateral	A	ADHD	> 0.2	< 0.1
AM 9	Total Stimuli	4-9, 5 ms	Unprocessed	Bilateral	A	ADHD	> 0.38	< 0.001
AM 10	FM1,2,3 & BM1,2,3	7-9, 5ms	W136	Bilateral	A	ADHD	> 0.41	< 0.001

Table 3: *Identified ADHD traits for males.*

Table 3 depicts 10 significant male ADHD traits that were extracted following screening, most of which were found using Trait Type A (i.e. high correlation to norm ADHD curve). Some traits were specifically identified using masking click-stimuli (i.e. AM3, 6, 7, 10). The majority of identified traits could be observed in the 6-9 ms ABR region, representing thalamus (wave VI) and the thalamocortical region (wave VII). All p values were calculated by t-test group comparisons of disease group compared with gender-specific healthy control group.

Trait ID	Stimulus	Time	Processing	L/R	Trait type	Norm Curve	Cutoff for disease	P-value (t-test)
SF 1	0.	7-9, 5 ms	Unprocessed	Left	A	SZ	> 0.4	< 0.001
SF 2	Total Stimuli	7-9, 5 ms	Unprocessed	Right	A	SZ	> 0.4	< 0.001
SF 3	FM1	2-3 ms	Unprocessed	Bilateral	A	SZ	> 0.8	< 0.1
SF 4	Total Stimuli	6-8, 5 ms	Unprocessed	Left	A	SZ	> 0.6	< 0.01
SF 5	Total Stimuli	2-9 ms	W136	Left	A	SZ	> 0.5	< 0.01
SF 6	Total Stimuli	2-9 ms	W136	Right	A	SZ	> 0.3	< 0.1
SF 7	FM1	8, 5-9, 5 ms	W136	Bilateral	B	Healthy	< -0.38	< 0.001
SF 8	Total Stimuli	3-9 ms	Unprocessed	Bilateral	A	SZ	> 0.44	< 0.1
SF 9	Total Stimuli	6-8, 5 ms	Unprocessed	Right	A	SZ	> 0.5	< 0.001
SF 10	BM3	6-7 ms	Unprocessed	Bilateral	B	SZ	< 0	< 0.001
SF 11	Total Stimuli	2-9 ms	W68	Bilateral	D	Healthy	< 1	< 0.001

SF 12	Total Stimuli	5-7 ms	W68	Bilateral	A	SZ	> 0.33	< 0.01
SF 13	Total Stimuli	3-8 ms	W136	Bilateral	A	SZ	> 0.6	< 0.001
SF 14	HP1	8-9 ms	W68	Left	B	Healthy	< -0.25	< 0.1
SF 15	Total Stimuli	5-9 ms	Unprocessed	Bilateral	A	SZ	> 0.67	<0.001
SF 16	FM1	8-9 ms	W68	Bilateral	C	Healthy	< -0.006	< 0.01
SF 17	Total Stimuli	1-9 ms	W136	Bilateral	B	Healthy	> 0.8	< 0.1

Table 4: *Identified Schizophrenia traits for females.*

Table 4 depicts 17 significant female SZ traits that were extracted following screening, most of which were found using Trait Type A (i.e. high correlation to norm SZ curve). Some traits were specifically identified using masking click-stimuli (i.e. SF3, 7, 10, 16) or high pass click-stimuli (i.e. SF14). The majority of identified traits were observed in the 6-9ms region, representing thalamus (wave VI) and the thalamocortical region (wave VII), peaking at 8ms in between these regions. Several identified traits could also be observed in the 3-5ms region between cochlear nucleus (wave III) and the superior olivary complex (wave IV), peaking at 3ms in cochlear nucleus as previously reported.

Trait ID	Stimulus	Time	Processing	L/R	Trait type	Norm Curve	Cutoff for disease	P-value (t-test)
SM 1	Total Stimuli	2-3 ms	W136	Bilateral	C	SZ	< 0	< 0.001
SM2	HP1	4, 5-5 ms	W136	Right	D	Healthy	< -0.15	< 0.1
SM3	Total Stimuli	7-9,5 ms	W136	Bilateral	A	SZ	> 0.36	< 0.001
SM4	Total Stimuli	4,5-6,5 ms	W68	Bilateral	A	SZ	> 0.36	< 0.01
SM5	FM1	5-7 ms	W68	Bilateral	B	Healthy	< 0.22	< 0.1
SM6	Total Stimuli	2-9 ms	W68	Bilateral	A	SZ	> 0.55	< 0.1
SM7	Total Stimuli	4,5 ms	W68	Bilateral	C	SZ	< 1	< 0.1
SM8	HP1	4,5 ms	W136	Right	E	n.a.	< 7	< 0.1
SM9	HP1	1,5ms	W68	Right	E	n.a.	< 6	< 0.1
SM10	Total Stimuli	1,5 ms	W68	Bilateral	B	Healthy	< -0.1	< 0.01
SM11	FM2	7-8 ms	Unprocessed	Bilateral	C	SZ	< 0.54	< 0.01
SM12	LA	8,5-9 ms	W136	Left	A	SZ	> 0.33	< 0.01
SM13	LA	8,5-9 ms	W136	Left	A	Healthy	< -0.3	< 0.01
SM14	LA	8,5-9 ms	W136	Right	B	SZ	> 0.65	< 0.01
SM15	Total Stimuli	7-9,5 ms	W136	Bilateral	A	SZ	> 0.4	< 0.001

