EVENT-RELATED POTENTIALS IN ADULTS WITH ATTENTION DEFICIT / HYPERACTIVITY DISORDER (AD/HD)

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Abstract : Objective: A specific disorder at the stage of cognition and/or information processing might be involved in attention deficit/hyperactivity disorder (AD/HD). We measured negative difference (Nd) and mismatch negativity (MMN), the early negative components which reflect the attention function, in addition to P300. In earlier studies we examined these ERPs in children with AD/HD. In the present study, we examine the attentive and cognitive disturbances associated with adult AD/HD, measuring the auditory Nde, MMN, and P300.

Method: 15 adults with DSM-IV-diagnosed AD/HD and 15 healthy control subjects were studied.

Result: P300 and early Nd (Nde) amplitudes were smaller in the adult AD/HD group as compared with the healthy control group.

Conclusions: When performing selective attention tasks, the same specific disturbances in the active stimulus selection process and the selective attention maintenance process occur in adults with AD/HD as in children with AD/HD.

Key words : adult attention deficit/hyperactivity disorder (adult AD/HD), event-related potential (ERP), P300, negative difference (Nd), mismatch negativity (MMN)

INTRODUCTION

Attention deficit/hyperactivity disorder (AD/HD) is one of the most prevalent childhood psychiatric disorders[1, 2]. It is thought to affect 3-5% of all school-aged children and is characterized by hyperactivity, inattentiveness, and impulsivity[3]. Into the 1960s, it was accepted that AD/HD was a childhood disorder, and that is naturally improved with maturity. But in the revised DSM it is accepted that AD/HD also exists in adults. In DSM-IV[4] in 1994, regardless of hyperactivity, AD/HD is an accepted diagnosis for all age groups. Now many people have received a diagnosis of adult AD/HD, and many adults who wonder "Do I have AD/HD ?" consult a psychiatrist. However, there has been no intensive biological investigation of adult AD/HD.

A specific disturbance at the stages of cognition and/or information processing is presumed to be involved in AD/HD. For example, abnormal reaction time, decreased hit percentages, and increased errors have been demonstrated in the Continuous Performance Test (CPT)[5,6]. These are, however, just end products of information processing, which occurs in stages. In contrast, the study of event-related potentials (ERPs) reveals the stimulus-evoked brain that precedes the final output, prompting an increasing number of researchers to engage in various ERP investigations in childhood AD/HD.

We measured early negative difference (Nde) and mismatch negativity (MMN), the early negative components which reflect attention function, in addition to P300. MMN reflects an automatic cerebral discrimination process, not under attentional control[7] . Nd is a negative component reflecting selective attention[8]. In particular, disturbance of the P300 component, an indicator of cognition, has been suggested[9,10]. However, P300, a potential generated in the final stage of sensory and cognitive processing, is likely to be affected by the cognitive factors present prior to P300 generation, limiting investigation based solely on the P300. Consequently, among the pre-P300 potentials that reflect information processing itself, early negativity that is strongly related to attention deficit has become a focus of interest.

We have already reported these ERPs in childhood AD/HD. These ERPs were compared between the AD/HD group and the healthy control group. Our observations of ERPs in childhood AD/HD include: a) in the AD/HD group, prolonged latency and reduced amplitude of P300 compared to those of normal controls, and b) in the AD/HD group, reduced amplitude of Nde and MMN compared to those of normal controls[11].

Although our studies and others have reported ERPs in childhood AD/HD, a report[12] has been published concerning the P300 of adult AD/HD patients, which is the subject of the present investigation. However, there are no reports which examined Nd and MMN of adult ADHD patients. Our purpose was to investigate whether the biological dysfunction which exists in childhood AD/HD is also present in adult AD/HD.

SUBJECTS AND METHODS

Subjects

Fifteen adult subjects (2 male and 13 female) aged 28−42 years (mean 35.8±5.45) diagnosed with AD/HD according to DSM-Ⅳ with no mental retardation and with no history of AD/HD treatment were compared with 15 aged- and sex-matched healthy control subjects (2 male and 13 female) aged 25−40 years (mean 33.5±4.73) (Table 1).

