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Effects of Methylphenidate on Quantitative EEG of Boys with Attention-deficit Hyperactivity Disorder in Continuous Performance Test

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The purpose of this study was to investigate the effects of methylphenidate, a psychostimulant, on quantitative electroencephalography (QEEG) during the continuous performance test (CPT) in boys with attention-deficit hyperactivity disorder (ADHD). The QEEG was obtained from 20 boys with ADHD. The amplitudes of 4 bands (α, β, δ, and Θ) in the QEEG, as well as the Θ/β ratio, before and after the administration of methylphenidate were compared during both the resting and CPT states. Methylphenidate induced a significant increase of α activities in both the right and left frontal and occipital areas, an increase of β activities in almost all areas except for the temporal region, a decrease of Θ activities in both the occipital and right temporo-parietal areas, a mild decrease of δ activities in the occipito-parietal areas, and an increase of the Θ/β ratio in the right frontal and parieto-occipital, and left temporal areas during the CPT state. No significant QEEG changes were induced by the administration of methylphenidate in the resting state. These data suggest that methylphenidate has greater electrophysiological influences on the cerebral topographical activities during the performance of attentional tasks, as compared to the resting state, in boys with ADHD.

Key Words: ADHD, methylphenidate, CPT, QEEG

INTRODUCTION

Attention-deficit hyperactivity disorder (ADHD) is one of the most common behavior disorders during childhood. Although ADHD is a neurobiological disease with diverse etiological findings incorporating neurophysiological, neuroanatomical, and neurobiochemical aspects, it is diagnosed on the basis of patterns of observable behaviors. The administration of psychostimulants, and that of methylphenidate (MPH) in particular, significantly improves the behaviors of children with ADHD both at home and in school.[1] In addition, psychostimulants show positive effects on the cognitive tasks performed by ADHD children. One of the widely used methods of identifying psychostimulant effects on ADHD is the continuous performance test (CPT).[2,3] Although the effectiveness of psychostimulant therapy has been clearly established, it is still unclear how these effects are realized.

Although various brain imaging methods, such as PET, SPECT, MRI and MRS, have recently been used to investigate the localization of the cerebral functional abnormalities and psychostimulant effects in children with ADHD, these approaches are limited in the sense that they are invasive, expensive and require the use of radio-isotopes.

The advantages of the QEEG method in comparison with these other brain imaging methods are that it allows attentional tasks to be performed simultaneously, as well as being safe and inexpensive. This technique quantifies the EEG recorded across the more than 19 regions included in the International 10/20 system, and has been shown

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to be a sensitive indicator of cortical electrophysiological dysfunction in neuropsychiatric disorders.[4-6]

Studies using QEEG have previously attempted to investigate the cerebral functional changes in ADHD. However the results of these previous studies were inconsistent. Callaway et al. reported that ADHD children showed decreased α wave and β wave activities in the parietal and occipital cortex compared to normal children,[7] whereas Kuperman et al. reported a relative increase of β wave activities in ADHD children.[8] Some researchers reported an absolute increase of activities in all EEG bands, and suggested that there were two subtypes of ADHD: the first exhibiting a slowing-down of EEG activities in the frontal regions and the second showing increased EEG activities in the frontal regions.[9,10]

There have been a few reports on the influence of psychostimulants on the EEG changes in ADHD. Most of the studies which used EEG to investigate ADHD were based on the effects of methylphenidate on the resting EEG, and no significant changes in EEG activity were observed in these studies.[8,10-13] Very few researchers have reported the changes in the EEG activity measures induced by the administration of methylphenidate in relation to the task condition, especially in the case of the continuous performance test. Verbaten et al. found that there were apparent increases of the parietal P3 and frontal N2 activities in response to the attentional task condition and a significant increase in the percentage of hits to targets under the influence of methylphenidate in ADHD children.[14] Winsberg et al. reported that ADHD children being treated with methylphenidate showed a higher amplitude and earlier peak for P3 in the task condition, as compared with those taking a placebo.[15]

The purpose of this study is to carry out an acute dosage study, and to investigate the effects of methylphenidate in boys with ADHD by measuring the QEEG during the attentional task (continuous performance test), in order to gain a better understanding of the manner in which methylphenidate affects the cerebral functional localizations.

