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Effects of Methylphenidate in Children with Attention Deficit Hyperactivity Disorder: A Comparison of Behavioral Results and Event-Related Potentials

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1. Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is one of the most common mental disorders in children and adolescents, with an estimated 3–5% of children diagnosed with this disorder [1,2]. ADHD is characterized by symptoms of inattention, impulsivity and hyperactivity. It has been suggested that a core deficiency in inhibitory control accounts for many deficits in executive function observed in ADHD that underlie most of the dysfunctional behaviors associated with this syndrome [3]. The apparent importance of executive dysfunction in children with ADHD has thus led to an increasing number of investigations in this area.

Executive control is engaged in situations requiring decision making, conflict resolution, error correction, and response inhibition. An important aspect of executive function is the inhibition of a prepared response, where inhibition refers to the ability to actively suppress, interrupt or delay an action [4]. Without inhibition, there is no capacity to avoid the execution of inappropriate responses, or ensure attainment of appropriate responses, thereby preventing realization of an intended result.

One commonly used paradigm in the investigation of executive function is the continuous performance test (CPT), which is a classical GO/NOGO paradigm. CPT was firstly used as a measure of sustained attention [5], and has since been widely applied in the investigation of cognitive response control and response inhibition, in both clinical groups and healthy subjects [6].

Event-related potentials (ERPs) are electroencephalogram (EEG) recorded changes that are time locked to sensory, motor, or cognitive events. Event-related potentials provide a safe, noninvasive approach to study of the psychophysiological correlates of mental processing.

GO/NOGO tasks are a particularly suitable paradigm for investigating response inhibition with ERPs. In this task, subjects are usually required to respond either overtly or covertly to a given target stimulus (a tone or a letter) (GO condition). In a second condition, however, subjects are required to withhold a response to a given stimulus (NOGO condition). The ERPs of CPT tasks are investigated by comparing ERP differences induced by the GO condition (“9” after “1”) and NOGO condition (no “9” after “1”). The NOGO condition has a more significant N2 component between 200 and 300 ms over the frontocentral scalp than the Go condition, and the subsequent frontal-central region a larger P3 component; the GO stimulus has a larger P3 component in the parietal region. The NOGO-N2 and the NOGO-P3 components are related to response inhibition [7]. The GO-P3 component is related to the attention of the GO stimulus [8]. An increasing body of recent evidence suggests that the NOGO-N2 is related to conflict monitoring, while the NOGO-P3 is related to response inhibition [9, 10]. The source of response inhibition has been localized in the anterior cingulate cortex (ACC).

Stimulant medication [11,21], particularly methylphenidate (MPH), is the most common treatment for children with ADHD, and has been shown to improve attention and behavior; low doses of MPH are highly effective and widely prescribed for the treatment of ADHD [12]. ERP analysis has been employed in efforts to gain knowledge about stimulant mechanisms and their relationship to appropriate effect, and studies have suggested that ERPs may predict the clinical response of children with ADHD to MPH [13]. Low dose MPH has been associated with reduced impulsivity (fewer false alarms) and decreased P3 latencies, whereas the higher doses have been associated with reduced impulsivity and less inattention (more hits), in addition to increased P2 and N2 latencies and decreased P3 latencies [14]. The Continuous Performance Test (CPT) is an appropriate instrument for assessment of the correlates between attention-related electrical activity levels in the brain and responses to stimulant medication [15].

This study investigates the effect of Methylphenidate on the relationship between the ERP waveform and behavioral results of children with ADHD. Therefore, based on their behavioral results pre- and post-administration of MPH, the ADHD children were divided into two groups: an ADHD good performance group and an ADHD poor performance group. We are interested in whether the changes in the ERP waveform correlate with the behavioral results, and the ERP waveform differences from the control group waveforms.

2. Materials and methods

2.1. Subjects

2.1.1. ADHD group

Twenty-eight children aged from 6 to 13 years (24 males and 4 females, mean age = 9.25 ± 1.86 years) with a primary diagnosis of ADHD participated. Children with ADHD were recruited from the ADHD clinic at the Third Affiliated Hospital of Soochow University. All of the children were identified as meeting DSM-IV criteria for ADHD based on a structured clinical

interview and parent rating scales. Excluded from the study were subjects with a conduct disorder, internalizing disorder (e.g. anxiety), low intelligence ($IQ < 85$), and gross neurological and other organic disorders. All subjects had not taken any stimulant medication. ADHD children were given a low dose of 0.3mg/kg of methylphenidate (MPH). Verbal assent was provided by the subjects and written informed consent obtained from their parents.

