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Altered Auditory P300 Performance in Parents with Attention Deficit Hyperactivity Disorder Offspring

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Objective: Altered event-related potential (ERP) performances have been noted in attention deficit hyperactivity disorder (ADHD) patients and reflect neurocognitive dysfunction. Whether these ERP alterations and correlated dysfunctions exist in healthy parents with ADHD offspring is worth exploring.
Methods: Thirteen healthy parents with ADHD offspring and thirteen healthy controls matched for age, sex and years of education were recruited. The auditory oddball paradigm was used to evaluate the P300 wave complex of the ERP, and the Wechsler Adult Intelligence Scale-Revised, Wisconsin Card Sorting Test, and continuous performance test were used to measure neurocognitive performance.
Results: Healthy parents with ADHD offspring had significantly longer auditory P300 latency at Fz than control group. However, no significant differences were found in cognitive performance.
Conclusion: The presence of a subtle alteration in electro-neurophysiological activity without explicit neurocognitive dysfunction suggests potential candidate of biological marker for parents with ADHD offspring.

KEY WORDS: Attention deficit disorder with hyperactivity; Cognition; Evoked potentials; P300; Parents.

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is the most common neurodevelopmental illness of childhood, with influences continuing to adulthood if not being appropriately treated. Relevant research exploring the pathophysiology is ongoing, and neuroelectrophysiological techniques, such as brain event-related potential (ERP), have been widely used. Previous studies have indicated altered ERPs in subject with ADHD in neurocognitive tasks related to domains of attention, inhibitory control, information processing, and reward processing [1-16]. Varied ERP components were ever mentioned; they include P300, N100, N200, P100, P200, contingent negative variations, selection negativity, feedback negativity, late negativity, late positivity, error-related negativity, and error-related positivity [17]. The diverse results of altered ERP patterns in attention orientation and allocation, stimulus discrimination and processing, attention switching, and response inhibition suggest the heterogeneity of the underlying mechanism accounts for explicit symptoms in ADHD.

In addition to the association between altered ERPs and neurocognitive performance in ADHD subjects, varied form of ERP component was noted among subtypes of ADHD. For example, cue P300 amplitude could be used to differentiate subtypes of ADHD and was thought to be a neurophysiological marker of alerting deficits [18]. Other studies revealed ERP component as predictor of treatment response. Sangal *et al.* reported that the P300 topography could predict stimulant efficacy [19-21], and P300 amplitude is related to response to atomoxetine [22]. The potential use of ERP in diagnosis and tailored pharmacological treatment for ADHD subjects addressed

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the importance of further research in this area.

Biological heredity in ADHD and family vulnerability to ADHD-related brain dysfunction has also been noted. Shared characteristics in activation of prefrontal system and related neural circuits (e.g., frontal-cerebellar circuits, frontal-frontal-striatum circuits, frontal-parietal circuits, etc.) and executive dysfunction exist in unaffected siblings and parents of ADHD subjects [23-30]. McLoughlin *et al.* [31] ever mentioned about altered ERPs in fathers with ADHD children; they displayed significantly weaker error and conflict monitoring, as indexed by the smaller error negativity (Ne) and the N2 components. We speculated that shared characteristics could also be observed in ERPs. Exploring these characteristics and identifying biological markers of ADHD further are of clinical concern, not only for more understanding of pathophysiology but also for tailored individual treatment.

The aim of present study was to compare the ERPs and neurocognitive performances of parents with ADHD children and healthy controls. Since the P300 wave is of greatest interest and has been widely examined in ERP studies, we used the auditory oddball paradigm to evaluate the P300 wave complex in this study. We speculated that parents with ADHD children would have poorer neurocognitive function and differed ERPs pattern when comparing with healthy controls.

METHODS

Participants

We enrolled 13 healthy parents (9 males and 4 females) of children with ADHD from child psychiatry outpatient clinics of a National Cheng Kung University Hospital. The inclusion criteria were as follows: (1) have a child who fulfilled the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria for child ADHD; (2) be aged between 20 and 60 years; (3) have no physical illness and stable vital signs; and (4) have no evidence of substance abuse/dependence as assessed during the clinical interview with the research psychiatrist at the time of enrollment.

A group of healthy controls (n = 13) with a similar age, sex, and number of years of education, without a child who fulfilled the DSM-IV criteria for child ADHD, was also enrolled from the community. Both the parents and healthy controls were confirmed by a senior psychiatrist to be free of any psychological disorder by the Mini-International Neuropsychiatric Interview (MINI).

