Auditory Brainstem Timing and Cortical Processing in Attention Deficit Hyperactivity Disorder

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ABSTRACT

Introduction: Attention-Deficit Hyperactivity Disorder (ADHD) is one of the most common psychiatric disorders of childhood with a prevalence rate of approximately 5–8%. Three subtypes have been identified in the Diagnostic and Statistical Manual (DSM)-IV according to the constituent symptom profiles of inattention and hyperactivity/impulsivity. The combined subtype (ADHD/C) is the most prevalent (61%).

Aim of the Study: This study was designed to explore the processing of sounds through brain stem and higher cortical regions in a sample of children with Attention Deficit Hyperactivity Disorder/combined (ADHD/C) subtype using Auditory Evoked Potentials.

Subjects and Methods: Fifteen ADHD/C children were compared to 15 age matched normal control, age between five and ten years. Mini-International Neuro-psychiatric Interview for Children and Adolescents was performed to confirm the diagnosis, subtype, and to exclude co-morbid conditions. All children were subjected to Auditory Brain Stem Evoked Response (ABR) to click and speech stimuli and cortical Mis-Match Negativity (MMN).

Results: Thirty-three percent of ADHD/C showed marked prolongation of absolute and/or inter-peak wave latencies of click ABR compared to normal group. The peak latency of the onset waves for speech ABR were abnormal in 87% of the study group. Only three children gave normal MMN.

Conclusion: Abnormal brainstem timing with reduced cortical functions was a characteristic in ADHD/C group. Sub-cortical encoding of auditory information might be used to characterize a subgroup within the ADHD population that is homogenous on a particular biological indicator. Further research can be used to determine whether individuals within these sub-groups share a similar perceptual pro.

Key words: Attention deficit hyperactivity disorder, auditory brainstem evoked potential, cortical processing, auditory brainstem response, Mis-Match negativity.

Current Psychiatry; Vol. 17, No. 1, 2010: 15-21

INTRODUCTION

Attention-Deficit Hyperactivity Disorder (ADHD) is one of the most common psychiatric disorders of childhood with a prevalence rate of approximately 5–8% [1]. Three subtypes have been identified in the Diagnostic and Statistical Manual (DSM)-IV according to the constituent symptom profiles of inattention and hyperactivity/impulsivity. The combined subtype (ADHD/C) is the most prevalent (61% of identified cases) compared to 30% for the inattentive and 9% for the hyperactive/impulsive type[2].

Although ADHD has long been viewed as a neurological condition, the relationship between the observable features of the disorder and the underlying neuro-cognitive impairment is not clear. The existence of multiple neural networks of attention associated with various cognitive processes complicates the identification of a core deficit in ADHD[3]. Convergent data from neuro-imaging, neuro-psychology, genetics and neuro-chemical studies consistently pointed to the involvement of the fronto-striatal network as a likely contributor to the patho-physiology of ADHD. This network involves the lateral prefrontal cortex, the dorsal anterior cingulate cortex, the caudate nucleus and putamen[4].

Moreover, a growing literature demonstrates abnormalities affecting other cortical regions and the cerebellum. The exploratory brain regions of interest in which abnormalities have been identified, but that were not predicted by cognitive models of ADHD, are the temporal lobe, parietal lobe, occipital lobe and lateral ventricles[5]. Defects in midbrain dopamine systems were recently implicated in ADHD pathogenesis[6]. The midbrain-forebrain dopaminergic circuits were thought to regulate a diverse set of behaviors, from the control of movement to the modulation of cognition and desire. ADHD is characterized by the impact of abnormal

reward prediction error signals carried by the midbrain dopamine system on frontal brain areas that implement cognitive control[7].

Auditory evoked potentials are considered biological markers that provide information about neural timing with fractions of millisecond precision[8]. The two physiological mechanisms considered here in relation to the biological basis of ADHD were the Auditory Brainstem Response (ABR) to click, speech stimuli and the cortical Mis-Match Negativity (MMN).

ABR provides information about the functional integrity of brainstem nuclei along the ascending auditory pathway up to midbrain inferior colliculus[9]. On the other hand, MMN is a cortical response arising as a result of an acoustic change in a repetitive sound sequence[10], MMN sub-serves involuntary call for attention to stimulus change and provides a link between the pre-attentive detection of change and subsequent attention processes[11].

