Sibel Kocaaslan Atli*, Nihal Olgaç Dündar, Onur Bayazit, Nur Evirgen Esin, Uğraş Erdoğan, Gönül Çatli, Mehmet Cemal Kahya and Bumin Nuri Dündar

Auditory event-related potentials demonstrate early cognitive impairment in children with subclinical hypothyroidism

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Abstract

Background: The aim of this study was to examine the cognitive functions of children with subclinical hypothyroidism (SH) and healthy children with the use of auditory event-related potentials (AERPs) and neuropsychological tests.
Methods: Twenty children aged between 8 and 17 years, diagnosed with SH, and 20 age-matched healthy controls were included in this study. A classical auditory oddball paradigm was applied during the electroencephalography (EEG) recordings, and event-related potentials (ERPs) were evaluated between the 0.5- and 20-Hz frequency intervals. P1, N1, P2, N2 and P3 amplitudes and latencies were measured in Fz, FCz, Cz, CPz, Pz and Oz electrodes. Additionally, a number of neuropsychological tests evaluating the reaction time and various cognitive functions were carried out.
Results: In children with SH, P3 amplitudes in FCz, Cz and CPz electrodes were significantly lower than those in controls ($p < 0.05$). In addition to this, the P1N1 and N1P2 peak-to-peak amplitude values were also found to be smaller for children with SH than controls ($p < 0.05$). With regard to the neuropsychological tests, no significant difference was observed between the SH and control groups on any of the cognitive test parameters, reaction time or correct response rates.
Conclusions: In the present study, while children with SH did not differ from controls with respect to their cognitive functions evaluated via neuropsychological tests, cognitive differences were detected via electrophysiological investigations. This result implies that implicit changes in cognition which are not yet overtly reflected on neuropsychological tests may be detected at an early stage in children with SH.

Keywords: auditory event-related potentials; children; cognitive functions; subclinical hypothyroidism.

Introduction

Thyroid hormones are known to have effects on the functions of the central nervous system such as intelligence, emotional state, behavior and cognitive functions [1, 2]. Many studies have pointed out that hypothyroidism leads to cognitive impairments and emotional-state changes [3–5]. Among the most common cognitive disorders in hypothyroidism are forgetfulness, lack of attention, slow information processing and depression [3, 6].

However, findings related to neurocognitive impairments in subclinical hypothyroidism (SH) are still contradictory. Studies on adult subjects have reported that working memory in SH patients is impaired, and their frontal regions and therefore executive functions are affected [7]. On the other hand, cross-sectional or longitudinal neuropsychological tests have shown that SH has no significant cognitive effects [8–10].

There are only few studies investigating cognitive functions in children and adolescents with SH [4, 11–13]. SH in childhood is of specific importance because of the consequences it may have on the central nervous system. Neurocognitive function tests have shown that children with SH have attention problems [4, 11, 12]. Aijaz et al. [4] reported that SH children had attention problems when compared to normal children, but they did not differ in

***Corresponding author: Asst. Prof. Dr. Sibel Kocaaslan Atli,** PhD, İzmir Katip Çelebi University, Faculty of Medicine, Department of Biophysics, İzmir, Turkey, Phone: (+90) 530 500 5832, E-mail: sibel.kocaaslan@gmail.com
Nihal Olgaç Dündar: İzmir Katip Çelebi University, Faculty of Medicine, Department of Pediatric Neurology, Izmir, Turkey
Onur Bayazit: Aydın University, Faculty of Medicine, Biophysics Department, Istanbul, Turkey
Nur Evirgen Esin: Turkish Psychological Association, Izmir, Turkey
Uğraş Erdoğan: Izmir Institute of Technology, Faculty of Engineering, Department of Electrical – Electronics, Izmir, Turkey
Gönül Çatli and Bumin Nuri Dündar: Izmir Katip Celebi University, Faculty of Medicine, Department of Pediatric Endocrinology, Izmir, Turkey
Mehmet Cemal Kahya: İzmir Katip Çelebi University, Faculty of Medicine, Department of Biophysics, İzmir, Turkey

terms of verbal and visual processing, motor speed, coordination and success. Ergür et al. [11] reported that SH subjects had poor performance in attention tests compared to the control group.

In most of the studies investigating the effects of SH on cognitive functions, the neuropsychological and behavioral characteristics of patients are evaluated with the aid of cognitive batteries. These tests are often designed to expose major impairments in the cognitive processes. Accordingly, they may not be able to display the fine defects due to mild thyroid disease. Thus, susceptible methods providing more objective evidences are required. In this respect, event-related potentials (ERPs) stand out as a good candidate.

