The Effects of Methylphenidate on Transcranial Magnetic Stimulation Parameters in Children with Attention Deficit Hyperactivity Disorder

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ÖZET:
Dikkat eksikliği hiperaktivite bozukluğu olan çocuklarda metilfenidatın transkraniyal manyetik stimulasyon parametrelerine etkileri

Amaç: Bu çalışmanın amacı, dikkat eksikliği hiperaktivite bozukluğu (DEHB) olan çocuklarda metilfenidatın (MPH) tedavi öncesi ve sonrası transkranial magnetik stimulasyon (TMS) parametreleri üzerine etkisini incelemektir.
Yöntem: Yaşları 7 ila 13 arasında değişen, 24 DEHB olan erkek çocukta MPH tedavisi öncesi ve sonrasında kontrlateral sessiz period (CSP), servikal latans (CL), istirahat motor eşiği (RMT) ve santral motor iletim zamanı (CMCT) ölçümleri yapılmıştır.
Bulgular: MPH tedavisi CMCT'de anlamlı bir azalmaya yol açmıştır (p<.001). DEHB olan bireylerde RMT, CL ve CSP verilerinde tedavi öncesi ve sonrasında, anlamlı bir farklılık saptanmamıştır. Ayrıca yaş ve RMT değeri arasında anlamlı düzeyde negatif korelasyon gözlenmiş (Pearson correlation= -.47; p=.03), diğer TMS parametrelerinde anlamlı bir korelasyon bulunmamıştır.
Sonuç: Santral motor iletim zamanı (CMCT); eksitasyon, kortikal hücrelerin bilgi işleme ve kortikospinal traktus yolu ile aksonal iletim zamanı sürelerini içermektedir. MPH çok kısa bir süre içinde aksonal myelinleşmeyi ve CL'ı etkileyemeyeceği için CMCT'deki azalma, MPH tedavisinin kortikal hücrelerin bilgi işleme sürecinde ortaya çıkardığı değişimler ile ilişkili olabilir. Önceki çalışmalar, bilgi işleme sürecinin MPH ile artırılabileceğini belirtmekle birlikte; MPH etkisi altında CMCT ve bilgi işleme süreci arasındaki ilişkiyi inceleyen daha fazla araştırmaya gerek vardır.

Anahtar sözcükler: Transkraniyal manyetik stimulasyon (TMS), dikkat eksikliği hiperaktivite bozukluğu (ADHD), metilfenidat

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ABSTRACT:
The effects of methylphenidate on transcranial magnetic stimulation parameters in children with attention deficit hyperactivity disorder

Objective: The aim of this study was to investigate transcranial magnetic stimulation (TMS) parameters in children with attention deficit hyperactivity disorder (ADHD) before and after methylphenidate (MPH) treatment.
Methods: Contralateral silent period (CSP), cervical latency (CL), resting motor threshold (RMT), and central motor conduction time (CMCT) were measured before and after MPH medication in 24 ADHD boys, aged between 7 and 13 years.
Results: MPH treatment resulted in a significant decrease in the CMCT (p<.001). There was no significant difference in the RMT, in the CL, and in the CSP between before MPH and under MPH treatment in ADHD subjects. In addition, there was a moderate but significant negative correlation between age and the RMT (Pearson correlation= -.47; p=.03), but not with other TMS parameters (p>.05).
Conclusions: The central motor conduction time (CMCT) includes the times of excitation, information processing of cortical cells, and axonal conduction time via corticospinal tract. Since MPH can not affect the axonal myelination such a short time, and since MPH did not affect CL, we speculate that the decrease in the CMCT may be imputed to increased information processing of cortical cells following MPH administration. Although previous studies suggested that information processing may be increased by MPH, further studies are warranted investigating relationship between information processing and CMCT under the effect of MPH effect.