MATERIALS AND METHODS

Subjects

The subjects of this study consisted of 6 to 12 year old boys who visited the Child and Adolescent Psychiatric Clinic, Yonsei University Medical Center, Seoul, Korea, and who were diagnosed with ADHD according to the DSM-IV (Diagnostic and Statistical Manual-IV) criteria[16] by two child psychiatrists.

Four of the initial 24 subjects dropped out. The reasons for their dropping out were as follows: three did not comply with the attentional task procedure, and one subject refused to take methylphenidate. Finally, twenty subjects completed the study. Only subjects who were right-handed were selected for this study, in order to control for the influences of sex differences and cerebral laterality of the brain function. Subjects with an IQ below 70 were excluded. We also excluded subjects with significant medical problems and/or psychiatric disorders, as well as subjects who encountered any difficulties in performing the study procedures. Consent was obtained both from the subjects and their parents prior to participation in this study. This study was not reviewed by the Institutional Review Board.

Attentional task and behavioral evaluations

The parents and school teachers of all of the subjects performed an abbreviated-version of the Conners Rating Scale (CRS), in order to evaluate the severity of the ADHD symptoms before the EEG assessments were conducted. All of the subjects also performed the Test of Variables of Attention (TOVA), one of the continuous performance tests (CPT) as an attentional task.

Conners parent rating scale-revised

The 93-item original version of the Conners Rating Scale (CRS) was developed by Keith Conners in 1970. Conners revised the original CPRS in 1978, reducing the number of items to 10, and this abbreviated version is the one currently in common use.[17] Those items of the revised CPRS that are rated by parents and school teachers, are very useful for assessing ('0' to '3' rated) the behavioral symptoms of ADHD, viz. inattentiveness, hyperactivity and impulsivity.

Test of variables of attention

One of the most widely studied laboratory measures of vigilance or attention span within the ADHD population is the continuous performance test (CPT). TOVA is a computerized CPT program that includes two successive 15-minute vigilance tasks, wherein the child has to press a button each time a specified, randomly presented visual target (square shaped) appears. This device assesses and calculates the omission errors, commission errors, response time, and standard deviation of the response time.[18]

Methylphenidate administration

The subjects required a 7 day drug wash-out period, free of any drugs including psychostimulants, prior to the study. A single, body weight-adjusted dose of 0.7 mg/Kg of methylphenidate (mean dose 20.8 (±6.1)mg, range from 15 to 35 mg) was administered one hour prior to each QEEG assessment.

Quantitative EEG measurement

A Neuronics QEEG system was used to record the EEG, and the amplified EEG signals were analyzed by a computer manufactured by Mirae Engineering Inc. (1995), Seoul, Korea. Artifacts were screened automatically, and 256 EEG samplings per epoch were obtained. Subsequently, a minimum of 1 minute of artifact-free EEG could be obtained. Then, artifact-free EEG data was recorded for 20 - 50 seconds through monitoring. The stored EEG per epoch from each channel was converted from the time to the frequency domain via Fast Fourier Transformation (FFT). The results of the FFT were used to calculate the absolute power, the amount of energy within the alpha (α), beta (β), delta (δ) and theta (Θ) frequency bands, as well as the Θ/β ratios of the amplitudes of the 30 electrodes, and then (these results were?) spectro-analyzed. Brain map imaging was obtained from the calculated α, β, δ, Θ values, and Θ/β ratio (μV) from each electrode.[10,19]

Procedures

The first QEEG assessment was performed in all subjects in both the resting state and CPT state (while performing TOVA), without methylphenidate administration (MPH-free). One week later, QEEG was repeated in all subjects both before and 1 hour after the administration of MPH (MPH-loaded).

