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Abnormal brainstem auditory response in young females with ADHD

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ABSTRACT

Studies have shown that the auditory brainstem response (ABR) is often affected in neurodevelopmental disorders. The aim of this study is to investigate possible differences in ABR between young females with ADHD compared to control subjects. This study focuses on young females, age 7–17 with ADHD, comparing the ABR of 43 young females with ADHD to 21 age- and gender-matched control subjects. Young females with ADHD have a significantly different ABR in a region between cochlear nucleus and superior olivary complex as well as in the thalamic region compared to control subjects. These data indicate specific differences in ABR between girls with ADHD compared to female controls.

1. Introduction

Attention deficit hyperactivity disorder (ADHD) has been recognized as a common early onset neurodevelopmental disorder with high heritability (Faraone et al., 2006). It is a heterogeneous disorder with persistent symptoms of hyperactivity, inattention and impulsiveness (American Psychiatric Association 2000). ADHD is the most prevalent psychiatric disorder of childhood (Faraone et al., 2006). The estimated worldwide prevalence of ADHD in children is around 5% (Polanczyk and Rohde, 2007). The diagnosis frequently persists into adulthood and is associated with psychiatric and somatic morbidity and is a considerable burden to the affected individual and to society (Kieling and Rohde, 2012; Perou et al., 2013).

An ADHD diagnosis should be based on a neurodevelopmental and a clinical history (American Psychiatric Association, 2000). Neuropsychological testing and rating scales are used as tools that can provide indicative evidence in the diagnostic process. Many recent studies focus on trying to find objective neuropsychological testing methods for the diagnostics of ADHD (Shur-Fen and Shang, 2010).

Auditory brainstem response (ABR) was first described in 1971 (Jewett and Williston, 1971). ABR is stated to be an objective method that reflects the subcortical neuronal electrical activity in the auditory pathways, 10 ms after a brief auditory stimuli. The ABR consists of a sequence of seven positive peaks (wave I–VII) that normally occur within 10 ms following the onset of a stimulus recorded by surface electrodes on the mastoid processes of each ear and on the forehead. 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 (Klin, 1993; Parkkonen et al., 2009) (Fig. 1).

The ABR wave-pattern provides information in terms of the latencies and amplitudes of these peaks. Analysis of the ABR wave patterns normally comprises measurements of inter-peak latencies as well as peak amplitude ratios (Musiek and Lee, 1995; Sand, 1990). ABR is an objective method that does not require active patient participation and is said to be an objective approach to investigate brainstem function. Specifically, complex stimuli may reveal aberrations, which may not be assessed by standard audiological ABR procedures. Complex stimuli (e.g. forward masking) were therefore used in the present study to increase the possibility of detecting variances in comparison with matched healthy children. The importance of using complex stimuli is also stated for autism spectrum disorder, ASD (O´Connor, 2012).

Several studies have shown that ABR is often affected in ASD (Hitoglou et al., 2010; Källstrand et al., 2010; Kwon et al., 2007; Maziade et al., 2000; Taylor et al., 1982; Wong and Wong, 1991). In