The exclusion criteria for all participants were as follows: (1) other co-morbid psychiatric illnesses or neurological illnesses; (2) mental retardation or intelligence quotient (IQ) < 70.

Before any procedure was performed, written informed consent was obtained from the participants. The Ethics Committee for Human Research at the National Cheng Kung University Hospital approved the study protocol (A-BR-101-118).

Event-related Potentials

ERPs were recorded using an auditory oddball paradigm, based on methods that have been established previously [32]. Electroencephalograms (EEGs) were recorded using recording apparatus (NuAmps; Compumedics Neuroscan, El Paso, TX, USA). Recordings were performed using an electrocap (Neuroscan Quik-cap - 10/20 electrodes placement, Ag/AgCl Sintered electrode; Comp umedics Neuroscan) in a sound-attenuated, electrically-shielded environment with an acoustic Celotex board. The number of EEG channels was 32. The EEG and eye channels were appropriately amplified (EEG Gain = 19, Sampling = 1,000/seconds, 22-bit A-to-D conversion) and filtered (band pass = 0.1－30 Hz). Eye movements were recorded by an electrode lateral to both eyes, which was near the outer regions of the canthus. Auditory stimuli were delivered binaurally through headphones, and the interstimulus interval was between 1 and 2 seconds. Random target tones (2,000 Hz; probability, 0.2) that differed from the non-target events (1,000 Hz; probability, 0.8) in pitch were established. Participants were instructed to look at the "＋" target on the screen, and press the button as soon as possible when they identified one of the target tones. P300 potentials were recorded from the electrodes referenced linked to the mastoids. EEG epochs starting 150 ms before stimulus onset were averaged off-line by computer. Trials with electrooculography amplitudes over 50 μV were excluded from the average. Subjects would receive 200 trials in total; those who completed fewer than 20 accepted trials for the target were excluded. The P300 amplitude was measured relative to the mean of the 100-ms prestimulus baseline, with peak latency defined as the time point associated with the maximum positive amplitude during the 200－400-ms inter-

val following the stimulus. Both the amplitudes and the latencies were recorded by technicians.

Wechsler Adult Intelligence Scale-Revised (WAIS-R)

The WAIS-R [33] was used to evaluate the individuals' intelligence. This test gives a full-scale IQ (FIQ) and 2 different dimensions of IQ. The six-subtest short-form combination was composed of digit symbol, block design, object assembly, digit span, similarity, and arithmetic tests. We used the former three to obtain an estimated performance IQ, while the latter three were used to obtain an estimated verbal IQ. The mean FIQ score in this test is 100 (the standard deviation is 15).

Wisconsin Card Sorting Test (WCST)

To measure executive function, all participants were administered a 64-card version of the WCST, conducted by an experienced clinical psychologist. The participants were required to match response cards to four stimulus cards in one of three dimensions (color, form, or number) on the basis of sign feedback (correct or wrong). After sorting a series of 10 cards in one category, the subject was asked to sort the cards again in a different category. The definitions of the indices were as described in the WCST manual [34]. In this study, we examined the index of perseverative errors [35,36], which is one of the most commonly-used indexes.

Continuous Performance Test (CPT)

The CPT [37] is a vigilance task requiring rapid information processing and the detection of briefly-presented target stimuli. A higher-processing-load version of the CPT has been proven to be useful for measuring an individual's attentive capacity and ability to process visual information. In this study, each test consisted of a 2 minute practice session, a non-masked task session, and a masked task session. During the masked session, a pattern of snow was used to toggle the background and foreground so that the image was visually distorted. Subject responses were recorded automatically on a diskette using a CPT machine (Sunrise Systems V2.26, Pembroke, MA, USA).