ERPs have been shown to be a reliable, reproducible and sensitive method for assessing cognitive abilities [14, 15]. Spontaneous electrical activity of the brain can be monitored by electroencephalography (EEG). The EEG activity in response to repetitive stimuli (sound, light, etc.) is called ERP [16, 17]. The phasic neural activity obtained for auditory stimuli form auditory event-related potential (AERP) responses. Those responses that occur after 200 ms reflect the cognitive functions of the brain, while those that occur before them reflect the sensory processes. Particularly when a participant is given the task of attending to a target (T) stimulus within a stimulus sequence, the P300 response is recorded as a positive deflection in voltage at a latency of roughly 300 ms. P300 (P3) is the response most associated with cognition in psychophysiological surveys [18, 19]. It is considered to be related to the recognition of stimulus, focused attention and short-term memory [14, 15].

The aim of the present study was to evaluate the effect of SH on AERPs and the neuropsychological test scores in children. We hypothesized that there would be differences in the AERP responses and neuropsychological test scores of children with SH compared to controls and that these differences would reflect cognitive alterations.

Materials and methods

Twenty children who were admitted to our Pediatric Endocrinology Clinic and diagnosed with SH were included in this study. The control group also consisted of 20 healthy children. SH was defined on the basis of elevated serum thyroid-stimulating hormone (TSH) levels (TSH, 4.94–20 μIU/L) and serum free thyroxine (fT4) levels within the normal range [20]. Children with any systemic disease, neurological, psychiatric disorder or hearing impairment, or those taking medications/iodine-containing drugs and medication that affects the cognitive processes were excluded in both the SH and the control groups. The research was conducted with the permission of the Izmir Katip Celebi University Clinical Research Ethics Committee (approval number: 173). Parents of the children signed the written informed consent and received a copy of it.

Auditory stimuli

The participants were presented with auditory stimuli consisting of 1500 Hz and 2000 Hz frequency pure sound tones of 500 ms duration and 80 dB. The stimuli were applied by means of an earphone (Koss Ruk30, Milwaukee, WI, USA). The 1500 Hz and 2000 Hz stimuli were defined as nontarget (NT) and T, respectively. A total of 120 auditory stimuli were applied, 32 of which were T and 88 were NT. The T stimuli were pseudo-randomly distributed within the series of stimuli. In order to ensure focused attention and working memory, each subject was asked to mentally count the T stimuli during the test and report the number at the end of the session.

Electrophysiological recordings

All electrophysiological recordings were conducted by means of a BrainAmp 32-channel system (Brain Products GmbH, Gilching, Germany). The participant's electrical brain activity was recorded using 30 Ag/AgCl electrodes mounted in an elastic cap according to the International 10–20 electrode placement system. The EEG channels were referenced by two electrodes attached to the earlobe (A1 + A2). The ground electrode was designated as FCz. Electrode impedances were less than 5 kΩ. EEG was digitized at a sampling rate of 1000 Hz/sec with a 0.1–70 Hz band pass filter. A 50-Hz notch filter was also applied.

Data analysis

EEG data were segmented from 500 ms before to 1000 ms after stimulus onset of Ts and NTs, and filtered at 0.5–20 Hz. Epochs contaminated by artifacts were rejected. The corresponding AERP component measurement was made from the most prominent positive and negative peaks consecutively.

Neuropsychological assessment tools

In this study, tests adapted from the Psychology Experiment Building Language (PEBL) battery [21] which evaluates the response time and various cognitive functions were applied on a computer. In addition, forward and backward digit span (DS) tests were used to evaluate attention and auditory short-term memory functions.

Simple reaction time test: The participants were required to press the key as soon as they saw the visual stimulus (an orange circle with a diameter of 2 cm) appearing on the screen with intervals ranging from 2 to 12 s. The test adapted for our study, from the Wilkinson and Houghton Psychomotor Vigilance test, measures psychomotor vigilance, alertness, sustained attention and simple response time [22].

Go-no-go test: Participants were required to press the key as soon as they saw the T letters (1.5 × 2.0 cm in size) in the center of the screen, but when they saw the NT stimulus X, they had to inhibit the key press

action. In our research, this test adapted from Conners' Continuous Performance test assessed alertness, sustained attention, selective attention, inhibition ability and recognition reaction time [23].

Simon test: Participants were required to press the left button on the keyboard when they saw the red circle, and the right button when the blue circle appeared on the screen regardless of the position of the stimulus of 4.5 cm diameter. The test measures response time, selective attention, inhibition and resistance to interference ability, and choice reaction time [24].