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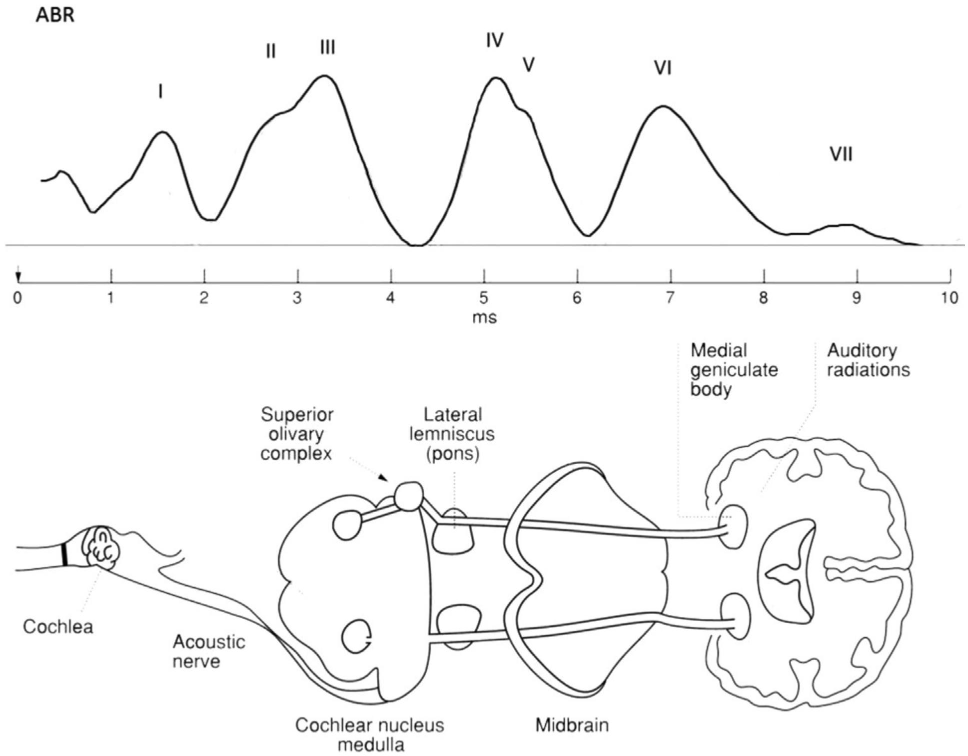

Fig. 1. Illustration of wave pattern of the standard ABR and corresponding anatomical structures within the first 10 ms after stimulation.

studies involving ASD (Källstrand et al., 2010), it was found that under forward masking conditions wave III amplitudes were significally lower in the ASD group compared to the control group. However, taking into consideration the high ADHD prevalence, there are surprisingly few studies on children with ADHD. In one article, no significant abnormalities were found in wave I–V in children with ADHD (Ismail and Amin, 1999). In another study on children with ADHD all children had normal ABR with normal latency for wave V (Schochat et al., 2002).

There is also a lack of studies done on young females with ADHD. The ratio between boys and girls is approaching 1:1, shown in an epidemiological study (Froehlich et al., 2007), which justifies focus on the young female group.

This study aims to investigate brainstem response in female children with ADHD compared to an age-and gender-matched control group.

2. Methods

2.1. Subjects

This study included a total of 43 females with ADHD (mean 13.3 years, SD 3.0) and 21 female control subjects (mean 13.6 years, SD 2.7). Patients and control subjects were in the age range of 7–17. All patients were recruited from the child and adolescent psychiatry outpatient department of Lund, a city in the south of Sweden. All patients were diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV). All diagnoses were confirmed by the same senior psychiatrist. Patients with concurrent psychiatric diagnoses were excluded to avoid comorbidity. All patients were drug naïve. Control subjects as well as ADHD patients with hearing impairment, verified by interviews with parents, were excluded from the study. The control groups were recruited from schools in Lund and recruited subjects had no previous record of any psychiatric disorder. All patients, both the ADHD group and the control group were in the normal intellectual range.

Written informed consent was obtained from all the subjects and their parents/guardians. The study was approved by the regional ethics committee at the Lund University (Dnr: 2010-120).

2.2. Apparatus and stimulus

A total of 1024 evoked potentials were recorded for each sound stimulus using brainstem audiometer ABR. The sound stimuli included square-shaped click pulses (0.136 ms duration including 0.023 ms rise and fall; 192 ms interstimulus interval), high pass filtered pulses (a Butterworth high-pass filtered square shaped click pulse with a cutoff of 3000 Hz), forward masking (12.3 ms gap from masker to click pulse) and backward masking (12.3 ms from click pulse to the masker) stimuli (Källstrand et al., 2010). 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.