During the recording of the QEEG, the subjects were seated comfortably in a sound- and light-attenuated room. Electrode caps produced by Electro-Cap Inc. (1994), Eaton, Ohio, U.S.A. were used to place the recording electrodes over the 30 regions defined by the International 10/20 system, and these were referenced to the linked ears (Fig. 1). All impedance levels were kept below 10kΩ.

Data analysis

The TOVA variables during the MPH-free and MPH-loaded periods were compared by means of the t-test and Wilcoxon signed ranks test. Also, the α, β, δ, Θ values and Θ/β ratio were calculated from the amplitudes of the QEEG during both periods. T-statistical probability maps (t-SPM) were constructed for all 4 bands and for the Θ/β ratio for each electrode by means of the t-value (the paired t-test). The entire statistical analysis was processed by the Statistical Analysis System (SAS) with $p<.05$.

RESULTS

The characteristics of the subjects and dosage of MPH

The mean age of the subjects was 8.6 (± 1.4) years (range 6.9 - 11.5), and the mean body weight was 30.8 (± 9.6)Kg (range 21 - 52). The mean full-IQ was 100.3 (± 17.3) (range 74 - 127): Verbal IQ 101.0 (± 18.4) and Performance IQ 102.0 (± 17.3). The average CRS score for the parents was 18.8 (± 3.2) (range 14 - 24), and the mean CRS score for the teachers was 19.6 (± 6.1) (range 7 - 30) (Table 1).

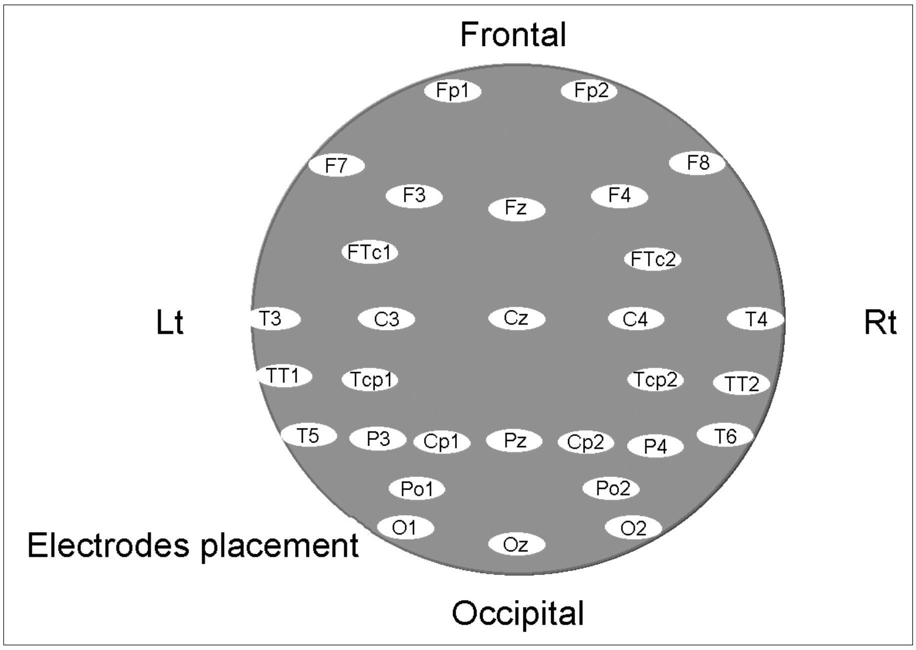

Fig. 1. The combined measure consists of all 30 electrodes sites within the left and right hemispheres.