Subjects underwent a standard clinical assessment comprising a psychiatric evaluation, a structured diagnostic interview, a cognitive battery, and a medical history. The structured diagnostic interview used was the Structured Clinical Interview for DSM-Ⅳ(SCID)[13]. Two experienced child psychiatrists (J.I, H.W) confirmed the diagnosis of AD/HD. As to AD/HD subtype, there were 10 (67%) inattentive-type patients and 5 (33%) combined-type patients. The healthy control group consisted of healthy volunteers without AD/HD, attention deficit alone, psychosis, affective disorder, anorexia/bulimia or an organic disease of the nervous system.

Furthermore, all subjects with AD/HD underwent assessment on the WAIS-R, and the Global Assessment Scale (GAF scale). The performance (mean score ± SD) of the AD/HD

Table 1. Subjects of AD/HD patients and healthy controls

	Healthy Controls	AD/HD	
N(man: woman) [peoples]	15(2: 13)	15(2:13)	N.S.
Age[years] Mean(SD)	33.5(4.73)	35.8(5.45)	N.S.

Note: AD/HD = attention- deficit/hyperactivity disorder;
N.S. = not significant

Table 2. AD/HD patients' background

		Mean (S.D.)
WAIS- R	PIQ	94.8 (18.6)
	VIQ	97.3 (14.1)
	FIQ	95.4 (15.7)
GAF scale		62.4 (8.75)

Note: WAIS-R = Wechsler Adult Intelligent Scale-Revised;
PIQ = Performance Intelligence Quotients; VIQ = Verbal Intelligence Quotients; FIQ = Full Intelligence Quotients; GAF scale = Global Assessment of Functioning scale.

group was as follows: 94.8±18.6 (FIQ) on the WAIS-R, and 62.4±8.75 on the GAF scale. FIQ estimates for all patients were within the normal range (Table 2).
Written informed consent was obtained from all patients.

Methods

Stimulus and task presentation:

According to the guidelines for evoked potential measurement, the P300 and MMN were measured using auditory odd-ball tasks, and the Nde using selective attention tasks. A NEC Multi Stim was used as the auditory stimulus system.

(1) P300 measurement

Infrequent target stimuli were presented as tone bursts at 2000 Hz (P=0.2) and frequent target stimuli as tones at 1000 Hz (P=0.8), with each stimulus lasting 50 msec. Both types of stimuli were given at intervals of 1.5 seconds at an intensity of 80 dB. Infrequent and frequent target stimuli were given in random order through headphones. Patients and healthy control subjects were instructed to pay attention to the target stimuli with their eyes open, and to press the button as quickly as possible when each target stimulus was

delivered.

(2) Nd measurement

Stimuli were given as tone bursts (each lasting 50 msec) at a fixed intensity (80 dB). To the right ear non-attended standard stimuli at 400 Hz (P=0.7) and non-attended deviant stimuli at 500 Hz (P=0.3) were delivered in random order. To the left ear attended standard stimuli at 800 Hz (P=0.7) and attended deviant stimuli at 1000 Hz (P=0.3) were given. These infrequent and frequent stimuli were presented at 1.5 sec intervals binaurally through headphones. Patients and healthy control subjects were instructed to pay attention to the sounds delivered to the left ear to detect deviant stimuli and to ignore the sounds presented to the right ear. They were also instructed to press the button as quickly as possible when each deviant stimulus was presented in the attended channel.

(3) MMN measurement

Standard stimuli (P=0.9) were tone bursts at 1000-Hz and deviant stimuli were tones at 1100-Hz (P=0.1), with all stimuli lasting 50 msec at 500-msec intervals and an intensity of 80 dB. These infrequent and frequent stimuli were given in random order through headphones. The MMN was measured while patients and healthy control subjects were reading books or magazines of their choice, without paying particular attention to the auditory stimuli given, as instructed (under the READ condition).

ERP recordings and analyses

ERP recordings:

ERPs were recorded with a NEC SYNAX 1200. Electroencephalograms (EEG) were obtained at Fz, Cz and Pz on the scalp using disk electrodes, with both ear lobes as the reference electrode sites. The resistance of the electrodes was set at $\leqq 5k\Omega$.

The P300 was analyzed over the period between 160 msec pre-stimulus and 640 msec post-stimulus, and the Nd between 120 msec pre-stimulus and 480 msec post-stimulus. The MMN was analyzed through 400 msec post-stimulus.