2.1.2. The control group

The control group consisted of 28 age- and gender-matched healthy children, 6.8-13.2 years old (mean age = 9.15 ± 1.94 years), were right-handed, with Screened $IQ \geq 85$, visual or corrected visual acuity greater than 1.0, without diseases of the nervous system, and no special learning difficulties or language barriers. They were tested only one time. Verbal assent was obtained from the children and their teachers, with written informed consent obtained from their parents.

2.1.3. Behavioral results—basis for group division

Children with ADHD were tested twice. They were tested once following diagnosis (pre-administration of MPH); and a second time two hours post-administration of MPH (0.3mg/kg body weight).

The ADHD good performance group: after taking MPH, behavioral results were improved, with the number of omission errors and/or commission errors reduced by a factor of five in a total of 12 patients (1 female), mean age 9.17 ± 2.19 years old. Prior to administration of MPH, the number of omission errors and commission errors (respectively 8.37 ± 3.92 , 7.78 ± 5.10) were significantly higher than the results obtained of 2 hours post-administration of MPH (respectively 2.92 ± 3.61 , 3.91 ± 2.62) ($P < 0.05$).

The ADHD poor performance group: post-administration of MPH, behavioral results were not significantly improved, with behavioral changes not meeting behavioral improvement standards in a total of 16 patients (3 females), mean age 9.31 ± 1.66 years old. Prior to administration of MPH, the number of omission errors and commission errors (respectively 7.95 ± 4.61 , 7.46 ± 5.81) were higher than the results obtained 2 hours post-administration MPH (respectively 5.79 ± 2.71 , 5.83 ± 2.91), but the differences were not statistically significant ($P > 0.05$).

2.2. Electrophysiological paradigm

The participants were investigated electrophysiologically in an electrically shielded, dimly lit room, sitting on a comfortable chair in front of a computer screen to perform the CPT tasks, with a viewing distance of 80 cm, horizontal visual angle of 0.7° , and a vertical visual angle of 1.4° . During the task, digits were presented in a random order, and subjects instructed to press a response button whenever the digit “9” appeared immediately after the digit “1”. The whole stimulus set consisted of 400 digits, with 80 prime conditions (digit “1”), 40 GO (“9” after “1”) and NOGO (no “9” after “1”) conditions and 240 distracters (other digits, including the digit “9”, without a preceding “1”) (see fig.1). The digits were presented for 200 ms each, followed

by an inter-stimulus interval of 1400 ms, resulting in a total duration of approximately 11 minutes. After a short training session, subjects performed this version of the CPT while an ongoing EEG was recorded.

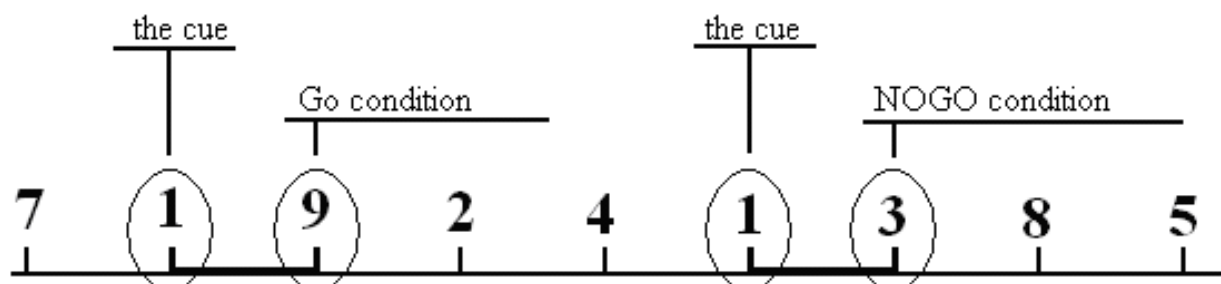


Figure 1. The sequence of stimulus presentation

2.3. EEG recording

Scalp voltages were collected with a Stellate™ System 32 channel Digital Video EEG (Stellate System Inc., CA) connected to a 32-Channel Digital Amplifier (LA MONT MEDICAL Inc., Montreal, CA). The EEG was recorded from 23 scalp electrodes which were placed according to the International 10-20 system at FP_1 , FP_2 , F_z , F_3 , F_4 , F_7 , F_8 , C_z , C_3 , C_4 , T_3 , T_4 , P_z , P_3 , P_4 , T_5 , T_6 , O_z , O_1 , O_2 , M_1 , M_2 and a common reference. Vertical electro-oculogram (VEOG) electrodes, located at 2 cm above and below the left eye, were used to subtract the eye movement artifact. Impedances was $<5\text{ K}\Omega$, bandpass filtered from 0.1 to 35 Hz and digitized at 500 Hz. A midline electrode was used as the common reference for recording.

