Possible Effects of Copper and Ceruloplasmin Levels on Auditory Event Potentials in Boys with Attention Deficit Hyperactivity Disorder

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ABSTRACT

Introduction: The aims of the present study were to investigate the relationship between levels of plasma copper (Cu) and ceruloplasmin (Cp) and amplitudes and latencies of P1, N2, and P3 in the parietal and frontal areas of children with attention deficit hyperactivity disorder (ADHD) as well as to compare these Cu levels and event-related potentials (ERPs) indices in controls.

Methods: Boys (n=41) with ADHD were divided into two subgroups according to a median split of plasma Cu and Cp levels, separately. ERP indices from the parietal and frontal regions were recorded in children with ADHD and 24 normal boys (control group) using an auditory oddball paradigm.

Results: Parietal P3 latency was significantly longer, and parietal P3 amplitude, frontal P3 amplitude, and frontal N2 amplitudes were smaller in children with ADHD than in controls (all p values <0.017). Parietal P1 and frontal P1 latencies were significantly shorter in the higher Cu

group than in the lower Cu group (both p values <0.017). Decreased latency of parietal P1 was dependent on plasma levels of Cu (p<0.05). Frontal N2 and parietal N2 amplitudes were significantly lower in the ADHD group with lower Cp levels than in the ADHD group with higher Cp levels (both p values <0.017). Decreased frontal N2 and parietal N2 amplitudes were dependent on plasma levels of Cp (both p values <0.05).

Conclusion: Plasma Cu and Cp levels may have an effect on ERPs in ADHD, thus indicating the existence of effects on information processing. Cu levels may have a negative effect on the neuronal encoding of sound, whereas Cp levels may have a positive effect on the processes of cognitive control, conflict monitoring, and stimulus discrimination in children with ADHD.

Keywords: Attention deficit hyperactivity disorder; N2, P1, P3, Copper

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is a common childhood psychiatric disorder with the core symptoms of developmentally inappropriate levels of attention, hyperactivity, and impulsivity. Having high temporal sensitivity and correlations with underlying sensory and cognitive processes, event-related potentials (ERPs) could be a useful tool in exploring different processing states in ADHD. Previous studies have reported altered latency and amplitude of various ERP indices, including N1, N2, P1, P2, and P3, in ADHD (1,2,3), which suggested altered information processing in ADHD. A complex range of ERP deficits in preparatory processes, auditory and visual attention systems, and frontal inhibition system was reviewed by Barry et al. (4). Additionally, in a review study, Johnstone et al. (3) reported that there are strong differences between children with ADHD and healthy children for a significant number of ERP correlates shown in early orienting, inhibitory control, and error-processing components.

Copper (Cu) is an essential trace element in human physiology. Many enzymes (i.e. ferroxidases, lysyl oxidase, dopamine β -hydroxylase, monoamine oxidase, tyrosinase, and Cu/zinc superoxide dismutase) include Cu as an essential constituent for their functions. In addition to a functional component of cuproenzymes, Cu may have an important role on non-enzymatic functions in processes, such as angiogenesis, nerve myelination, and endorphin action (5,6). Previous studies showed the existence of an inverse relationship between Cu and cognitive functions in normal individuals (7,8,9) and various neuropathologies, such as Wilson disease (10) and Alzheimer disease (11). Ceruloplasmin (Cp) is major Cu-carrying protein in plasma (12), and it is considered as an acute phase protein (5). In addition to Cu metabolism, Cp has physiological functions including the oxidation of organic amines, regulation of cellular iron lev-

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els, ferroxidase activity, antioxidant activity, glutathione peroxidase activity, and ascorbate oxidase activity (13). Previous studies reported lower (14,15,16) and similar (17,18) levels of Cu, and similar levels of Cp (18,19) in subjects with ADHD compared with healthy groups. However, Kul et al. (18) showed no correlation between either serum Cu or Cp level with scores of ADHD symptoms on rating scales.

It was reported that trace elements, including lead, iron, and zinc, may have an effect on ERPs in ADHD (2,20,21,22,23,24). Although Cu and Cp may have an effect on cognitive functions including attention, to the best of our knowledge, there has been no study investigating the relationship between ERPs and Cu and Cp levels in children with ADHD. The aims of the present study were to investigate the relationship between levels of plasma Cu and Cp and amplitudes and latencies of P1, N2, and P3 in the parietal and frontal areas of children with ADHD. In addition, we also aimed to compare these Cu levels and ERP indices in controls.