Table 5: *Identified Schizophrenia traits for males.*

Table 5 depicts 15 significant male SZ traits that were extracted, several of which were found using Trait Type A (i.e. high correlation to norm SZ curve). Some traits were specifically identified using masking click-stimuli (i.e. SM5, 11), high pass click-stimuli (i.e. SM2, 8, 9) or low amplitude click-stimuli (i.e. SM12, 13, 14). The majority of identified traits could be observed in the 7-8ms ABR region, representing the latter half of wave VI thalamus region.

Figure 2A & B show individual Patient´s Disease Match (PDM) for ADHD & schizophrenia, respectively, using a 50% cutoff value. Figure 2A shows that 26/29 (89.7%) of ADHD patients match more than 50% of ADHD-specific traits as compared to 1/33 (3.03%) of

schizophrenia patients (p < 0.0001; Fisher´s Exact test) and 3/39 (7.69%) of control subjects (p < 0.0001; Fisher´s Exact test). Figure 2B shows that 26/33 (78.8 %) of schizophrenia patients match more than 50% of schizophrenia-specific traits as compared to 3/29 (10.3%) of ADHD patients (p < 0.0001; Fisher´s Exact test) and 2/39 (5,13%) of control subjects (p < 0.0001; Fisher´s Exact test).

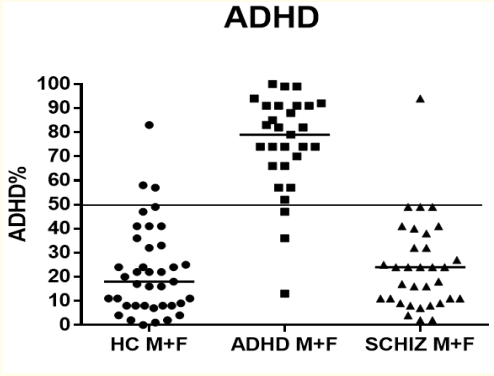

Figure 2A: *Individual Patient´s Disease Match (PDM) for ADHD.*

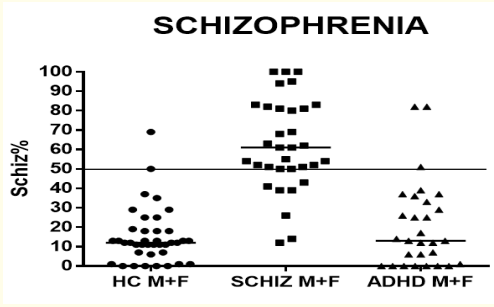

Figure 2B: *Individual Patient´s Disease Match (PDM) for Schizophrenia.*

	ADHD		Schizophrenia		Healthy Controls	
	Male	**Female**	**Male**	**Female**	**Male**	**Female**
Match	14	12	14	12	18	17
No Match	0	3 (2 SZ, 1 HC)	3 (3HC)	4 (1 ADHD, 3 HC)	1 (1 ADHD)	3 (1 SZ, 1 ADHD, 1 SZ+ADHD)
Sensitivity	100%	80%	82.4%	75%	94.7%	85%
Specificity	97.2%	91.7%	100%	88.6%	ND	ND
Sensitivity (M+F)	89.7%		78.8%		89.7%	
Specificity (M+F)	94.4%		92.6%		ND	