Trials were discarded from analysis if they contained eye movements (vertical EOG channel differences greater than $100\mu\text{V}$) or more than five bad channels.

2.4. Data analysis

Grand average ERP waveforms were used to determine the individual NOGO-N2 and NOGO-P3 time window. NOGO-N2 at Fz and Cz electrodes were maximal from 250-300 ms, 280-350 ms at Pz electrode; NOGO-P3 at Fz and Cz electrodes were maximal from 400-500 ms, 420-520 ms at Pz electrode. In each time window, the amplitudes of NOGO-N2 and NOGO-P3 at Fz, Cz, Pz electrodes were measured. Latency represented the time from the stimulus onset to the wave peak; amplitude represented the vertical distance from the baseline to the wave peak.

2.5. Statistical analysis

SPSS12.0 statistical software was used for data processing, using t-test for the difference between two groups and ANOV for the differences among multiple groups. All data were expressed as Mean \pm SD ($\bar{x} \pm s$), with the difference was considered significant if the P value was smaller than 0.05.

3. Results

3.1. ERP results of the ADHD good performance group

Comparing the results of this group, both pre- and post-administration of MPH, with the control group, the amplitude of the NOGO-N2 displayed no significant difference ($P > 0.05$). Pre-administration of MPH, the amplitude of the NOGO-P3 was significantly lower than the results obtained 2 hours post-administration of MPH and by the control group; at the Fz and Cz electrodes the differences were statistically significant ($P < 0.05$). Compared to the control group, the amplitude of the NOGO-P3 2 hours post-administration of MPH showed no significant difference ($P > 0.05$).

See Table 1 for details.

electrode	ERP	pre- - administration of MPH	2 hours post- administration of MPH	the control group	F value	P value
Fz	N2(250-300ms)	-7.17±5.81	-5.84±4.71	-7.67±4.32	0.62	0.54
	P3(400-500ms)	20.34±11.42	30.24±10.78 ⁽¹⁾	33.26±9.83 ⁽²⁾	6.49	0.003
Cz	N2(250-300ms)	-3.01±4.68	-2.08±3.37	-4.76±6.60	1.09	0.34
	P3(400-500ms)	16.28±6.36	22.20±5.07 ⁽¹⁾	23.67±8.14 ⁽¹⁾	4.52	0.02
Pz	N2(280-330ms)	-1.73±3.63	-0.28±2.71	-1.25±3.94	0.51	0.60
	P3(420-520ms)	14.34±5.72	18.20±4.41	18.88±7.69	2.00	0.15

(1) Comparing to pre- administration of MPH, $P < 0.05$;

(2) Comparing to pre- administration of MPH, $P < 0.01$.

Table 1. The ADHD good performance group pre- and post-administration of MPH and the control group at Fz, Cz, Pz electrodes amplitudes of the NOGO-N2 and NOGO-P3 comparison ($\bar{x} \pm s$) (μv)

3.2. ERP results of the ADHD poor performance group

As with the ADHD good performance group, in comparing the results pre- and post-administration of MPH with the control group, the amplitude of the NOGO-N2 also displayed no significant difference ($P > 0.05$). However, in this case both pre- and 2 hours post-administration of MPH, no statistically significant difference in the amplitude of the NOGP-P3 ($P > 0.05$) was found. Pre- and post-administration of MPH, the amplitude of the NOGO-P3 at the Fz electrode was significantly lower than that of control group ($P < 0.05$). At the Cz electrode, the amplitude of the NOGO-P3 pre-administration of MPH was also significantly lower than that of the control group ($P < 0.05$). However, compared to the control group, the amplitude of the NOGO-P3 post-administration of MPH showed no significant difference ($P > 0.05$).