METHODS

Subjects

Forty-one drug-free boys, aged 7–12, who were admitted to the Gulhane Military Medical Academy Child and Adolescent Psychiatric Department and diagnosed as mixed-type ADHD according to the DSM-IV criteria (25), were included in this study. In addition, patients were assessed using parent-completed 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) (26). No patient had a comorbid disorder (clinically excluded) and previous medical treatments for ADHD. All of the ADHD children were outpatients and were not prescribed medication within the study period. The ADHD group was divided into two subgroups according to a median split of plasma Cu levels: the ADHD group with lower Cu levels ($n=21$, Cu level ≤ 120 $\mu\text{g/dL}$; mean $=96.2 \pm 14.6$ $\mu\text{g/dL}$) and the ADHD group with higher Cu levels ($n=20$, Cu level > 120 $\mu\text{g/dL}$; mean $=150.0 \pm 28.2$ $\mu\text{g/dL}$). Similarly, according to a median split of plasma Cp levels, the ADHD group was separated into two subgroups as the ADHD group with lower Cp levels ($n=22$, Cp level ≤ 49 mg/dL ; mean $=40.7 \pm 9.8$ mg/dL) and the ADHD group with higher Cp levels ($n=19$, Cp level > 49 mg/dL ; mean $=57.6 \pm 7.6$ mg/dL). Twenty-four mentally and physically healthy boys, clinically assessed, were included in the study as normal control group. The control group was also divided into two subgroups according to a median split of plasma Cu levels: the control group with lower Cu levels ($n=12$, Cu level ≤ 106 $\mu\text{g/dL}$; mean $=95.3 \pm 5.5$ $\mu\text{g/dL}$) and the control group with higher Cu levels ($n=12$, Cu level > 106 $\mu\text{g/dL}$; mean $=117.8 \pm 6.8$ $\mu\text{g/dL}$). All subjects in the study were Caucasians. Subjects who had seizure disorders, mental retardation, autistic disorders, organic brain damage, psychotic disorders, conduct disorders, and any other acute or chronic physical illnesses were excluded from the study. Subjects with a history of any drug use during the previous month, based on the parent and self-report, were excluded from the study. All procedures were conducted with adequate understanding from the participants and their parents. Parents and legal guardians of the subjects were asked to provide a written informed consent. The study was conducted in accordance with the tenets of the Declaration of Helsinki, with the approval of the local ethics committee.

Procedures and Measurements

Measurement of ERPs

Subjects were tested in a sitting position with eyes closed in a silent room. An ESAOTE BIOMEDICA 4-Channel (Italy) EMG-EP device was used for all tests. The skin of the scalp was cleaned. Bioelectrical signals were re-

corded using surface electrodes (plate shaped electrode, 11 mm diameter; DANTEC Electronic A/S, Denmark) placed along the midline (Pz and Fz) according to the 10-20 International System of EEG electrode placements. To evaluate the frontal lobe functions in detail, we used an extra electrode for recording at Fpz instead of Cz. Subjects were grounded using a surface ground electrode located midway between Fpz and Fz. The reference electrode was placed on the mastoids and an electrode was placed infraorbitally on the right side to monitor eye movements. Impedance was <5 KW and the filter band pass was 0.5–50 Hz. All the potentials were analyzed in a 1000-ms width window and the delay time was 200 ms. To detect the existence of a hearing problem, all subjects' hearing thresholds were determined by manually increasing the tone intensity. The hearing threshold was approximately 60 dB HL (range, 55–65 dB for both 2000 and 3000 Hz at a rate of 0.7 ms) and a further 30 dB was added for each subject. The test was performed at 90 dB. A further minute of counting aloud served as a practice and ensured that the task was understood.

Auditory ERPs were elicited with an auditory discrimination task paradigm. Non-target (frequent 3000 Hz) and target (rare 2000 Hz) stimuli were binaurally presented over headphones with 5.3 ms rise/fall times and 0.3 ms durations. The tones were presented at a rate of 0.7 Hz. Subjects were asked to randomly count the target tones (2000 Hz) that occurred among non-target tones (3000 Hz). The frequency of target tones was 20% and 80% for non-target tones. A total of 40 target stimuli artifact-free trials were acquired and the test was repeated twice. If the second trial potentials were not well-matched from the first trial potentials, or if there were movement artifacts, the trials were excluded from the study. If the counting performance of a subject was more or less than 10% of 40 target tones (36-44), this subject was also excluded from the study. Data of P1, N2, and P3 from Pz and Fpz obtained from the target stimuli are presented in this article. In the analysis of potentials, the amplitudes were measured for P3 from the midline of the N2 peak to the midline of the P3 peak; for N2, the amplitudes were measured from the midline of the P1 peak to the midline of the N2 peak; and for P1, the amplitudes were measured from the first positive deflection of the isoelectric line to the P1 peak recorded at Pz and Fpz. We measured the latencies of the potentials from the midline of the peaks. The testing procedure was performed in the afternoon for all subjects.