Artifact-free responses to stimuli were added and averaged, with EEG data $\geqq 70$ (V in amplitude and eye movements removed. The amplitude was measured with the baseline potential set to the average potential for 100 msec before a stimulus. To prevent the subjects from getting tired of, or getting used to, performing the tasks, each trial was conducted only once under the specified conditions. Examiners who were blind to diagnoses measured ERPs (P300, Nd, MMN).

(1) P300

Thirty responses to infrequent standards stimuli were averaged. Among the ERPs obtained, P300 was identified as a positive wave with peak latency at 280−450 msec. Latency and amplitude were measured.

(2) Nde

Forty responses to attended and forty responses to unattended standards stimuli were averaged separately. The waveform of the latter response was subtracted from that of the former; the Nd was identified as negativity lasting from about 50 msec until about 800 msec post-stimulus based on the subtraction waveform. The Nd is bimodal; the negativity that emerges at about 50 msec after stimulus presentation up to about 200 msec was termed early

Nd (Nde), and the slow negativity component that continued after that was termed late Nd (Ndl). We observed Nde in the present study. The latency and amplitude of Nde were measured.

(3) MMN

One hundred responses to infrequent deviant stimuli and 900 responses to frequent standard stimuli were averaged separately. The waveform of the latter response was subtracted from that of the former; the MMN was identified as negativity with the peak latency at 100−250 msec based on the subtraction waveform. The MMN latency and amplitude were compared with those of each component obtained from measured ERPs between the AD/HD group and the healthy control group.

Statistical analyses:

For two-group comparisons, homogeneity of variance was assessed by the Bartlett test. Parametric comparisons used analysis of variance (ANOVA). The significance of individual differences was evaluated by using the Scheffe test if ANOVA was significant.

RESULTS

(1) P300 (Table 3)

Table 3 shows the mean values of positive reaction time, percentage of hits, latency, and amplitude. AD/HD patients responded significantly slower than normal healthy controls ($p < 0.05$). P300 amplitudes were smaller in the adult AD/HD group as compared with the healthy control group ($p < 0.001$).

(2) Nde (Table 4)

Table 4 summarizes the mean values of positive reaction time, percentage of hits, latency, and amplitude. In the AD/HD group, the positive reaction time was significantly slower compared to the healthy control group ($p < 0.01$). Nde amplitudes were smaller in the adult

Table 3. Comparison between AD/HD group and control group in regard to P300

		Healthy Controls MEAN (S.D.)	AD/HD MEAN (S.D.)	
P300 Reaction time[msec]		353 (117)	443 (114)	*
P300 % Hits [%]		99.6 (0.43)	98.1 (3.48)	N.S.
P300 Latencies [msec]				
	Fz	311 (17.3)	309 (31.6)	N.S.
	Cz	310 (16.3)	307 (31.5)	N.S.
	Pz	314 (16.2)	314 (36.0)	N.S.
P300 Amplitudes [μ V]				
	Fz	- 18.0 (4.44)	- 7.15 (5.14)	**
	Cz	- 17.2 (3.73)	- 8.63 (4.55)	**
	Pz	- 18.4 (3.86)	- 11.1 (4.11)	**

Note: N.S. = not significant

*p < .05 **p < .001

Table 4. Comparison between AD/HD group and healthy control group in regard to Nde

		Healthy Controls MEAN (S.D.)	AD/HD MEAN (S.D.)	
Ne Reaction time [msec]		474 (89.9)	603 (111)	*
Nd % Hits [%]		97.2 (3.75)	94.8 (5.24)	N.S.
Nde Latencies [msec]				
	Fz	219 (42.8)	206 (60.0)	N.S.
	Cz	219 (44.1)	219 (32.0)	N.S.
	Pz	218 (44.3)	218 (33.2)	N.S.
Nde Amplitudes [μ V]				
	Fz	11.8 (6.77)	6.00 (4.15)	N.S.
	Cz	9.77 (3.77)	5.05 (4.06)	*
	Pz	8.42 (3.34)	4.87 (3.90)	*

Note: N.S. = not significant

*$p < .01$

Table 5. Comparison between AD/HD group and healthy control group in regard to MMN

		Healthy Controls MEAN (S.D.)	AD/HD MEAN (S.D.)	
MMN Latencies [msec]				
	Fz	173 (32.6)	170 (27.0)	N.S.
	Cz	174 (32.0)	171 (27.7)	N.S.
	Pz	174 (32.0)	172 (28.3)	N.S.
MMN Amplitudes [μ V]				
	Fz	4.71 (2.47)	3.17 (2.97)	N.S.
	Cz	4.09 (1.95)	2.79 (2.21)	N.S.
	Pz	3.63 (1.84)	2.32 (2.29)	N.S.