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 & Kjaer 2203 sound level meter and Type 4152 artificial ear (Bruel & Kjaer S&VMeasurement, Naerum, Denmark). The acoustic output from the earphones corresponds to SPL (sound pressure level): 80 dB HL or 109pe SPL (peak equivalence).

All stimuli were constructed using MATLAB Signal Processing Toolbox (The MathWorks, 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.

2.3. Procedure

All tests were performed in a soundproof slightly darkened room. Participants were comfortably seated in an armchair with their legs on a small footstool to assure a resting position. Surface electrodes were applied one on each mastoid bone behind the left and right ear, with a ground electrode and a reference electrode placed on the forehead. To make sure of a good transmission the sites were washed with disinfectant and abrasive paste were used to stick the electrodes. Absolute impedances and interelectrode impedance were measured before and after the experiments to verify that electrode contact was maintained (below 5000 Ω). Earphones were fitted to cover both ears. The subjects were instructed to turn off their cellular phones and relax with their eyes closed and were permitted to fall asleep. The test requires no active participation other than being subjected to sound stimulation. The click sounds were presented to the subjects beforehand to make them acquainted with stimuli. The subjects were tested one at a time and the duration of the testing procedure was approximately 30 min.

2.4. Data analysis

The ABR curve quality check was measured through whole curve correlation (Spearman´s rho, 0–10 ms) between the specific patient and the norm ABR curve. The mentioned norm ABR curve consisted of the median representation from a group of normal hearing healthy controls.

This is a standard operating procedure of this method in order to grant ABR quality. Collected evoked potentials for each sound stimulus from each individual was imported to Microsoft Excel (Microsoft Corp, Redmond, WA, USA) and analyzed using Senso-Detect® BAS.

In order to identify specific pathologies along the auditory pathway (i.e. TR6 and TR15), correlation values to a normative ABR curve were calculated for different sections of the ABR. Values ranging from −1 to +1 were obtained using Spearman rho. High, positive values indicate similarity, e.g. no pathology, values around zero indicate no relation, and low values close to −1 indicate inverse relationship. After the *r*-values for all sections of the total ABR curve (0–10 ms) had been computed, the results were ranked. Thus, the test subject's most aberrant ABR region, when compared with the norm curve, depicts a high number, and vice versa.

The same principle was used in order to identify occurrence of high frequencies in the ABR curves of the test subjects (TR14). A mathematically constructed artificial ABR (a sine wave with the frequency 3500 Hz) was used as norm. The correlation value was calculated for each possible starting point in the ABR and the *r* (max) was used to indicate occurrence of the specific frequency. As the ambition with this operation was to see whether the test person had an occurrence of the frequency or not, the outcome were ranked from 1 for all values between $r=-1$ to $r=+0{,}1$ and thereafter 2 for $r=0{,}1$ to $r=0{,}2$ and so forth, with 10 for $r=0{,}9$ to $r=1$, indicating a perfect match to the norm ABR.

For measuring statistically differences between groups the nonparametric test Mann–Whitney *U* was used.

3. Results

Comparing the ABR of 43 girls with ADHD to 21 age correlated control subjects three traits were identified, denoted TR6, TR14 and TR15 (Fig. 2).The higher value in TR6, specific for the ADHD females ($p=0.0004$), as compared with the female controls, is