Blood Analysis

Blood was withdrawn into EDTA-containing (for plasma) and non-anti-coagulant-containing (for serum) evacuated blood collection tubes in the morning (between 9 and 10 a.m.) from patients who had undergone overnight fasting. Within 3 h, the blood samples were centrifuged at 4000 rpm for 15 min at 4°C and the plasma and serum were separated and stored at -70°C until the day of analysis. Plasma Cu levels were measured using an atomic absorption spectrophotometer (Varian, 30/40, Australia). Cp levels were measured with nephelometry (Beckman-Array 360 Nephelometry) using commercial reagents. Cp levels of the control group were not determined.

Statistical Analysis

Kolmogorov-Smirnov Test was used to assess homogeneity of distributions. Non-normally distributed variables including measures of ERP indices (amplitudes and latencies) and plasma Cu and Cp levels in children with ADHD and control subjects were compared using Kruskal-Wallis test. The level of significance for evaluating Kruskal-Wallis test results was set at 0.05. For post hoc group comparisons, statistically significant results were analyzed again using Mann-Whitney U test. Z values, including corrections for ties, in the data analyzed using Mann-Whitney U test were recorded. Bonferroni correction for multiple comparisons was used to re-

duce Type I error. Because there were three groups, the *p* value (0.05) divided by 3 was 0.017. After Bonferroni correction, the level of significance was 0.017. Because of a significant difference in age between the lower Cu and higher Cu subgroups of the ADHD group, linear regression analysis was performed. The dependent variable was any ERP indices, and the independent variables were plasma Cu levels and subjects' ages. Using the same model, we also analyzed the lower and higher Cp level subgroups of the ADHD group. In addition, Pearson correlation test was used to determine the association between ERP indices and levels of plasma Cu and Cp.

RESULTS

Comparison of Demographic and Clinical Characteristics Among Groups

The age range of the ADHD group was 7–13 years (9.3 ± 1.2 years) and that of the normal control group was 7–13 years (10.3 ± 1.7 years). There was no significant difference for the ages of the children between the two groups ($Z = -1.871$; $p > 0.05$). The mean age of the higher Cu subgroup of the ADHD group (mean = 10.3 ± 2.0 years) was higher than that of the lower Cu subgroup (mean = 8.3 ± 1.3 years; $Z = -3.76$; $p < 0.05$). Similarly, the higher Cp subgroup of the ADHD group were older (mean = 10.1 ± 1.9 years) than the lower Cp subgroup (mean = 8.4 ± 1.5 years; $Z = -2.590$; $p < 0.05$). There was no significant difference in age between the lower and higher Cu subgroups of the control group (9.27 ± 1.79 vs. 9.18 ± 1.78 , respectively, $Z = -0.134$, $p = 0.894$). There was no significant difference in the levels of plasma Cu between the children with ADHD and controls (122.9 ± 35.3 $\mu\text{g/dL}$ vs. 106.6 ± 13.0 $\mu\text{g/dL}$ respectively; $Z = -1.936$; $p = 0.053$). Between higher and lower Cu level subgroups of the ADHD group, there was no significant difference in attention deficit and hyperactivity scores (16.79 ± 4.39 vs. 19.16 ± 4.15 , respectively, $Z = -1.713$, $p = 0.087$ for attention deficit; 16.89 ± 5.58 vs. 16.58 ± 6.48 , respectively, $Z = -0.190$, $p = 0.849$ for hyperactivity). Between higher and lower Cp level subgroups of the ADHD group, there was no significant difference in attention deficit and hyperactivity scores (17.40 ± 4.90 vs. 18.05 ± 4.11 , respectively, $Z = -1.385$, $p = 0.700$ for attention deficit; 18.20 ± 5.21 vs. 16.75 ± 5.95 respectively, $Z = -0.718$, $p = 0.473$ for hyperactivity).