Table 1. Demographic and Clinical Characteristics of Subjects (n=20)

	Mean (SD)	Range
Age (yrs)	8.6 (1.4)	6.9 - 11.5
Body weight (Kg)	30.8 (9.6)	21 - 52
Full IQ	100.3 (17.3)	74 - 127
verbal IQ	101.0 (18.4)	80 - 123
performance IQ	102.0 (17.3)	72 - 128
CPRS score	18.8 (3.2)	14 - 24
CTRS score	19.6 (6.1)	7 - 30

CPRS, Conners Parent Rating Scales; CTRS, Conners Teacher Rating Scales.

Table 2. TOVA Scores between MPH-free (MPH-) and MPH-loaded (MPH+) periods (n=20)

	MPH (-) mean(SD)	MPH (+) mean(SD)	t	*p*
Omission error (%)	59.3 (10.3)	53.1 (7.7)	5.16	<0.01
Commission error (%)	45.2 (9.4)	48.6 (10.6)	0.93	0.371
Response time (msec)	66.2 (14.1)	58.7 (13.4)	1.99	<0.05
Standard dev. (msec)	65.7 (15.3)	57.5 (14.0)	4.69	<0.01

TOVA

The changes in the TOVA scores are shown in Table 2. The means of the following variables showed significant decreases between the MPH-free period and the MPH-loaded period: omission errors decreased from 59.3% to 53.1%; the response time decreased from 66.2 msec to 58.7

msec; and the standard deviation decreased from 65.7 msec to 57.5 msec.

These data were also analyzed by means of a non-parametric analysis (Wilcoxon signed ranks test). There were no significant differences in the changes of TOVA (omission errors z=5.48, $p < .01$; commission errors z=1.02, p=.352; response time z=2.39, $p < .05$; standard deviation z= 4.73, $p < .01$) as compared to the results obtained by means of the t-test.

Quantitative EEG

The t-statistical probability maps (t-SPM) showed differences in the QEEG activities between the methylphenidate-free and methylphenidate-loaded periods in both the resting state and CPT state. As shown in Fig. 2, the colors of the map represent the statistical p-value: the darker the red color, the more statistically significant the p-value. In general, the T-SPM in the CPT state gave rise to a map with a darker red color than that for the resting state.

Compared to the resting state, in the CPT state, there were more significant QEEG activity changes in the absolute power of the 4 bands (α, β, δ, Θ) between the methylphenidate-free and methylphenidate-loaded periods in several regions, as follows: increased α activities in both the frontal and both occipital areas, increased β activities in almost all areas except for the temporal region, decreased Θ activities in both the occipital and right temporo-parietal areas, and mildly decreased δ activities in the occipito-parietal areas.

The relative power ratio of Θ to β was also calculated, as this has more sensitivity to localized electrophysiological cerebral activity in response to the stimulatory test. The mean Θ/β ratio showed more localization of the QEEG response to methylphenidate administration in the right frontal and parieto-occipital regions, and the left temporal areas in the CPT state, as compared to that observed in the resting state (Fig. 2, 3).