Key words: Transcranial magnetic stimulation (TMS), attention deficit hyperactivity disorder (ADHD), methylphenidate

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INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is a common psychiatric disorder of childhood with the core symptoms of developmentally inappropriate levels of attention, hyperactivity, and impulsivity. One of the essential theories proposes that ADHD is most often the result of dysfunction in fronto-striatal motor intentional circuits that are critical for an organism's "preparedness of acts" associated with impairments in information processing (1,2). ADHD is associated with deficits in response selection, motor response preparation, motor response inhibition, motor persistence, motor adjustment, and inhibition of prepotent responses (2-6).

Stimulants are most widely prescribed drugs in children with ADHD and highly effective in alleviating ADHD symptoms (7). Methylphenidate (MPH) is a short acting compound, with an onset of action within 30 to 60

minutes and a peek clinical effect is seen usually between 1 and 2 hours after administration, lasting 2 to 5 hours. Stimulants have been demonstrated to improve hyperactivity and cognitive function as measured by tests of vigilance, impulsivity, reaction time, short term memory, and learning verbal nonverbal material in children with ADHD (5,6).

Transcranial magnetic stimulation (TMS) may be a useful neurophysiologic tool to study cortical changes in ADHD, and is sensitive to the effects of many drugs (8,9). TMS is a brief and intense magnetic field, created by a strong electric current circulating within a coil resting on the scalp, penetrates human tissue painlessly and, if the current amplitude, duration, and direction are appropriate, induces in the brain (or in spinal roots, or in nerves) electric currents that can polarize neurons and their axons. A contraction in the contralateral corresponding muscle can be observed about 30 ms after a magnetic pulse to the motor cortex, which can be measured as motor evoked potentials (MEPs) (10,11).

Resting motor threshold (RMT) refers to the lowest TMS intensity capable of eliciting small MEPs, and is usually defined as more than 50 µV in amplitude in muscles at rest or 200 µV in active muscle in at least five out of 10 trials. (12). No significant differences in the RMT were found between ADHD and healthy subjects in previous studies (13-17). In addition, MPH treatment did not affect the RMT in ADHD patients (9,10,13,17,18,19).

In a voluntarily contracted muscle, the MEP elicited by a single suprathreshold TMS pulse is followed by a period of EMG inhibition called the contralateral silent period (CSP). No significant difference in the CSP was found between ADHD subjects and normals (13). Previous studies reported that MPH administration did not change the CSP in ADHD subjects (13,18).

Central motor conduction time (CMCT) is an estimate of the conduction time of corticospinal fibers between motor cortex and spinal (or bulbar) motor neurons. It includes the times for excitation of cortical cells, conduction via corticospinal (or corticobulbar tract) and excitation of the motor neuron sufficient to exceed its firing threshold. The estimate is made by subtracting the spinal motor neuron to muscle latency from the cortex to muscle latency (12). The CMCT in ADHD subjects was found to be increased in previous studies (20,21). However, other studies did not find differences in the CMCT between healthy children and children with ADHD (16,17,19). MPH did not alter the CMCT in ADHD children (16,19).

Until now, limited studies investigated the effects of MPH on the RMT, the CSP, and the CMCT in ADHD patients. The aim of the present study was to investigate the effects of MPH on these parameters. We hypothesized that the RMT would reflect the excitability of motor system neuronal membranes which was affected mainly by voltage gated sodium channels (8,22). Because the MPH has no an effect on voltage gated sodium channels, we hypothesized that MPH would not change the RMT in children with ADHD. It is believed that ADHD is associated with deficient inhibitory control in central nervous system (CNS) that impairs adaptive motor control (23). The CSP is suggested to be due to inhibitory mechanisms mainly at the level of the motor cortex, and may show inhibitory interneuronal control of the output of cells in the motor cortex (24,25). Since inhibitory responses were mostly induced by dopamine (26), we hypothesized that the MPH would increase the CSP in children with ADHD. Since it is believed that ADHD is associated with decreased information processing rate (27-30) and MPH may be effective on impaired information processing in ADHD (28,31,32), we also hypothesized that MPH would decrease the CMCT in children with ADHD.