Comparison of Indices between ADHD Group and Controls

Neither amplitudes nor latencies of potentials showed statistical significances between Fpz and Fz ($p > 0.05$). Therefore, we only considered the potentials obtained from Fpz. Parietal P3 latency was significantly longer, and parietal P3 amplitude, frontal P3 amplitude, and frontal N2 amplitudes were smaller in children with ADHD than in controls ($Z = -2.449$, $Z = -3.043$, $Z = -2.917$, $Z = -2.962$, $Z = -2.542$, respectively; all *p* values < 0.017 ; Table 1). No significant difference was found in other ERP parameters between the two groups (all *p* values > 0.017 ; Table 1).

Comparison of Indices between Lower Cu and Higher Cu Level Subgroups

The only difference between the lower Cu and higher Cu level subgroups of the ADHD group was that parietal P1 and frontal P1 latencies were significantly shorter in the higher Cu level group than in the lower Cu level group ($Z = -2.388$, $Z = -2.795$, respectively; both *p* values < 0.017 ; Table 1). Linear regression analysis showed that decreased parietal P1 latency was dependent on plasma levels of Cu (Beta = -0.354 , 95% confidence interval [CI] = -0.622 to -0.026 , $p = 0.034$), but not on the ages of the children with ADHD (Beta = 0.098 , 95% CI = -3.833 – 7.159 , $p = 0.544$). No other indices were found to be dependent on plasma Cu levels of the subjects ($p > 0.05$). Also, among all indices, only parietal P1 latency was significantly correlated with plasma Cu levels ($r = -0.387$, $p = 0.01$). In the control group, there was no significant difference for all indices between the higher and

lower Cu level groups (all *p* values > 0.05). Also, no indices were significantly correlated with plasma Cu levels of the controls (all *p* values > 0.05).

Comparison of Indices between Lower Cp and Higher Cp Level Subgroups

The amplitudes of N2 in frontal and parietal regions were significantly lower in the ADHD subgroup with lower Cp levels (≤ 49 mg/dL) than in the higher Cp level (> 49 mg/dL) subgroup ($Z = -2.770$, $Z = -3.690$, respectively; both *p* values < 0.017 ; Table 1). Decreased frontal N2 and parietal N2 amplitudes were dependent on plasma levels of Cp (Beta = -0.414 , 95% CI = 0.037 – 0.281 , $p = 0.012$, and Beta = 0.394 , 95% CI = 0.044 – 0.367 , $p = 0.014$, respectively), but not the ages of the children with ADHD (Beta = -0.204 , 95% CI = -1.274 – 0.277 , $p = 0.200$, and Beta = -0.288 , 95% CI = -0.984 – 0.070 , $p = 0.067$, respectively). No other indices were found to be dependent on plasma Cp levels of the subjects ($p > 0.05$). Also, among all indices, frontal N2 and parietal N2 amplitudes were significantly correlated with plasma Cp levels ($r = 0.473$, $p = 0.004$, and $r = 0.476$, $p = 0.003$, respectively). Scatter plots for the Cu-P1 latency and Cp-N2 amplitude relationships are shown in Figures 1 and 2.

DISCUSSION

The present study found that parietal P3 latency was longer, and frontal and parietal P3 and frontal N2 amplitudes were smaller in children with ADHD than in controls. Furthermore, in comparisons of both ADHD subgroups, frontal and parietal P1 latencies were shorter in the higher Cu level group with a dependence on plasma levels of Cu. Frontal and parietal N2 amplitudes were lower in the lower Cp level group with a dependence on plasma levels of Cp. These results suggested that plasma Cu and Cp levels may have an effect on ERP indices in children with ADHD. Picton (27) suggested that P3 reflects working memory updating and post decisional processes. In line with other studies (1,2,28,29,30,31), smaller P3 amplitudes in the frontal and parietal regions were found in children with ADHD than in controls in this study. Smaller P3 amplitudes in children with ADHD suggested that ADHD was associated with ineffective working memory updating and a problem with post decisional processes. Nevertheless, other studies did not find differences in P3 amplitude between control and ADHD subjects (32,33,34,35). The latency of the P3 component may reflect the timing of stimulus evaluation processes or the speed of information processing (36). The longer latency of P3 in children with ADHD than in controls in the present study was consistent with previous findings (1,2,29,31), but not others (28,32,33,35,37). These differences among studies may be attributed to methodological differences, heterogeneity of samples, and causes other than Cu or Cp levels. Longer P3 latencies in children with ADHD suggested that ADHD may be associated with longer stimulus evaluation process and preparation for the next stimulus (38). Moreover, no difference for P3 between ADHD subgroups suggested the possibly that elements such as Cu and Cp have no effect on working memory updating, post decisional processes, and timing of stimulus evaluation process in children with ADHD.