See Table 2 for details.

electrode	ERP	pre- administration of MPH	2 hours post- administration of MPH	the control group	F value	P value
Fz	N2(250-300ms)	-6.88±6.59	-7.08±8.18	-7.67±4.32	0.10	0.91
	P3(400-500ms)	23.51±11.97	25.88±13.96	33.26±9.83 ^{(1) (2)}	4.23	0.02
Cz	N2(250-300ms)	-2.79±6.61	-2.22±6.33	-4.76±6.60	0.92	0.40
	P3(400-500ms)	17.28±7.56	19.94±7.09	23.67±8.14 ⁽¹⁾	3.68	0.03
Pz	N2(280-330ms)	0.48±6.33	-0.36±4.68	-1.25±3.94	0.66	0.52
	P3(420-520ms)	15.21±6.17	16.34±5.90	18.88±7.69	1.63	0.20

(1) Comparing to pre- administration of MPH, $P < 0.05$;

(2) Comparing to 2 hours post-administration of MPH, $P < 0.05$.

Table 2. The ADHD poor performance group pre- and post-administration of MPH and the control group at Fz, Cz, Pz electrodes amplitudes of the NOGO-N2 and the NOGO-P3 comparison ($\bar{x} \pm s$) (μv)

3.3. ERP results of the two ADHD group pre-administration of MPH

The amplitudes of the NOGO-N2 and the NOGO-P3 showed no significant differences ($P > 0.05$).

3.4. Grand average ERP waves

As can be seen in Figure 2, the ERP components of the ADHD good performance group, the ADHD poor performance group and the control group were consistent; all showed N1, P2, N2 and P3 components. In the ADHD good performance group, the amplitudes of the NOGO-N2 pre- and post-administration of MPH showed no significant changes; At the Fz and Cz electrodes, the amplitude of the NOGO-P3 2 hours post-administration of MPH was significantly higher than pre-administration of MPH, while the amplitude of the NOGO-P3 at the Pz electrode showed no significant changes. In the ADHD poor performance group, the amplitudes of the NOGO-N2 and NOGO-P3 at the Fz, Cz, Pz electrodes showed no significant changes both pre- and post-administration of MPH; the amplitude of the NOGO-P3 was significantly lower than that of the control group.

4. Discussion

Central stimulants are the first choice for the treatment children with ADHD, and the most widely used is Methylphenidate. MPH can improve attention deficit and interpersonal relations, lower activity levels and impulsivity, and improve academic achievement, and have a positive effect on children with ADHD. While there is a previously reported efficiency of approximately 75% [11], our clinical work indicates an efficiency rate was below this number. This study uses the continuous performance test (CPT) to investigate the relationship

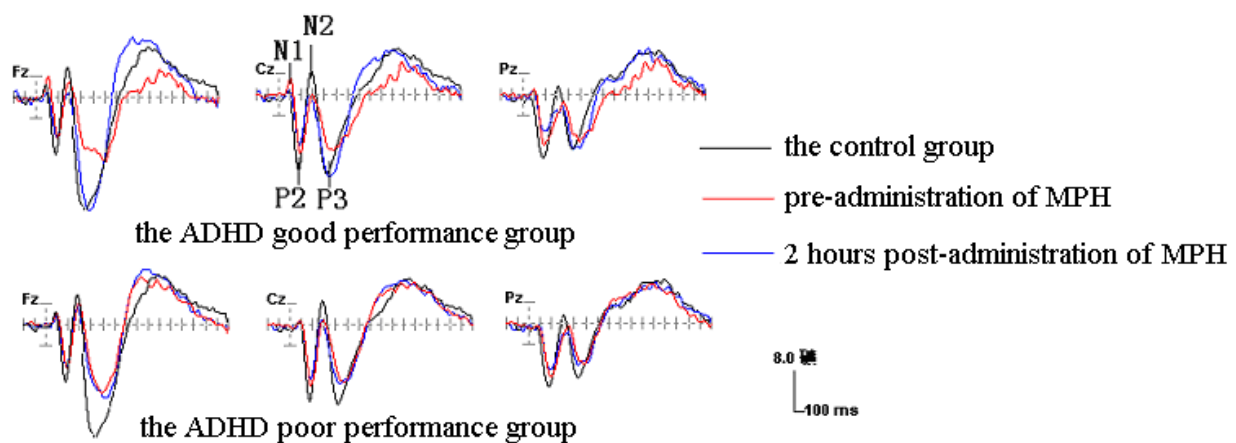


Figure 2. The grand average ERP waveforms

between behavioral results and ERP changes pre- and post-administration of MPH in children with ADHD, and compares these results to a control group.