This study was designed to explore the processing of sounds through the auditory pathway in a sample of ADHD/C children compared to age matched normal controls using ABR and MMN. This might represent a step further to improve the clinical diagnosis and treatment of these disorders. Moreover, understanding how complex acoustic stimuli are encoded and processed in the brainstem and how this processing is related to lower as well as higher areas of the auditory pathway, might lead to a better understanding of processes underlying normal and abnormal human communication in ADHD.

SUBJECT AND METHODS

Fifteen ADHD/C Arabic speaking children (10 Males and 5 females) were included in the present study. Their age ranged between 5- 10 years (mean±SD of 7.4±2 years). They were compared to 15 age matched normal children with no history suggestive of behavioral, attention problems, medical, or neurological disorders. All children exhibited normal bilateral hearing (pure tone thresholds < 20dBHL for frequencies 500-4000-Hz). An Intelligent Quotient (IQ) was not less than 90 on Wechsler intelligence scale.

ADHD children were collected from the outpatient Child/ Adolescent Psychiatry Clinic, Institute of Psychiatry and from the Audiology unit, ORL Department, Faculty of Medicine, Ain Shams University over the period from November 2008 to March 2009. Consent was taken from the parents to contribute in the work.

Procedures:

1. Clinical psychiatric assessment:

- Developmental and psychosocial history of the child was obtained in an intake interview with the parents.
- Wechsler intelligence scale was applied for IQ assessment.
- The Mini-International Neuro-psychiatric Interview for Children and Adolescents (MINI-Kid) was performed to confirm the ADHD diagnosis, subtype and to exclude other co-morbid conditions. MINI-Kid is a short, structured interview designed to assess symptoms of several Axis I disorders as listed in the DSM-IV and the International Statistical Classification of Diseases and Related Health Problems. The MINI-Kid has been found to demonstrate good reliability and diagnostic sensitivity[12].

2. Audiological work up:

ABR to click, speech stimuli and MMN were done for all children using auditory evoked potential equipment SMART-EP. To ensure subject cooperation and to promote stillness, all children watched a videotape with the sound presented at low level <40-dB sound pressure level (SPL). They were instructed to attend to the video rather than the stimulus. All children were tested in single session. All stimuli were presented monaurally to both ears via TDH-39 headphones. Responses were recorded using Ag-Agcl scalp electrodes.

I. Evoked potentials recordings:

ABR was done using both click and speech stimuli. Click stimuli were presented at 90dBnHL. The responses were collected according to the widely used procedures described by Jacobson[9].

Speech ABR was elicited using a five-formant speech syllable 40ms/da/stimulus with an onset burst during the first 10ms and a fundamental frequency range of 105–121Hz. The syllable /da/ was presented at 80dB SPL in alternating polarities with an inter-stimulus interval (ISI) of 51ms. Responses were differentially recorded at sampling rate of 20,000Hz from Cz (active) to the right earlobe (reference), with the forehead as ground. They were band pass filtered online from 100 to 2000Hz, 6 B per octave. Three blocks of 1000 repetitions were collected at each polarity. On-line averaging of the responses was done with a 70ms recording window starting 10 ms before stimulus onset.

MMN were evaluated using an oddball paradigm. The stimuli were syllables taken from the /da/-/ga/ speech continuum. Stimuli along this continuum differ in the onset frequency of their third formant (F3). The first stimulus on the continuum (/da/) served as the deviant occurring with a probability of 20% (F3=2580 Hz). The standard stimulus, occurring 80% of the time, was the token with F3=2500Hz, representing a barely perceptible difference[13].

The /da/-/ga/ stimuli were presented at 80dB SPL in a pseudorandom order, with at least three standard stimuli in between two deviants. Responses were collected with 590ms recording window starting 90ms before stimulus onset. Sampling rate was 1000Hz. Responses were off-line filtered from 0.1 to 40Hz (12dB per octave roll off). Two hundred fifty responses were collected for the deviant and 2200 for the standard. Two active electrodes were placed at Fz and Cz sites referenced to mastoid electrode. The ground electrode was placed at FPz.

II. Evoked potentials data analysis:

For the ABR click-evoked response, absolute latencies of ABR waves (I, III, V) and inter-peak latencies (I-III, III-V, I-V) were identified for each subject. On the other side, ABR to speech stimuli is divided into transient portion and the frequency following response. As known, speech ABR roughly reflects the acoustic parameters of the speech sound /da/ stimulus[14].