Note: N.S. = not significant

AD/HD group as compared with the normal healthy control group ($p<0.01$).

(3) MMN (Table 5)

Table 5 gives the MMN latency and amplitude. The MMN latency and amplitude did not differ significantly between groups.

DISCUSSION

To our knowledge no previous studies on Nd and MMN of adult AD/HD have been reported. In the present study, to examine the attentive and cognitive disturbances associated with adult AD/HD, we measured the auditory Nde and MMN, and P300.

We have shown that P300 and Nde amplitudes were smaller in the adult AD/HD group as compared with healthy controls. These ERP results are the same as those obtained in

childhood AD/HD. This means that the childhood dysfunction persists into maturity.

The adult AD/HD group showed reduced amplitude of the P300, consistent with the report of Strandburg et al. in children[8]. In 1990, Satterfield reported that P3b amplitude declined in AD/HD children in an age-dependent fashion between ages 6 and 8, compared to normal children[14]. Similarly, Jonkman et al. pointed out shortened P3b amplitude, and furthermore reported that methylphenidate treatment improved the performance of AD/HD patients in given tasks and also increased their P3b amplitudes[15].

The P300 is considered to be related to the updating of internal imaging and memory templates and correction of schemes that enable the use of current information. The above results indicate the presence of a specific disorder in the information processing stages of a) transmission, b) automatic processing, and/or c) controlled processing of information in adult AD/HD as well as childhood AD/HD.

The Nd, a component that reflects a conscious and active attention function, is regarded as an indicator of selective attention. This component is studied using a subtraction waveform, which is obtained by subtracting the ERP waveform generated in response to non-attentive stimuli from that generated in response to attentive stimuli under the double-selection task condition. Jonkman et al. investigated processing negativity (PN), which is considered to be a component similar to Nd, and reported that PN amplitudes obtained in the frontal region were shorter in the AD/HD group compared to the normal group and were increased by methylphenidate treatment[15]. However, relevant research information is limited, and Nd requires further investigation. The present study demonstrated a significantly reduced Nde amplitude for the adult AD/HD group compared to the healthy control group. This indicates a specific disorder, present in adult AD/HD as well as childhood AD/HD, in the stages of active stimulus selection and of selective attention maintenance in performing selective attention tasks, where controlled processing is dominant.

The MMN, which is involved in a distinctive stimulus discrimination process utilizing sensory memory of prior stimuli, is considered to play an important role as a mechanism for the rapid detection of changes in the outer world, except for those changes that concern the field of consciousness. The MMN component is often studied using a subtraction waveform, which is obtained by subtracting the ERP waveform generated in response to frequent standard stimuli from that generated in response to infrequent deviant stimuli under the stimulus-ignoring condition. Kemner et al. reported reduced amplitudes of MMN to auditory stimuli in individuals with AD/HD compared to normal controls[16]. Kilepelainen et al. also found shortened amplitudes of MMN in the frontal lobe in distracted 9-year-old children in a study comparing children with distractibility to normal controls[17]. In the present study, the MMN latency and amplitude did not differ significantly between groups. These results did not indicate a disturbance of automatic and precognitive processing aided by the memory of prior stimuli in adult AD/HD, suggesting that such dysfunction improves with maturation.

CONCLUSION

These abnormalities of P300 and Nde in adult AD/HD were the same as those observed in the childhood AD/HD. This means that the childhood dysfunction persists into maturity.

Although abnormalities in the component that reflects attention function have been indicated, only a limited number of such reports are available and no consensus has been reached. Further research is essential to elucidate the dysfunction of information processing in childhood and adult AD/HD.

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