This study found that in the ADHD group pre-administration of MPH the amplitude of the NOGO-P3 was significantly lower than that of the control group, while the amplitude of the NOGO-N2 showed no difference between the control group and the ADHD group pre-administration of MPH. This suggests the existence of frontal inhibition functional deficiencies rather than the conflict monitoring deficiencies, consistent with Fallgatter's study [16], confirming the existence of cingulate cortex dysfunction in children with ADHD.

In the ADHD good performance group, 2 hours post-administration of MPH, behavioral results were significantly improved; that is, omission errors and commission errors significantly reduced and the amplitude of the NOGO-P3 was significantly higher, although the amplitude of the NOGO-N2 showed no significant changes. Methylphenidate can improve attention deficit and the ability to inhibit impulsive reactions in children with ADHD. However, no significant changes in conflict monitoring ability were observed 2 hours post-administration of MPH. The amplitude of the NOGO-P3 was significantly increased, with no significant difference in comparison to the control group, suggesting MPH can normalize both the amplitude of the NOGO-P3 and the ability to inhibit impulsive reactions in children with ADHD.

In the ADHD poor performance group, 2 hours post-administration of MPH, behavioral results showed no significant improvement; that is, omission errors and commission errors were reduced, but the difference did not reach statistical significance. The amplitudes of the NOGO-N2 and NOGO-P3 showed no significant changes either pre- or post-administration of MPH; changes in ERP and behavioral results were consistent. This suggested that MPH had no significant impact on behavioral performance and ERP results, that it does not improve attention deficit and the ability to inhibit response, and there is no effect on the conflict monitoring and response inhibition. 2 hours post-administration of MPH, the amplitude of the NOGO-P3 was still lower than that of the control group, in which the frontal electrode had

statistical significance. The result suggests that MPH failed to improve the ability of response inhibition of children with ADHD to normal levels.

Methylphenidate can be effective in improving the symptoms of children with ADHD, primarily through the promotion of dopamine (DA) and norepinephrine (NE) release to reduce reuptake. The pre-frontal region is rich with DA and NE receptors, and it is assumed that MPH acts through these receptors. ADHD is associated with an irregularity in a variety of cognitive and behavioral processes [11]. Recent studies have found that low-dose MPH in the treatment of ADHD may activate the locus coeruleus - norepinephrine (LC -NE) system, by influencing the locus coeruleus neurons in different discharge modes (phase- and tension-type) to alter behavioral and cognitive processes [17]. Neuroimaging, neuropsychological and neurochemical studies have also implicated dysfunction of fronto-striatal structures [18]. An fMRI study found that fronto-striatal activation, significantly lower in an ADHD group compared to a control group, increased post-administration of MPH [19]. The frontal lobe plays an important role in attention, executive function, working memory, regulating activities and decision-making. Most of the studies of children with ADHD consider that the frontal lobe dysfunction causes attention deficit and presents obstacles to response regulation. MPH treatment may be either effective or ineffective in children with ADHD, dependent on their age and emotional state, with treatment least effective in older age groups [20]. While this present study did not find such factors, children are nevertheless primary candidates for MPH treatment, though it should be observed that individuals respond differently

Young ES, et al [13] used an auditory oddball P300 paradigm to compare the ERP changes pre-administration and 2 hours post-administration of MPH. A prediction of the long-term benefit of medication was then made, based on the magnitude of the acute changes in P3b amplitude. The MPH challenge classification accurately predicted the outcome in 81% of cases. This present study used CPT tasks to test children with ADHD pre-administration and 2 hours post-administration of MPH. According to their behavioral results, the ADHD group was divided into an ADHD good performance group and an ADHD poor performance group. In the good performance group, the amplitude of the NOGO-P3 was significantly higher; the poor performance group, however, showed no obvious changes. The results suggested the amplitudes of the NOGO-P3 pre-administration and 2 hours post-administration of MPH were consistent with the behavioral results. Therefore, it can be posited that the amplitude of the NOGO-P3 can predict the long-term clinical efficacy of MPH treatment for ADHD. Where the amplitude of the NOGO-P3 is significantly increased post-administration of MPH, MPH may be an effective treatment; where the amplitude of the NOGO-P3 shows no significant increase post-administration of MPH, MPH is less likely to be an effective treatment. This can be primarily used to predict the efficacy of Methylphenidate for the treatment of ADHD, and assist in the selection of suitable treatment for children with ADHD. Further clinical tests will determine the accuracy of the prediction of Methylphenidate efficacy in children with ADHD. The present study can not avoid confounding medication effects with retest effects; this variable should be eliminated in future studies.

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