Table 6: *Sensitivity and Specificity values for Patient's Disease Match.*

Table VI depicts sensitivity and specificity prediction values for separated male and female subjects with respect to disease-specific trait matching. 14/14 male ADHD patients (100% sensitivity) and 12/15 female ADHD patients (80% sensitivity) could be identified

using a 50% cutoff value for disease- and gender-specific traits. 0/17 male schizophrenia patients and 1/19 male healthy controls was identified as false positive for ADHD biomarkers providing 97.2% specificity for male ADHD patients. 1/16 female schizophrenia patients and 2/20 female healthy controls were identified as false positives for ADHD biomarkers providing 91.7% specificity for female ADHD patients.14/17 male schizophrenia patients (82.4% sensitivity) and 12/16 female schizophrenia patients (75% sensitivity) could be identified using a 50% cutoff value for disease- and gender-specific traits. 0/14 male ADHD patients and 0/19 male healthy controls was identified as false positive for schizophrenia biomarkers providing 100% specificity for male schizophrenia patients. 2/15 female ADHD patients and 2/20 female healthy controls were identified as false positives for schizophrenia biomarkers providing 88.6% specificity for female schizophrenia patients. In addition, 18/19 male and 17/20 female healthy controls could be identified using a 50% cutoff value for disease- and gender-specific traits providing 94.7% and 85% sensitivity, respectively. Collectively, the ABR- method could differentiate clinical ADHD & schizophrenia from each other, and from healthy control subjects, with a sensitivity of 89.7% & 78.8% and a specificity of 94.4% and 92.6%, respectively.

Discussion

This pilot study matches biomarker read-out derived from audiometry with clinical diagnoses of ADHD and schizophrenia. ABR-recording were processed and scrutinized to discriminate between indications in a gender-specific manner. This training material could be optimized to differentiate clinical ADHD and schizophrenia from each other, and from healthy controls, with a sensitivity of 89.6 % & 78.8 % and a specificity of 94.4 % and 92.6 %, respectively.

The study participants consist of healthy controls and of patients meeting clinical diagnostic criteria for ADHD and schizophrenia, respectively, and the diagnoses had been verified by experienced clinicians. ABR-recordings included in the analysis were collected from 15 different psychiatric units and were of sufficient quality. The auditory evoked brainstem waveforms were analyzed by experienced investigators. The test is non-invasive, easy to go through and no active participation is required. Sedatives are not known to affect auditory brainstem recordings [3] and can be used if patients are anxious, but were not used in this study. The testing procedure was mostly well tolerated.

There are some limitations to this study. First the number of participants was modest. Secondly in this study the norm curves from which the traits were extracted were from the same ADHD, schizophrenia and healthy control materials. This, however, was thought to have only a minor impact, as one subject's impact on the median curve was very low. Furthermore the material was split into training- and test sets and the training set findings were validated using the test group and the whole material was calibrated in order to obtain the complete diagnostic indexes. A third limitation is that the clinical diagnoses were not accompanied by systematic information regarding ADHD and schizophrenia participants on neither DSM-IV diagnosis, nor [3]. nor symptom evaluation e.g. PANSS (the positive and negative symptom scale for schizophrenia) [9,20]. or ASRS (ADHD symptom rating scale) [21]. A fourth limitation is that all but one of the schizophrenia patients were on antipsychotic medication and there was an overweight for 2nd generation antipsychotics. Antipsychotic medication is however known to mainly affect cortical evoked potentials and not the brainstem evoked potentials and should thus constitute a minor problem [3]. Regarding prescribed medication and commonly abused substances we relied on report. Neither blood - nor urine-tests were collected. Furthermore, replicative tests were not performed to secure reproducibility and diagnostic stability of the method.

Seven schizophrenia (21,2%) participants had false-negative test results. This might reflect either a short-coming of this new test or inadequate clinical diagnostic procedures. All male ADHD participants were correctly diagnosed with this test, but three female ADHD participants failed to get an ABR diagnosis of ADHD and one female fulfilled both ADHD- and schizophrenia diagnostic criteria. For male healthy controls there was one no match, but for female healthy controls there were three no match individuals. Sensitivity and specificity was thus clearly higher for male participants than for females. These gender differences raises questions about the gender-specific ABR-indexes that were developed, but also about how adequate actual clinical diagnostic criteria and procedures are for female patients.

Possibly this method could be further refined with a larger patient material characterized in more detail. Multisite studies, both blinded and open are needed involving larger samples in each subgroup and other psychiatric diagnoses. Medication effects for antipsychotic -, CS medication and mood stabilizers need to be investigated in an on/off-medication approach. Other issues to be addressed in future studies are trait versus state and comorbidity and its effect on auditory brainstem response outcomes.

Conclusion

The present method with detailed analyses of auditory brainstem waveforms in this open evaluation study identified patients with ADHD and schizophrenia in relation to healthy controls, respectively, with high sensitivity and specificity. These findings call for further investigations regarding this method.

Acknowledgements

The authors would like to thank Dr Olle Olsson for the theoretical framework.

Conflict of Interest

All authors hold shares in Senso Detect AB.

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