Digit span test: In this test, which is one of the verbal subtests of the Wechsler Intelligence Scale for Children, perception and recall of verbal auditory stimuli, attention, short-term memory and working memory functions were evaluated. The participant was asked to recall the numbers in the correct order of the number sequences read to them according to manual directions [25].

Statistics

SPSS 15.00 (Leadtools, Charlotte, NC, USA) program was used for statistical analysis of data. The normality of data distribution was tested using the Kolmogorov-Smirnov test. Paired and independent sample t-tests were applied to data with normal distribution. Findings with a p value less than 0.05 were accepted to be statistically significant.

Results

The age of the subjects was comparable among the SH (12.8 ± 3.5; 11 females) and control groups (13.6 ± 2.7; 14 females). TSH was significantly higher in SH children (7.21 ± 2.7) compared to controls (1.83 ± 0.48) ($t[32] = -7.606$, $p < 0.001$). Although within normal ranges in both groups, fT4 of the SH group (1.28 ± 0.14) was lower than that of the control group (1.13 ± 0.21) ($t[32] = -2.547$, $p < 0.05$).

AERP components

The amplitude (μV) and latency (ms) values of P1, N1, P2, N2 and P3 wave components of distinct AERP responses obtained from the SH and control group children were measured. These wave components occurred for both T and NT stimuli.

Comparison of NT and T AERP components in children with SH

Latency and amplitude values of AERP responses obtained for NT and T stimuli were examined and compared. No significant difference was found in the latency values.

In the Fz electrode, the NT P1 amplitude value (1.46 ± 1.46) was weakened in comparison to the T P1 amplitude value (3.33 ± 1.24) ($t[15] = -2.522$, $p < 0.05$) (Figure 1A).

In the CPz electrode, a significant increase was found in the T P3 amplitude (4.10 ± 2.20) when compared to the NT P3 amplitude (2.13 ± 2.26) ($t[11] = 2.654$, $p = 0.05$) (Figure 1A).

There was no significant difference in T and NT AERP response amplitudes in any of the other EEG channels.

Comparison of NT and T AERP components in the control group

No significant difference was found in the latency values of AERP responses obtained for NT and T.

The amplitudes of P3 responses obtained for T stimuli were significantly increased in all channels (Figure 1B). In the FCz electrode, the T P3 amplitude (4.23 ± 2.56) was increased in comparison to the NT P3 amplitude (-1.18 ± 1.44) ($t[6] = 3.363$, $p < 0.005$). In the Cz electrode, the T P3 amplitude (6.39 ± 2.78) was increased in comparison to the NT P3 amplitude (-0.66 ± 1.50) ($t[17] = 4.172$, $p < 0.001$). In the CPz electrode, the T P3 amplitude (7.38 ± 2.48) presented a significant increase compared to the NT P3 amplitude (-0.40 ± 1.62) ($t[17] = 4.488$, $p < 0.001$). In the Pz electrode, the T P3 amplitude (8.54 ± 2.56) was significantly higher than the NT P3 amplitude (1.56 ± 1.22) ($t[15] = 5.029$, $p < 0.001$). In the Oz electrode, the T P3 amplitude (6.38 ± 1.78) was increased in comparison to the NT P3 amplitude (2.09 ± 1.70) ($t[10] = 5.809$, $p < 0.001$) (Figure 1B).

There was no significant difference in AERP amplitudes in the rest of the EEG channels.

The SH and control groups' T and NT AERP responses were displayed superimposed on top of each other as in Figure 2, which distinctly shows the formation of P1, N1, P2, N2 and P3 wave components. A much larger P3 response was observed for T stimuli (depicted in red) in comparison to NT stimuli in the control group. On the other hand, in children with SH, no prominent increase in the T P3 response in comparison to NT P3 was observed.

Comparison of the SH and control group children's AERP components in response to target stimuli

There was no statistically significant difference between the latencies of the AERP components in response to T stimuli among the SH and control groups.