The speech ABR analysis in the study focused mainly on the transient portion of the response as it encodes the stimulus onset and offset timing. Both are measures of neural synchrony. The onset response was represented by waves V, A, C, while the offset response was presented by wave O. Furthermore, the VA complex encoded the brief consonant portion of the /da/ stimulus while wave C reflected the onset of voicing. An example of speech ABR obtained from a child of the study is shown in (Figure 1).

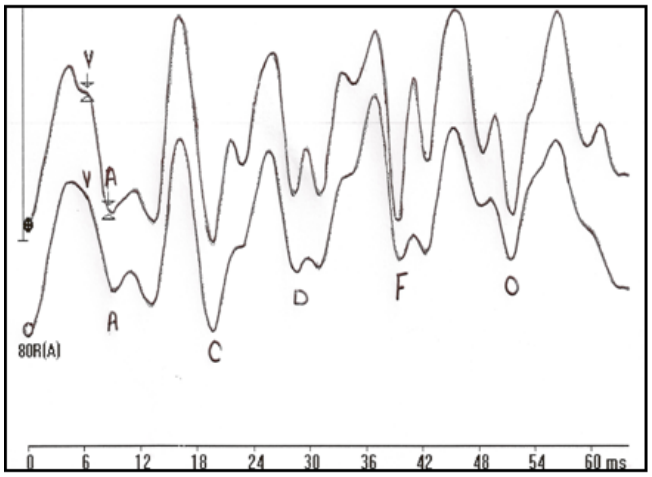

Figure 1: A typical brainstem response to speech.

The peak latency and amplitude for onset peaks (V, A, C) and offset peak (O) were determined. The VA onset complex was further analyzed by calculating VA duration and VA slope of the V-to-A transition (the inter-peak amplitude divided by the inter-peak duration).

As regards cortical MMN, grand average waveforms were computed based on all available repetitions after artifact rejection for each stimulus (/da/ as a deviant, frequent/ ga/) in each subject. Difference waves were computed by subtracting the frequent stimulus from the /da/ deviant response. MMNs were identified in the individual difference waves as a prominent first negative peak in the domain of 100 to 250ms after the P1 response[15]. Peak latency was measured from the stimulus onset to the maximum negative peak of the MMN. The amplitude was measured between the baseline and the following negative trough. It is measured relative to a baseline calculated as the mean amplitude over the 50ms preceding the stimulus. Responses from right, left and binaural side of stimulation were analyzed.

RESULTS

Results of ABR: ABR using click stimuli was obtained from all tested ears of both study groups. Wave V was traced for all children down to 30dB nHL. Generally, a shift in absolute latency of wave III and inter-peak latencies (I-III, I-V) was noted in ADHD children in both ears. This shift reached statistical significant difference between the two study groups by Student t test (Table 1). Marked latency shift (beyond 2SD) was observed in five ADHD children (33 %).

Table 1: Results of click ABR in both groups.

ABR waves		I		III		V		I-III		III-V		I-V	
		X	SD	X	SD	X	SD	X	SD	X	SD	X	SD
ADHD	**Right**	1.4	0.1	3.7	0.1	5.5	0.2	2.1	0.2	1.8	0.2	4	0.3
Normal	**Right**	1.4	0.1	3.5	0.1	5.5	0.1	1.7	0.1	1.9	0.1	3.8	0.1
t value		0.2		8.6		0.01		26		0.23		12.2	
p value		0.6		<0.001		0.9		<0.001		0.6		<0.001	
ADHD	**Left**	1.3	0.1	3.7	0.2	5.4	0.3	2.2	0.2	1.6	0.3	3.8	0.4
Normal	**Left**	1.4	0.1	3.5	0.1	5.4	0.2	1.8	0.1	1.6	0.3	3.6	0.2
t value		1.3		9.7		0.02		21		0.03		2.6	
p value		0.2		<0.001		0.9		<0.001		0.9		<0.05	

The results of speech ABR (peak wave latencies and amplitudes) in normal children matched previous published reports[14,16]. Although ABR to speech syllable /da/ was recorded from all ADHD children, yet only two (13%) exhibited normal response parameters. Statistical significant difference in the latencies of transient peaks of the onset response (V, A, C and VA duration) and not offset wave O existed between the two study groups (Table 2). On the other hand, no amplitude difference was detected for any of the peaks studied between the two groups ($p>0.05$).