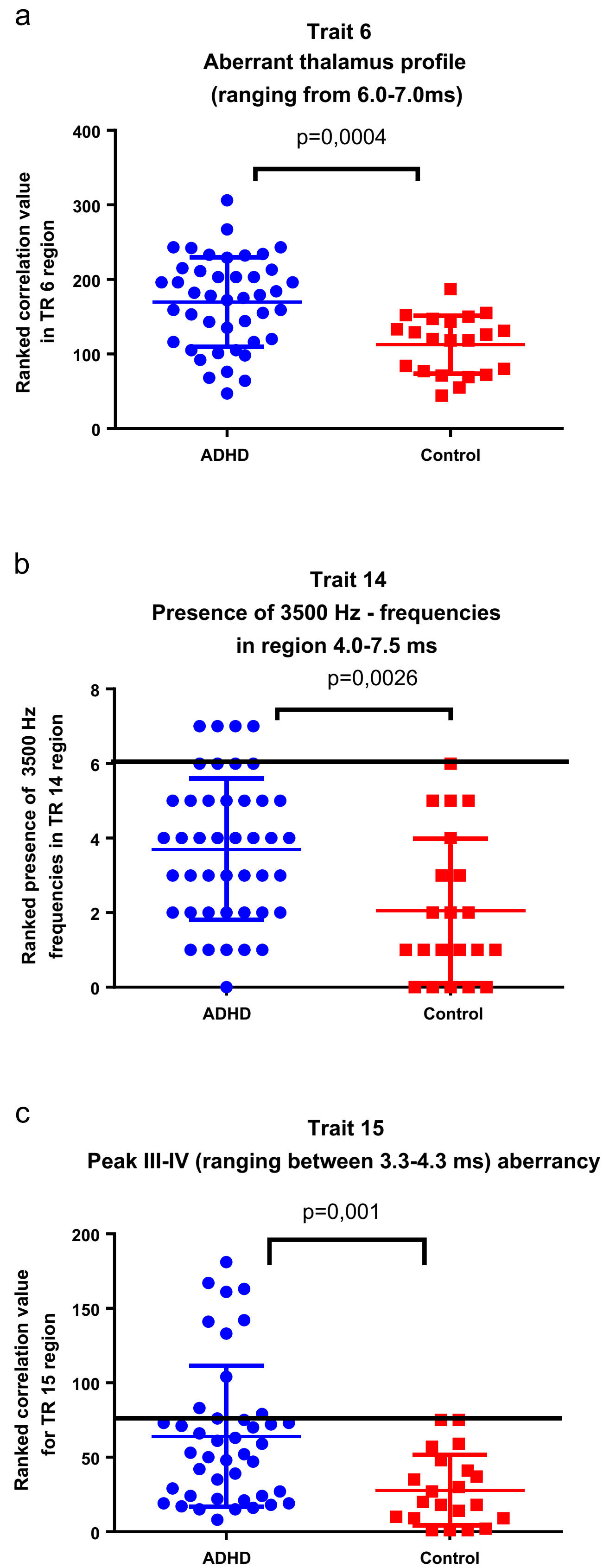

Fig. 2. Trait 6, 14 and 15 and their *p* values.

explained by more aberrant curve profiles in this region. In trait 14, a higher presence of 3500 Hz-frequencies in the region 4.0–7.5 ms (ranging from superior olivary complex to thalamus), was

Table 1
ABR results for girls with ADHD compared to controls.

Trait	ADHD group (*N*)	Controls (*N*)	ADHD mean (S. D.)	Control mean (S.D.)	*p* value
TR6	43	21	164.1 (61,9)	112.4 (38,8)	0.0004
TR14	43	21	3.73 (1,98)	2.05 (1,94)	0.0026
TR15	43	21	67.2 (49,7)	28.0 (23,8)	0.001
Age (7–17)	43	21	13.3 (3)	13.6 (3)	0.86

observed for the ADHD group as compared with controls ($p=0.0026$). The higher value in TR15, specific for the ADHD females ($p=0.0010$), as compared with the female controls, is explained by more aberrant curve profiles in this region (Table 1).

4. Discussion

The overall prevalence of ADHD among children and adolescents has increased in the last 10 years, and among girls more rapidly than among boys. Today the ratio between boys and girls is approaching 1:1 shown in an epidemiological study (Froehlich et al., 2007). Neurodevelopmental differences may, at least partially, explain why girls are diagnosed so much later than boys (Mahone and Wodka, 2008). There is a need to improve objective diagnosis of girls with ADHD. The aim of this study was to try to identify differences in brainstem responses in girls diagnosed with ADHD compared to a typically developed control group. Previous studies on adults with Asperger's disorder (Källstrand et al., 2010) and on adults with schizophrenia (Källstrand et al., 2012) have shown statistically significant differences in brainstem response in adult patients compared to non-clinical controls.