Table 1. Demographic data, event-related potential measurements, and cognitive functions of the parents of the parents of children with ADHD and their matched healthy controls

	Parents of children with ADHD (n = 13)	Healthy controls (n = 13)	Statistics		
			Wilcoxon signed rank test	*p* value	Effect size
Sex (Male/female)	9/4	9/4	-	-	-
Age (yr)	41.92 ± 8.10	41.86 ± 8.54	0.47	0.64	0.09
Years of education	13.38 ± 3.15	13.23 ± 3.06	0.18	0.86	0.04
Amplitude (μV)					
Pz	6.71 ± 4.42	7.44 ± 3.66	0.59	0.55	0.12
Cz	5.67 ± 3.67	7.01 ± 4.24	0.80	0.42	0.16
Fz	5.48 ± 3.78	7.84 ± 4.01	1.57	0.12	0.31
Latency (ms)					
Pz	341.08 ± 28.19	331.46 ± 30.96	0.38	0.70	0.07
Cz	339.00 ± 22.83	327.46 ± 31.90	1.08	0.28	0.21
Fz	342.54 ± 21.83	320.77 ± 27.28	2.17	0.03	0.43
WAIS-R					
Performance IQ	111.15 ± 13.95	104.15 ± 13.04	1.71	0.09	0.34
Verbal IQ	107.85 ± 16.44	101.23 ± 15.79	0.86	0.39	0.17
Full-scale IQ	110.00 ± 15.73	102.38 ± 14.03	1.30	0.20	0.25
WCST					
Perseveration errors	19.85 ± 13.63	14.54 ± 13.31	1.08	0.28	0.21
CPT					
Unmasked d'	4.47 ± 0.69	4.53 ± 0.41	0.80	0.42	0.16
Masked d'	4.19 ± 0.76	3.85 ± 0.64	1.38	0.17	0.31

Values are presented as number only or mean ± standard deviation.
ADHD, attention deficit hyperactivity disorder; Pz, parietal; Cz, central; Fz, frontal; WAIS-R, Wechsler Adult Intelligence Scale-Revised; IQ, intelligence quotient; WCST, Wisconsin Card Sorting Test; CPT, continuous performance test.

According to signal detection theory, the fundamental task in this test is to discriminate between the signal (target) and noise (non-target). The distribution of the attention test index, d', is a measure of the subject's ability to differentiate a signal from the background noise: a higher d' indicates a better processing capability.

Statistics

As the sample size was small and was matched for age, sex, and years of education, Wilcoxon signed-rank tests were used to examine the differences in age, years of education, ERP, and cognitive functions between groups. Spearman's ρ correlations and partial correlations, controlling for age and sex [38,39], were carried out to examine the associations between ERP and cognitive functions. The level of significance was set at $p < 0.05$ (two-tailed). All analyses were performed using SPSS software (version 17.0; SPSS Inc., Chicago, IL, USA).

RESULTS

No significant differences were found in age, sex, years of education, or cognitive performance in the WAIS-R, WCST, and CPT between groups, as shown in Table 1. The grand average waveforms (Fig. 1) and the topographic

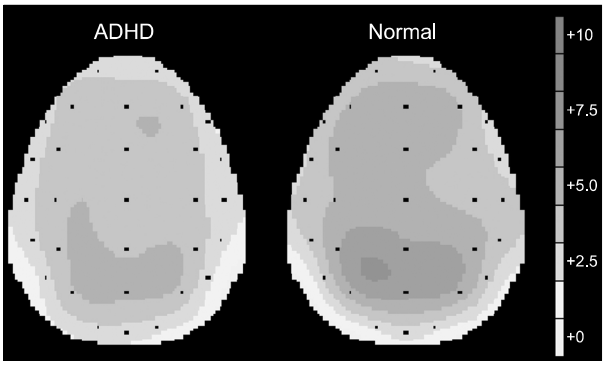
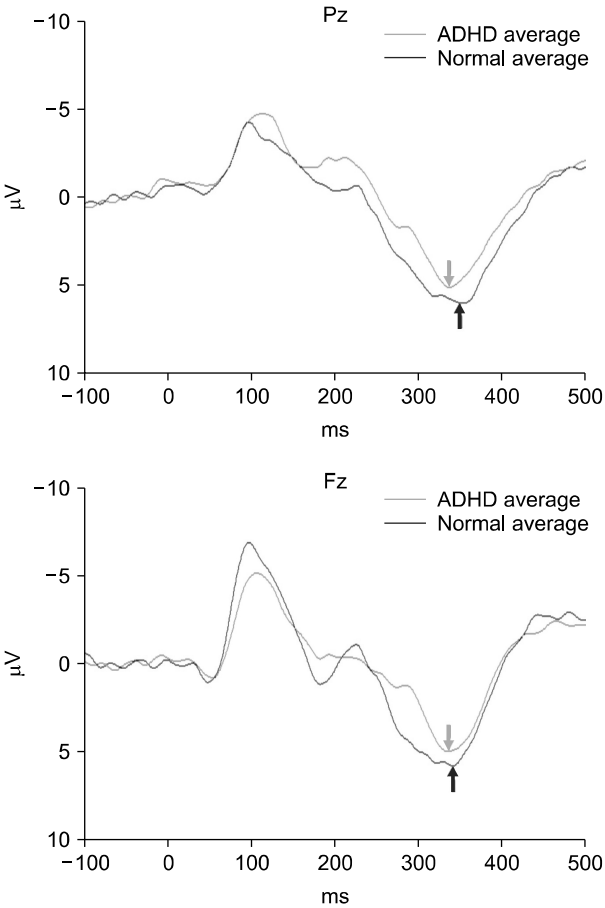