Table 2: Peak latency means and Standard Deviations for both study groups.

	V	A	VA Duration	VA slope	C	O
Normal						
Mean	6.7	7.7	1.1	0.3	17.5	48
SD	0.2	0.2	0.2	0.2	0.5	0.7
ADHD						
Mean	7.7	10	2.5	0.3	18.4	48
SD	1.3	2	1	0.2	1.3	2
t value	8.5	20	21	0.3	5	0.2
P value	< 0.001	< 0.001	< 0.001	0.8	<0.05	0.7

Results of MMN: MMN responses were obtained from all normal children. Mean ± SD latency was 169 ± 6ms, 157 ± 6ms and 157 ± 6ms for right, left ear and binaural stimulation ,respectively. The peak amplitude on corresponding side of stimulation was 10 ± 4, 8 ± 3 and 9 ± 3 microvolts.

In ADHD children, the picture was different. Only three children (20%) gave normal MMN responses. Two of them were those with normal speech ABR. Looking to individual data, the right ear stimulation elicited MMN responses in 14 (93%) children. In contrast, only 9 (60%) children gave responses on left ear stimulation.

There was a general trend for latency prolongation in ADHD children compared to normal group. The mean ± SD peak latency was 190 ± 43ms and 184 ± 20ms on right and left ear stimulation ,respectively with amplitude measure of 7.7 ± 2 and 7 ± 1 microvolts on corresponding side of stimulation. Binaural stimulation yielded shorter peak latency of 182 ± 39ms with mean ± SD amplitude 7 ±1 microvolts. This difference reached statistical significance for the left ear ($t=23$, $p<0.01$) and binaural stimulation ($t=14$,$p < 0.01$). Moreover, no statistical significant difference was detected in amplitude measures between the two study groups ($p > 0.05$).

Pearson Correlation Coefficient was studied to uncover any correlation between brain stem and cortical measures. In ADHD, statistical significant positive correlation between MMN on binaural stimulation and speech ABR wave C, VA complex duration ($r=0.7$ and, 0.6, $p < 0.001$ and < 0.05 ,respectively). Similarly, binaural MMN was correlated to click ABR wave V and I-V inter-peak latency ($r=0.7$ and 0.6, $p < 0.05$,respectively).

The neuro-physiological findings detected in brain stem and cortical timing in ADHD were most likely not attributed to maturational deficits. This was evident by the absence of statistical significant correlation existed between age and the different measures of ABR (click - speech) and MMN by Pearson Correlation for the two groups.

DISCUSSION

Simple (brief non speech) stimuli evoked an orderly pattern of responses from the auditory nuclei in low brainstem (wave I–III) and rostal midbrain IC (waves V) in all children of the study. A delay in transmission of impulses that started just beyond the auditory nerve on both sides existed in ADHD/C. Similar findings were previously reported[17]. On the contrary, Schochat etal.[18] found normal click ABR with normal wave latencies in 21 ADHD children.

While only five children (33%) exhibited marked delay in click ABR, abnormal speech ABR was observed in 13 ADHD/C children (87%). As emphasized by Johnson et al.[19] click and speech stimuli imposed different encoding demands imposed on the brainstem despite similar generator sites.

The speech ABR onset responses reflecting the upper brainstem (waves V, A) were prolonged and completely outside the range spanned by the normal group (Table 2). Accurate brainstem encoding of the onset of speech is essential for robust processing at the cortical level[20], normal patterns of hemispheric dominance, as well as cortical sensitivity to acoustic change.

It is possible that a response de-synchronisation in the auditory pathway might exist in these disorders. Deviations within fractions of milliseconds are clinically significant in assessment of brainstem function and latency prolongations are objective evidence of clinical or sub-clinical disease[8]. An accurate manifestation of stimulus timing in the auditory brainstem is a hallmark of normal perception[21]. The degree of myelination, axonal growth and synaptic function could be the reason of such underlying deficit[22].

Subsequently, a deficit in the processing of sequential information in this group of children could be expected. Cao[23] emphasized that different aspects of temporal information processing are known to be affected in ADHD. Some of these aspects could represent candidate endo-phenotypes for ADHD. Abnormal sub-cortical pitch-tracking, consistent with known deficits in prosody perception in this population was also reported[24].