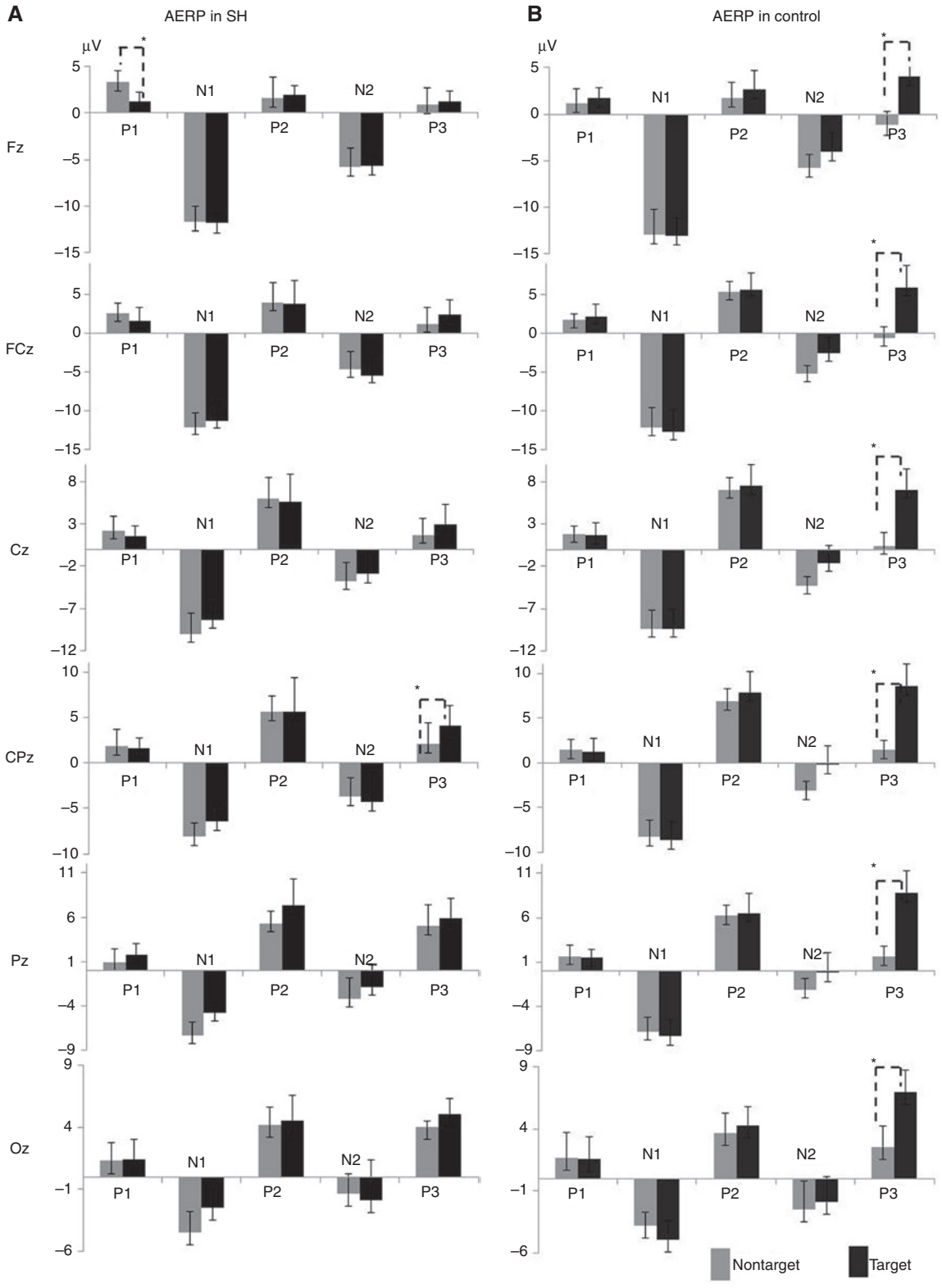

Figure 1: The amplitude-time graph for AERP (P1, N1, P2, N2 and P3) responses obtained (from central line electrodes) to nontarget (gray) and target (black) stimuli.
Electrodes are listed from top to bottom. (A) SH children's and (B) Control group children's AERP responses. Bars on the columns represent standard deviation and the dashed lines show statistical significance of the difference between the two values.