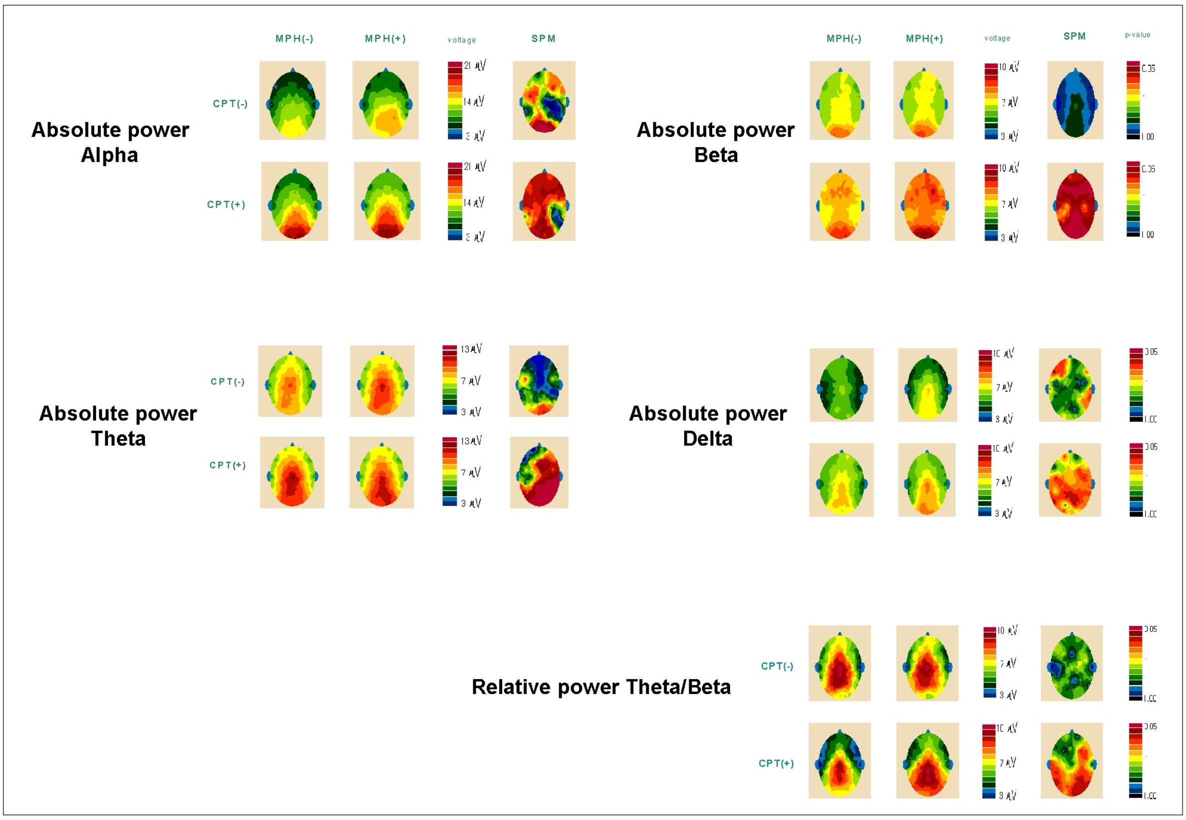

Fig. 2. Average topographic maps of Z-transformed monopolar absolute power of 4 bands and relative power of Θ/β. T-statistical probability map(SPM) means that the darker the red color, the more statistically significant the p-value.

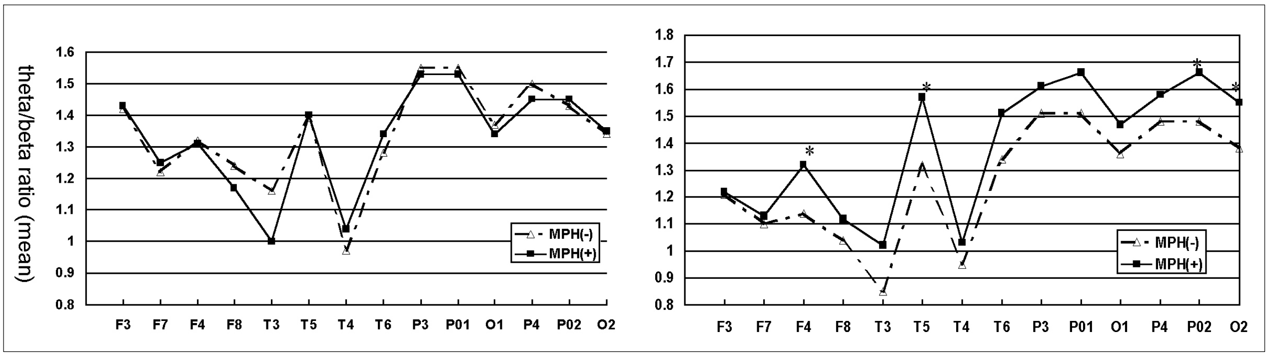

Fig. 3. Comparative theta/beta ratios of QEEG at resting (left) and continuous performance test (right) state between methylphenidate-free (MPH-) and methylphenidate-loaded periods (MPH+). *means $p<.05$ by t-test.