MATERIAL AND METHODS

Subjects

24 drug-free right handed boys, aged 7-13 years (mean 9.6±1.7), who were admitted to Gülhane Military Medical Academy, Child and Adolescent Psychiatric Department and diagnosed as ADHD (combined type) according to the DSM-IV criteria (33) by a child and adolescent psychiatrist were included in this study. In addition, patients were assessed using parent completed the Turgay Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV)-Based Child and Adolescent Behavior Disorders Screening and Rating Scale (T-DSM-IV-S) (34). All the ADHD children were outpatients and Caucasian. Only children who had the score ≥ 19 for hyperactivity and for attention deficit on T-DSM-IV-S were included in this study, which show more

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severe ADHD symptoms. 17 patients who did not meet the criteria of the study were excluded from the study. About 66.6% of subjects had comorbid oppositional defiant disorder. All patients' parents signed a written informed consent form. Patients who have seizure disorders, mental retardation, conduct disorder, pervasive developmental disorders, severe head injury, major depression, organic brain damage, tic disorder, obsessive compulsive disorder, any other acute or chronic physical or mental illnesses, and a history of any drug use during the last month excluded from the study. Gülhane Military Medical School's Local Ethic Committee approved this study.

Following initial baseline clinical evaluation and TMS measures were made in drug free ADHD subjects, MPH medication (0.70±.20 mg/kg) was administered by their parents. TMS investigation was conducted again approximately 1.5 hour following the MPH medication in ADHD subjects.

Procedures and measures

Left motor cortex stimulation was performed over the thumb area with a focal 8-shaped coil (Dantec B55) connected to MagLite (Medtronic Dantec, Denmark). The compound muscle action potentials (CMAP) were recorded with Key point (Medtronic Dantec) from the right abductor pollicis brevis (APB) muscle using surface electrodes with a belly-tendon montage. The RMT of the relaxed rAPB muscle was defined as the lowest stimulation intensity to produce a CMAP at least 50 μV measured peak to peak at least five of ten stimuli. This intensity was defined as the motor threshold and is expressed as percent of the maximum stimulator output. From the same stimulation point, to obtain a cortical MEP response, stimulation intensity was increased to 5% steps until the CMAP amplitude was no longer increased. The latency of the cortical MEP response was measured from the TMS trigger to the first positive deflection of the CMAP and its amplitude from peak to peak. The cervical responses were obtained using the same coil and the coil was placed just 1 or 2 cm. lateral to the right side of the 7th cervical vertebra. The CMCT was calculated by subtracting the cervical latency (CL) from the cortical latency (Figure 1). The latency variability of the potentials was calculated by averaging. For the silent period