It has been suggested that the N2 amplitude may reflect cognitive control, conflict monitoring, and stimulus discrimination (39). Ponton et al. (40) reported that N2 amplitude increased from age 4 to 10, and thereafter decreased to reach adult values by age 17. The amplitude of N2 in the frontal region was found to be significantly smaller in children with ADHD than in controls in the present study. In agreement with these results, previous studies reported smaller N2 waves in ADHD children (32,37,41,42). It was reported that N2 was smaller in younger patients, but larger than controls in older ones (43,44). The amplitudes of N2 in the frontal and parietal regions were significantly lower in the ADHD subgroup with lower Cp levels than in the higher Cp level subgroup. Interestingly, decreased frontal N2 amplitude and parietal N2 amplitude were

Table 1. Event-related potential indices in the ADHD group, control group, ADHD group with lower copper (Cu) level, ADHD group with higher Cu level, ADHD group with lower ceruloplasmin (Cp) level, and ADHD group with higher Cp level

	ADHD group		Control group				ADHD group with lower Cu		ADHD group with higher Cu				ADHD group with lower Cp		ADHD group with higher Cp			
	Mean	SD	Mean	SD	d	p	Mean	SD	Mean	SD	d	p	Mean	SD	Mean	SD	d	p
PP3L (ms)	360.4	55.0	324.7	32.6	0.8	0.014	365.6	57.1	354.4	51.9	0.2	0.473	349.5	51.8	368.5	58.4	-0.3	0.261
PP3A (μ V)	9.5	6.7	14.2	6.2	-0.7	0.004	9.4	6.5	9.7	7.0	0.04	0.903	9.5	4.7	9.5	7.7	0	0.368
PP1L (ms)	145.1	32.3	169.1	39.6	-0.7	0.058	158.7	26.3	132.2	32.8	0.9	0.017	149.5	26.2	128.8	32.9	0.7	0.102
PP1A (μ V)	4.7	4.3	5.2	4.5	-0.1	0.823	6.1	5.8	3.3	2.2	0.8	0.025	5.0	5.4	4.5	2.5	0.1	0.338
PN2L (ms)	225.4	35.5	236.5	30.1	-0.3	0.387	227.2	27.8	223.4	42.0	0.1	0.381	225.1	27.9	225.2	47.3	0	0.797
PN2A (μ V)	9.0	6.4	10.2	5.0	-0.2	0.154	8.6	6.6	9.7	6.3	-0.2	0.360	5.8	2.7	13.8	7.2	-1.5	<0.001
FP1L (ms)	149.1	28.4	161.0	42.0	-0.3	0.388	160.7	26.8	137.1	24.4	0.9	0.005	153.8	26.5	134.7	23.4	0.8	0.027
FP1A (μ V)	4.9	3.1	6.4	5.8	-0.3	0.807	5.8	3.4	4.5	3.5	0.4	0.141	4.7	2.9	5.3	3.5	-0.2	0.570
FN2L (ms)	221.5	30.6	226.5	38.7	-0.2	0.932	225.2	25.5	217.0	35.5	0.3	0.639	223.3	20.6	218.3	40.7	0.2	0.987
FN2A (μ V)	7.0	4.8	10.9	6.6	-0.7	0.011	6.4	4.0	7.7	5.4	-0.3	0.530	4.6	1.8	9.7	5.9	-1.2	0.006
FP3L (ms)	354.8	56.4	322.6	31.3	0.7	0.036	357.4	57.7	351.3	54.8	0.1	0.694	344.4	53.9	359.7	60.8	-0.3	0.451
FP3A (μ V)	8.7	5.6	14.0	7.5	-0.8	0.003	8.4	5.1	8.9	6.3	0.01	0.765	9.0	5.2	8.2	6.2	0.2	0.385

d: Cohen's d; PP3L: parietal P3 latency; PP3A: parietal P3 amplitude; PP1L: parietal P1 latency; PP1A: parietal P1 amplitude; PN2L: parietal N2 latency; PN2A: parietal N2 amplitude; FP1L: frontal P1 latency; FP1A: frontal P1 amplitude; FN2L: frontal N2 latency; FN2A: frontal N2 amplitude; FP3L: frontal P3 latency; FP3A: frontal P3 amplitude; Cu: copper; Cp: ceruloplasmin