DISCUSSION

In this study, we showed that methylphenidate improved some cognitive functions in the ADHD subjects by means of the TOVA. It is well known that methylphenidate has the effect of improving cognitive and behavioral functions such as attention, impulsivity and hyperactivity in children and adults with ADHD.[2] In the present study, all of the CPT measures except for the percent commission error were significantly improved by acute methylphenidate administration. Verbaten et al. and Winsberg et al. found that methylphenidate produced significant decreases of omission error and reaction time, with the exception of the commission error under the auditory CPT measures, in 14 hyperkinetic children.[15,16] Low to moderate doses of methylphenidate (as in our study) are more effective at improving attentional problems (measured by percent omission error) than impulsivity(measured by percent commission error) in patients with ADHD.[20] Moreover, the role of CPT in monitoring drug response is now widely accepted. Nevertheless, the value of the CPT has come under question.[21,22]

Through a computerized EEG spectral analysis in children with ADHD during the attentional task condition compared to the resting condition, our results revealed that the administration of a psychostimulant showed localized electrophysiological effects in the brain. Methylphenidate was found to increase the α and β activities in the frontal areas, and to decrease the δ and Θ activities in the occipital and parieto-occipital areas of the brain. Investigations using the ERP (Event-related Potentials) technique in ADHD, have reported that P3 can be used to differentiate ADHD subjects from normal subject for visual and auditory tasks. A few studies[7,23] have also reported that P3 can detect performance deficit in ADHD children. Several studies[15,24,25] reported decreased P3 latency and increased P3 amplitude under the measure of CPT performance in hyperkinetic children receiving methylphenidate. In the present study, the faster EEG activities (α, β) increased in the frontal areas, while the slower activities (δ, Θ) decreased in the occipital and parietal areas. These findings support the previous findings that the frontal lobe plays a key role in the executive performance functions of attention, while the parieto-occipital lobe is a major functional area as regards the organization of the attentional system.[26-29]

In this QEEG study, we found that the Θ/β ratio showed more significant sensitivity of the localized EEG responses to methylphenidate administration in the CPT state in the parieto-occipital areas of the right hemisphere. In t-SPM, the β activity showed more significance than the other bands in most cerebral regions, even though it had broader localizations. Moreover, the Θ activity showed narrower localizations. Lubar et al. found that improved task (TOVA) performance was positively correlated with increased β activity and resulted in more elevated Θ and δ activities with methylphenidate administration, whereas no such relationships were observed in the methylphenidate-free condition in the right hemisphere.[12] They suggested that the right posterior brain was a more specific cerebral localization for the organization of attentional functions. This result supports Lubar's suggestions. Some researchers have suggested that the Θ/β ratio is a more accurate measure of brain maturation than the absolute values in all of the frequency bands, and that it is more sensitive to localized electrophysiological cerebral activity in response to the stimulatory test.[11,30]

This study has the following limitations and recommendations. First, the effect of methylphenidate was assessed by means of the administration of a one-time acute dose. Matochik et al. investigated the metabolic changes of the cerebrum of ADHD adults using PET after the administration of methylphenidate for at least 6 weeks, and reported metabolic changes in only 2 out of 60 areas of the cerebrum.[31] However, there are also reports by Lubar et al. and Barkley suggesting that the acute effects of methylphenidate are as effective as its long-term use in the clinical and neuropsychological evaluation of children treated for ADHD.[12,32] Second, the subjects in this study performed only the visual attention task. A further study needs to be done using the auditory attention task, in order to investigate the cerebral activity of both visual and auditory attention. Third, a further study is needed in which girls with ADHD are included, in order to compare the lateralized activity of the cerebrum by gender. Currently, we are conducting a comparative study between ADHD children and normal children using common methods. We will present the results of this study in the near future.

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