measurement, the patients were asked to maintain a maximal activation of their rAPB before and during the stimulation and to relax their hand muscles afterwards in order to prevent fatigue. The reasons for choosing maximal contraction are the difficulty to standardize the level of contraction in children and the fact that the effect of background muscle contraction on silent period is minimal (35). Left motor cortex stimulation was performed with the same stimulation output of the cortical CMAP output. At least 5 trials were performed for each patient. The silent period was calculated from the beginning of the suppression of the tonic EMG activity to the restarting of the tonic EMG activity.
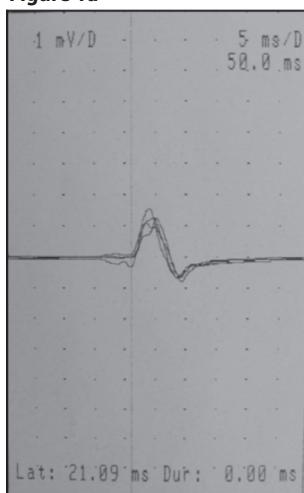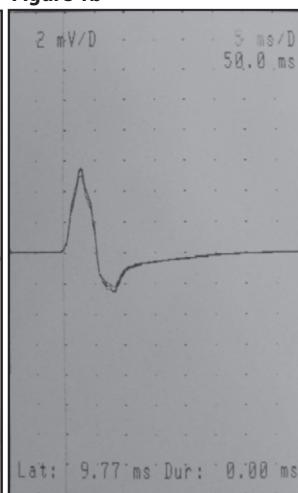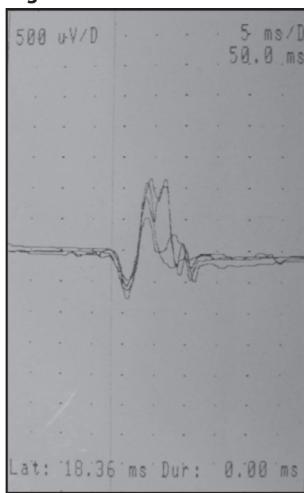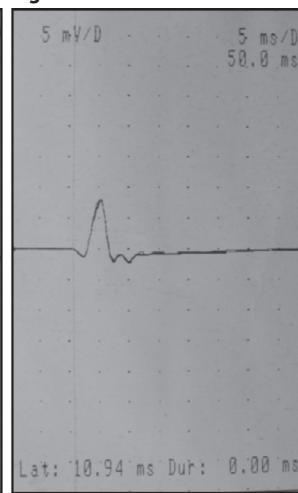

Figure 1: Cortical and cervical motor evoked potential latencies of a patient before (a and b) and after (c and d) MPH administration. The central motor conduction time (CMCT) is 11.25 msn and 7.42 msn respectively

Statistical analysis

The changes of the RMT, the CSP, and the CMCT under MPH treatment in ADHD subjects were analyzed by paired sample test. To examine the relationship between TMS indices and age, Pearson correlation test was used. All statistical tests of significance were made using two-tailed tests with P = 0.05.

RESULTS

MPH treatment resulted in a significant decrease in the CMCT (t=4.4; p<.001; Table 1). There was no significant difference in the RMT, in the CL, and in the CSP between before MPH and under MPH treatment in ADHD subjects (t=.2; t=-.2; t=.5 respectively; and all p values >.05; Table 1). No correlation was find between scores of T-DSM-IV-S and TMS indices. In addition, there was a moderate but significant negative correlation between age and the RMT (Pearson correlation= -.47; p=.03), but not other TMS parameters (p>.05).

Contrary to earlier studies; MPH treatment resulted in a significant decline in the CMCT of children with ADHD in this study. Conflicting results may be attributed to heterogeneity of the samples and the disorder. Possibly, CMCT includes the times of excitation, information processing of cortical cells, and axonal conduction time via corticospinal tract. Since MPH can not affect the axonal myelination such a short time, and since MPH did not affect CL, we speculate that the decrease in the CMCT may be imputed to increased information processing of cortical cells following MPH administration. Although previous studies suggested that information processing may be increased by MPH (28,31,32), further studies are warranted invastigating relationship between information processing and CMCT under the effect of MPH.

One of the main effects of MPH is to increase dopamine in the synaptic cleft (36). Earlier studies reported that dopamine innervations were highly concentrated in the motor, premotor, and supplementary motor areas of the cortex in humans, and in marked contrast with observations in rodents (26,37,38,39). The

Table 1: The effects of methylphenidate (MPH) on the measurements of the central motor conduction time (CMCT), the cervical latency (CL), the motor threshold (MT), and the contralateral silent period (CSP) in children with ADHD.