A temporal perception deficit in the range of milliseconds in ADHD may impact upon other functions such as perceptual language skills and motor timing. Furthermore, Yang et al.[25] supported the existence of a generic time perception deficit in this population. This is probably due to the involvement of a dysfunctional fronto-striato-cerebellar network, especially the presence of deficits in basic internal timing mechanisms.

As evident from this work, the processing of auditory information in the brain stem was impaired in a subgroup of ADHD/C children. Galbraith et al.[26] suggested the existence of crude attentional mechanisms at the level of the auditory brainstem. These mechanisms could serve to enhance auditory encoding by directing processing resources to the appropriate modality, or within the auditory modality to the appropriate ear. Moreover, recent studies demonstrated that subcortical encoding of sounds is affected by expertise input from other sensory modalities, attention and musical experience[27].

Interestingly, the abnormal processing of the /da/ speech stimuli continued to exist at the cortical level in ADHD/C children in this work. The peak MMN latencies were prolonged with reduced amplitude. The same was reported by Winsberg et al.[28]. Moreover, MMN component was absent in 6 (40%) ADHD/C children particularly when left ear was stimulated as previously reported[29]. The generation of MMN is thought to be related to the auditory cortex, contributions from the non primary auditory thalamo-cortical areas as well as input from the primary and association auditory cortex[13].

The absence of MMN on left ear stimulation was in line with previous research stating that reduced right hemisphere activity may characterize children with attention problems[25]. Support for right greater than left (but not exclusively right) hemisphere dysfunction 'prefrontal-striatal systems' in ADHD comes from structural MRI findings. This is in correlation with the reduced volume of right prefrontal cortex and regions of the basal ganglia in children with ADHD[30].

In the present study, abnormal auditory brainstem timing with reduced cortical functions was detected in 80% of ADHD/C (Figure 2). The co-occurrence of brainstem and cortical abnormalities in the current study does not indicate causality. Several studies suggested strong relationships between auditory processing at the brainstem and the cortex. This relation can be interpreted either through bottom up influence or top down feedback system.

Figure (2): Distribution of ADHD children according to speech ABR and MMN results

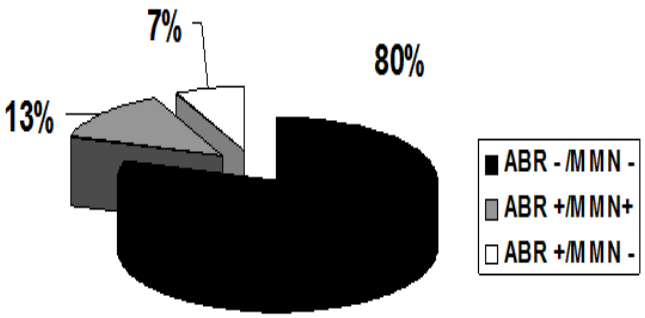

Figure 2: Distribution of ADHD (C) children according to combined results of speech ABR and MMN.

A Bottom up influence: Subtle timing deficit at the brainstem typically impedes the cortical ability to process sound under acoustic stress (noise, small differences between stimuli). This was supported by listening training that resulted in enhanced robustness of the cortical response in individuals with abnormal brainstem timing[31].

A Top down influences: Brainstem timing may be impaired as a result of abnormal feedback from the cortex. Because the auditory brainstem receives efferent inputs from the cortex, it could be argued that abnormal cortical function results in impaired cortical feedback on the brainstem, which ultimately generates an abnormal brainstem response[14]. Also the descending pathway could exert its influence by affecting selective attention, which in turn aids in gating of sensory information to the cortex.

Interestingly, the above mentioned dual relation was recently supported by the fMRI study that highlighted the relation between brainstem and cortical activation[33]. They demonstrated that the degree to which a given subject activated the brainstem subcomponent was highly predictive of the degree to which that same subject activated the right frontal subcomponent[32].

Given the behavioral and physiological heterogeneity of ADHD, the findings of the present study is important from a practical standpoint. The study emphasized that children with ADHD/C could have problems in the brain stem timing and subsequent processing of information to the cortex. Speech ABR can be used to characterize a subgroup within the ADHD population that are homogenous on a particular biological indicator. This measure might aid in deciding auditory training and its outcome in the course of therapy.

Further research is needed to determine whether individuals within these sub-groups share a similar perceptual profile. Nevertheless, it is recommended to explore the effectiveness of speech ABR in selection the ADHD subgroup who will get the utmost benefit from drugs targeting mid brain dopaminergic circuits.

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