Figure 1. Scatter plots for the plasma copper (Cu) level and P1 latency relationship. Frontal (left) and parietal (right) P1 latencies (P1L) were significantly shorter in the higher Cu level group (both p values <0.017). Decreased latency of parietal P1L was dependent on plasma levels of Cu (p<0.05). The line indicates the regression line

dependent on plasma levels of Cp, but not on the ages of the children with ADHD. Cp shows catechol oxidase activity towards catechol itself, such as dopamine and noradrenaline (45), which may have a role in the pathophysiology of ADHD, and a variety of substituted catechols including DOPA and 6-hydroxydopamine (13,46,47), although the physiological importance of catechol oxidase activity and its effects on ERPs remains unclear in ADHD cases. The lower amplitude of N2 in the ADHD group and subgroup with lower Cp levels and the dependence of that on the plasma levels of Cp pointed to the possibility of a positive effect for Cp level on the processes of cognitive control, conflict monitoring, and stimulus discrimination.

ADHD subjects with higher plasma Cu levels have significantly shorter parietal and frontal P1 latencies compared to the lower Cu level group in the present study. In addition, linear regression analysis showed that the decreased latency of parietal P1 was dependent on plasma levels of Cu, but not the ages of the children with ADHD. Shorter parietal P1 latency in ADHD children in the present study is in accordance with the study of Oades et al. (48), but not others (1,2,31). Neuronal generators of P1 include primary auditory cortex (Heschl's gyrus), lateral temporal regions, hippocampus, planum temporale, and likely subcortical regions (49). The P1-N1-P2 complex may reflect the neuronal encoding of sound at the auditory cortex level (49). The results of this study suggested that a shorter

Figure 2. Scatter plots for plasma ceruloplasmin (Cp) level and N2 amplitude relationship. Frontal (left) and parietal (right) N2 amplitudes (N2As) were significantly lower in the lower Cp level group (both p values <0.017). Decreased N2As were dependent on plasma levels of Cp (both p values <0.05). The line indicates the regression line

PI level in ADHD might show dysfunctional encoding in ADHD, and Cu levels may have an effect on the neuronal encoding of sound.

It is known that Cu is an essential element, but toxic in excess. Major sites of Cu accumulation are known to be the globus pallidus, putamen, claustrum, pons, vermis, dentate nucleus, thalamus, mesencephalon, and especially the locus coeruleus (50,51,52). These sites are also implicated in the attention function of the brain (53,54,55,56,57,58). Attention deficit may be the one of the first symptoms of the mild toxicity of these regions. It is plausible to hypothesize that a mild accumulation of Cu (or other toxic elements) may occur in the regions related to attention in a subgroup of ADHD children. This hypothesis has been supported with the inverse relationship between Cu levels and cognitive functions found in recent studies (7,8,9,10,11). The present study suggests that a subgroup of children with ADHD may be vulnerable to Cu and Cp.

Results of the present study suggest that Cu and Cp might affect information processing in ADHD, although the mechanisms of the effects remain unclear. However, results of the present study should be interpreted carefully. The sample size was small and all subjects were Caucasian, impeding generalization of the results to all races. Comorbid disorders were excluded only clinically, not by structured tools. Also, plasma Cu and Cp levels and ERP indices were analyzed at once. ERP indices of standard (non-target) stimuli were not analyzed. Moreover, whether intensities between ADHD and control groups were different was not analyzed. In addition, the regression between Cu, Cp, and ERP indices was medium. Therefore, the differences in ERP parameters measured might be ascribed to other causes that are not necessarily linked to blood Cu or Cp levels. Besides, plasma Cp levels in the controls were not determined. The contradictory results of published studies investigating ERP indices in ADHD may be attributed to methodological differences and heterogeneity of the samples. It is also probable to suggest that diverse subgroups of ADHD (i.e., according to different plasma levels of trace elements) with a problem in different processing stages may have similar symptom profiles in the clinical presentation.

In conclusion, the results suggest that plasma Cu and Cp levels may have an effect on ERPs in ADHD, pointing to the effects on information pro-

cessing. It is also suggested that Cu levels may have a negative effect on the neuronal encoding of sound, and Cp levels may have a positive effect on the processes of cognitive control, conflict monitoring, and stimulus discrimination in children with ADHD. However, it seems that Cu and Cp may not affect working memory updating, post decisional processes, and timing of stimulus evaluation processes found problematic in children with ADHD. Further studies are warranted for investigation of the effects of Cu and Cp on ERP indices, and thus, on information processing in children with ADHD.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Gülhane Military Medical Academy (1491-230-07).

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