Fig. 2. The topographic maps for the two groups (duration 300−399 ms).
ADHD, attention deficit hyperactivity disorder.



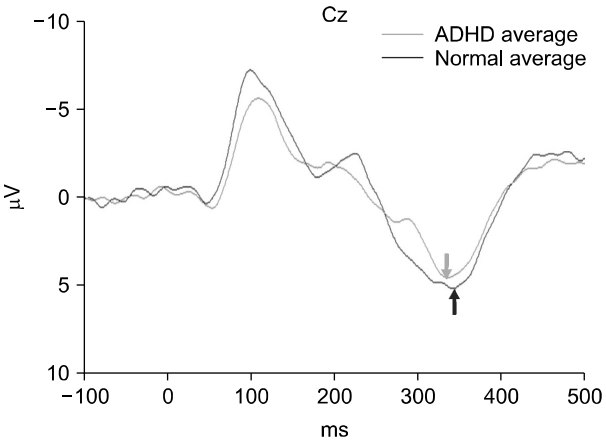


Fig. 1. The grand average waveforms for the two groups.
Pz, parietal; Cz, central; Fz, frontal.

Table 2. Spearman's ρ correlation between event-related potential and cognitive function in parents of children with attention deficit hyperactivity disorder

	Amplitude (μV)						Latency (ms)					
	Pz		Cz		Fz		Pz		Cz		Fz	
	ρ	*p* value	ρ	*p* value	ρ	*p* value	ρ	*p* value	ρ	*p* value	ρ	*p* value
WAIS-R												
Performance IQ	−0.05	0.88	0.01	0.98	−0.03	0.92	0.44	0.14	0.51	0.08	0.43	0.14
Verbal IQ	−0.24	0.43	−0.01	0.97	−0.02	0.96	0.33	0.28	0.25	0.41	0.19	0.52
Full-scale IQ	−0.21	0.48	−0.03	0.93	−0.01	0.96	0.45	0.12	0.43	0.15	0.33	0.27
WCST												
Perseveration errors	−0.23	0.46	−0.32	0.29	−0.31	0.30	0.11	0.71	−0.11	0.71	−0.04	0.90
CPT												
Unmasked d'	0.42	0.16	0.35	0.25	0.33	0.27	0.35	0.24	0.21	0.49	0.20	0.52
Masked d'	−0.10	0.77	−0.06	0.85	−0.06	0.85	0.51	0.11	0.51	0.11	0.50	0.12

Pz, parietal; Cz, central; Fz, frontal; WAIS-R, Wechsler Adult Intelligence Scale-Revised; IQ, intelligence quotient; WCST, Wisconsin Card Sorting Test; CPT, continuous performance test.

maps (Fig. 2) for the two groups were illustrated. However, the parents of children with ADHD had longer auditory P300 latency at Fz ($p = 0.03$) than the control group (Table 1). ERPs were not significantly correlated with cognitive function ($p > 0.07$) (Table 2), even when the age and sex was controlled ($p > 0.07$, data were not shown) in the parents of children with ADHD.

DISCUSSION

Our results show that the parents of children with ADHD had longer auditory P300 ERP latency but did not have altered cognitive performance compared with their controls. This suggests that although there was no significant difference in neurocognitive performance between the two groups, a subtle alteration in the neurophysiological performance could exist as a potential candidate of biological marker in this population.