TMS parameters	Before MPH treatment (n=24)		Under MPH treatment (n=24)			
	Mean	SD	Mean	SD	t	p
CMCT (ms)	9.3	1.7	8.4	1.4	4.4	<.001
CL(ms)	10.7	.98	10.7	.80	-.2	.84
RMT (%)	54.5	7.5	54.3	9.5	.2	.88
CSP (ms)	154.0	58.6	150.3	53.3	.5	.65

MPH; methylphenidate; MPH, methylphenidate; TMS; Transcranial magnetic stimulation; CMCT, central motor conduction time; RMT, resting motor threshold; TMS, Transcranial magnetic stimulation; CSP, contralateral silent period

DISCUSSION

The current study examined the consequences of clinical effective doses of MPH on the CSP, the RMT, and the CMCT in children with ADHD. TMS procedure was well tolerated by all 24 children. Earlier studies have shown that ADHD subjects have longer CMCT than healthy children (20,21). Uclés et al. suggested that increased CMCT in ADHD could be related to delay in the maturation of cortico-motoneuronal system (21). However, no difference was found in the CMCT between normal and ADHD subjects in some previous studies (16,17,19). Administration of MPH did not change CMCT in children with ADHD in earlier studies (16,19).

immunoreactivity of D1a, D2, and D5 receptors was observed in the pyramidal tract neurons in the rodent motor cortex (26). Prolonged (30 s) application of dopamine inhibits spontaneous firing rates for nearly all pyramidal tract neurons in the rodent motor cortex, with significant reductions from baseline spontaneous activity (71% of baseline) (26). In addition, dopamine may modulate excitatory inputs onto cortical pyramidal neurons by both pre- and post-synaptic mechanisms (40,41). Authors in this study suggested that MPH may contribute to effective excitation and information processing by decreasing baseline spontaneous activity by dopamine in pyramidal tract neurons, which may result in the decline in the CMCT. The targets of TMS and

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dopamine may be both pyramidal neurons and inhibitory interneurons, although the main roles of these cells on the results remain unclear.

Concerning the RMT, no significant difference was found between ADHD and the healthy subjects in previous studies (13,14,16,17,42). Consistent with earlier studies (9,1013,17,18,19), no significant difference was detected in the RMT between before and after administration of MPH medication in ADHD subjects in this study. In contrast to MPH that chiefly affects dopamine and norepinephrine, drugs which block voltage gated sodium channels increase the RMT (43-46), whereas ketamine that may indirectly increase neurotransmission through the AMPA receptor decreases it (8,47). The finding of unchanged RMT in ADHD subjects following MPH medication suggested that the MPH in clinical doses have no effect on the excitability of cortical neuron membranes within the motor cortex. In agreed with other studies (42), there was a moderate but significant negative correlation between age and RMT in ADHD children in this study. Similar finding has been reported for healthy children (25). Moll et al. suggested that the higher motor threshold in younger children may indicate a hypoexcitability of motor system neuronal membranes (25).

There was no difference in the CSP between ADHD group and healthy controls in a previous study (13). It was suggested that the CSP evoked in the muscles of upper limb originates largely from activation of cortical inhibitory interneurons, although spinal mechanisms are involved in the early part (12). The CSP can be affected by physiological phenomena that change cortical excitability, such as sleep deprivation (48), hyperventilation (49), and muscle fatigue (50). Although dopaminergic drugs increase the CSP in normal adults (51), in agreed with other studies (13,18), the MPH did not change the CSP in ADHD children in our study. This finding may be attributed to possible developmental delay in children with ADHD and might suggest that the MPH in clinical doses did not affect cortical inhibitory interneurons and cortical excitability in ADHD children. Consistent with this finding, the MPH in clinical doses did not increase seizure rates in ADHD subjects with epilepsy in small trials, and did not change electroencephalography findings, although more studies are needed to achieve a definite conclusion (52).

However, results of this study should be interpreted carefully. Because the comorbid disorders were excluded only clinically, not by a structured tools, and the sample size was relatively small, and the fact of that all subjects being Caucasian boys impedes generalization of the results to all races and both sex. In addition, lack of healthy control group in this study impedes to define the MPH effects as "normalization".

This study showed that the MPH treatment resulted in a significant decrease in the CMCT, which suggested increased information processing of cortical cells following the MPH administration. Since corticostriatothalamocortical loop may be involved in ADHD pathophysiology, further TMS studies are warranted to investigate motor cortex and inhibitory mechanisms.

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