Hearing process problems in ADHD could be explained by the known fact that external background auditive white noise can improve cognitive performance in inattentive school children (Söderlund et al., 2007, 2010). This is consistent with the suggestion that the neural noise level associated with dopamine tone in inattentive children is sub-optimal (Sikström and Söderlund, 2007). One can also speculate that noise in a general way increases arousal that makes the subject more alert, and less drowsy. Hyperactivity might be a homeostatic response to underarousal in order to achieve an optimal arousal level (Zentall and Zentall, 1983).

When comparing the brainstem response in girls with ADHD to girls with no known neurodevelopmental problems, three traits differed across groups, namely trait 6, trait 14 and trait 15.

These results support previous findings of aberrant ABR waveforms in neurodevelopmental disorders (Hitoglou et al., 2010; Kwon et al., 2007; Källstrand et al., 2010; Maziade et al., 2000; Taylor et al., 1982; Wong and Wong, 1991).

Looking at the results from a biological angle, the findings seem to be in line with earlier suggestions that children with ADHD have abnormalities in their pontine and thalamic regions (Cortese et al., 2013; Dickstein et al., 2006; Ivanov et al., 2010), not only structural abnormalities but also functional ones (Zhu et al., 2008). Thalamus is looked upon as a kind of switchboard of information, acting as a relay between a variety of subcortical areas and the cerebral cortex. The thalamus also plays an important role in regulating states of sleep and wakefulness (Steriade and Linás, 1988). Taking this into consideration it is clear that a thalamic dysfunction could lead to symptoms similar to characteristics of ADHD. In trait 6, we find an aberrant thalamic profile, in at least a subgroup of girls with ADHD.

In the pontine region we find locus involved in attention, e.g. the noradrenergic locus coeruleus and dopaminergic ventral tegmental area nuclei. It is known that brainstem abnormalities are important in ADHD (Johnston et al., 2014), and reports show on regulation of locus coeruleus activity by methylphenidates and by atomoxetin (Bari and Aston-Jones, 2013; Devilbiss and Berridge, 2006; Howells et al., 2012). We demonstrate the finding of an abnormal ABR in trait 15, which correlates to the pontine region, a region known to have low activity in ADHD children (Howells et al., 2012).

It has also been shown that extensive selective lesions of the locus coeruleus projections may reduce the psychostimulant effect of amphetamine in a novel environment (Harro et al., 2000). This strengthens the finding that exposure to a white background sound improves performance in children with ADHD (Söderlund et al., 2007, 2010).

Some early studies have shown documented age and gender differences in ABR (Allison et al., 1983), whereas there are other studies that demonstrate that the aging process is essentially a peripheral phenomenon, which does not involve the central part of the acoustic pathways (Burkard and Sims, 2001; Costa et al., 1990; Konrad-Martin et al., 2012). Since our material is age matched we have considered it fully compensated.

Future research areas of interest would be to investigate whether medication would decrease the ABR differences between the group of children with ADHD and healthy controls, and in that case which of the medications on the market is best for which trait and if that is possible to predict.

In summary, the present study suggests that ABR is a promising diagnostic tool for ADHD in girls, so far only on a research level. It is a non-invasive method that is easily administered to patients by any trained person, and it is not dependent on language skills or cultural background. An obvious limitation to this study is the relative small sample of patients and control subjects. Another limitation is that there is a need for child and adolescent control subjects from other psychiatric diagnosis. There are studies from adult populations with Asperger's syndrome (Källstrand et al., 2010) and schizophrenia (Källstrand. et al., 2002, 2012). Finally, longitudinal studies comparing brain-stem abnormalities in girls with ADHD to girls with other psychiatric diagnosis is needed to further substantiate the current findings.

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