Latency is an indicator studying the functions of attention, since it varies with the effort of discriminating different stimulus [40]. It is closely related to stimulus discrimination and evaluation but not duration of response selection and execution [41]. Correlation between P300 latency and cognitive capability was mentioned [42]. It was increasing with aging and was thought to be related to dementing process [43,44]. Previous studies had discussed about the P300 latency in ADHD patients. ADHD children had longer visual P300 latency and lower P300 amplitude when comparing with controls, indicating reduced involvement in post-decisional processing [45]. A study from Taiwan also showed longer P300 latency in ADHD children [6]. Prolonged latency in ADHD children, and effect of methylphenidate on decreasing latency was reported [46]. Yamamuro *et al.* [47] had mentioned about prolonged P300 latency in ADHD children at fronto-central, central-parietal, and parietal positions, and positive correlation between the level of prolongation and severity of inattention symptoms. These results suggested the P300 latency as a neurophysiological marker in ADHD and might be changed under medication treatment. Our study showed a similar increase in the latency of P300 at Fz in ADHD healthy parents. To date, there has been no other study discussing P300 wave characteristic that has focused on healthy parents with ADHD offspring; our result suggested prolonged P300 latency as a candidate of shared marker in this population. However, there were also studies revealing no differences in P300 latency [3,48]. The discrepancy might be caused by the subjects' heterogeneity and different methodologies. Further studies using more comprehensive method with measuring of subcomponents of P300, or investigating the P300 waveform differences in subgroups with ADHD characters, are needed.

It is worth noting that there was no significant difference in P300 wave amplitude between ADHD parents group and controls in our study. Reduced P300 amplitudes in child and adult ADHD patients were mentioned in many previous studies although with different neurocognitive tasks, stimulus modalities, and heterogeneous methodologies [8-12,49-51]. This might reflect deficits in

high level executive functions such as attention allocation [5], or ventral attention network dysfunction [16]. However, this tendency was not presented in healthy parents with ADHD offspring in our study. Putting these together, it might reflect the early stage of information processing, including the discrimination of different stimulus and stimulus evaluation, but not the late processing stage during attention task, as the main neurophysiological differences noted in this population.

The lack of a significant correlation between ERP alterations and neurocognitive performance, and the lack of deficits in cognitive function in healthy parents with ADHD offspring, might suggest that, as family members of ADHD patients, the underlying neural mechanisms of these tasks might be different in these individuals compared to the general population, despite the fact that they have no explicit attention, inhibition or executive dysfunction. We hypothesize that there are compensatory mechanisms in this population to maintain basic functionality. Since the neurophysiological alteration was subtle and mild in this study group compared with patients with clinically significant ADHD symptoms, the compensation from other parts of the neural processing was effective in adults with ADHD offspring to smoothly carry out the neurocognitive tasks. Another explanation is that the traditional neurocognitive tasks we used could not reflect subtle differences in explicit attention, inhibition control or executive function among the study group population. Considering our result of prolonged P300 latency, other neurocognitive tests involving the early information processing stage of attention task, like the selective attention task [52], should be considered in following study design. Further study is therefore required. The small sample size might be another reason for the lack of significant correlation between altered ERP and neurocognitive tasks.

There were several limitations in this study. Firstly, the sample size was small, and the significance of group difference was weak, therefore generalization of the results should be carried out with caution. Secondly, although the auditory oddball paradigm was used widely, subtle neurophysiological differences might not be elicited. Besides, other neurological tasks might be needed also to re-evaluate the correlation between the ERP alterations and neurocognitive performance. Thirdly, it would be better to check other ERP components that are known to be altered in ADHD to make the results more comprehensive. Finally, further studies that include ADHD adult patients as a comparison group are essential to explore the differences in ERPs and neurocognitive performance.

In conclusion, in parents with ADHD offspring, our findings provide preliminary evidence of altered neurophysiological correlates in the early information processing stage of attention task. Further investigation is needed to verify the association between neurophysiological correlates and explicit behaviors. Whether the prolonged P300 latency implicates the existence of potential biological marker and familiar association or not needs more exploration.

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■ Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

■ Author Contributions

Corresponding author Yen Kuang Yang designed the study and wrote the protocol. Authors Ching-Lin Chu and Po See Chen contributed to the statistical analyses. Author Mei Hung Chi wrote the first draft of the manuscript. Authors I Hui Lee, Yi-Ting Hsieh, Kao Chin Chen, and Yen Kuang Yang managed the data collection. All authors interpreted the analysis of the results and helped to revise the manuscript.

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