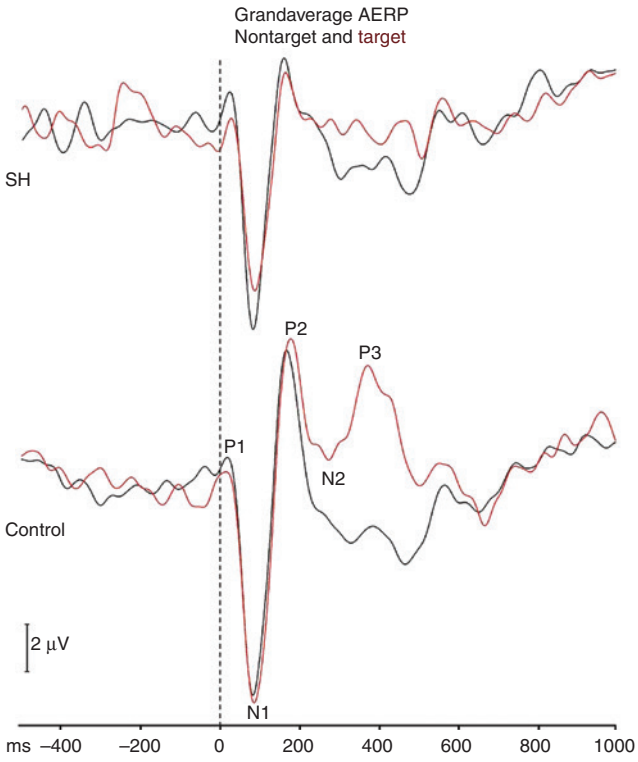

Figure 2: Grandaverage AERP responses: the grandaverage AERP responses of all children with SH are presented above and those of the control group children are presented below.
Shown on the horizontal axis is the 500 ms pre-stimulus and 1000 ms post-stimulus intervals, and the vertical dashed line marks the stimulus onset. Nontarget AERP is depicted in black and target AERP is depicted in red. Wave peak points P1, N1, P2, N2 and P3 are labeled.

The P3 amplitudes in response to T stimuli were found to be greater in the control group in comparison to those obtained from SH (Figure 3). The FCz T P3 amplitude was significantly higher in the control group (6.39 ± 2.78) than in the SH group (2.83 ± 1.78) ($t[35] = 2.334$, $p < 0.05$). The Cz target P3 amplitude was higher in the control group (7.38 ± 2.48) in comparison to the SH group (3.00 ± 2.26) ($t[34] = 2.688$, $p < 0.05$). The CPz T amplitude was also higher in the control group (8.54 ± 2.56) than in the SH group (4.10 ± 2.20) ($t[31] = 3.523$, $p < 0.005$).

Additionally, in all EEG channels, the amplitudes of the N1 component obtained from the control group in response to T stimuli were observed to be greater than those obtained from SH children (Figure 3). However, only the Pz T N1 amplitude was significantly increased statistically in the control group (–7.61 ± 1.88), compared to the SH group (–5.42 ± 1.14) ($t[33] = -2.107$, $p < 0.05$).

The amplitudes of N2 responses obtained for T stimuli from the control group were observed to be reduced in comparison to those from the SH group in all EEG channels (Figure 3). The T N2 amplitude was significantly smaller in the control group (–0.02 ± 2.16) when compared to the SH group (–4.17 ± 3.24) ($t[32] = 2.388$, $p < 0.05$).

Comparison of SH and control group children's "P1-N1" and "N2-P2" peak-to-peak amplitude values

The P1-N1 peak-to-peak amplitude value is the measure of the amplitude between the P1 peak and N1 peak. The P1-P2 peak-to-peak amplitude value is the measure of the amplitude between the N1 peak and P2 peak. The P1-N1 and N1-P2 peak-to-peak amplitudes were measured for both T and NT stimuli in the SH and control groups. There was no significant difference between the SH and control groups with respect to the peak-to-peak amplitude values obtained for NT stimuli. However, in the Cz electrode, the P1-N1 amplitude obtained in response to the T stimulus was significantly higher in the control group (12.01 ± 2.12) than in the SH group (8.90 ± 2.00) ($t[35] = 2.126$, $p < 0.05$). Similarly, in the Cz electrode, the N1-P2 amplitude for the T stimulus was also higher in the control group (18.12 ± 3.44) compared to the SH group (13.09 ± 3.22) ($t[35] = 2.122$, $p < 0.05$) (Figure 2).

Neuropsychological assessment

All the variables were found to have a normal distribution. No statistically significant difference was observed between the SH and control groups with respect to the response time or response accuracy on any of the cognitive test parameters. These parameters included simple reaction time, in which the stimulus is first perceived and a motor reaction is given; recognition reaction time, in which the stimulus is first recognized and then either responded to or motor response is inhibited; and choice reaction time, in which the stimulus is recognized and the motor response is chosen. The cognitive and executive functions tapped by these tests include psychomotor vigilance reflected by shorter reaction times (RT); sustained and selective attention reflected by shorter RT and correct response numbers; inhibition ability reflected by lower commission error number and higher T, foil accuracy rates; and resistance to interference ability reflected by higher correct resistance to interference response rate scores and shorter choice RT. DS scores reflect attention, short-term memory and working memory functions. The results are presented in Table 1.

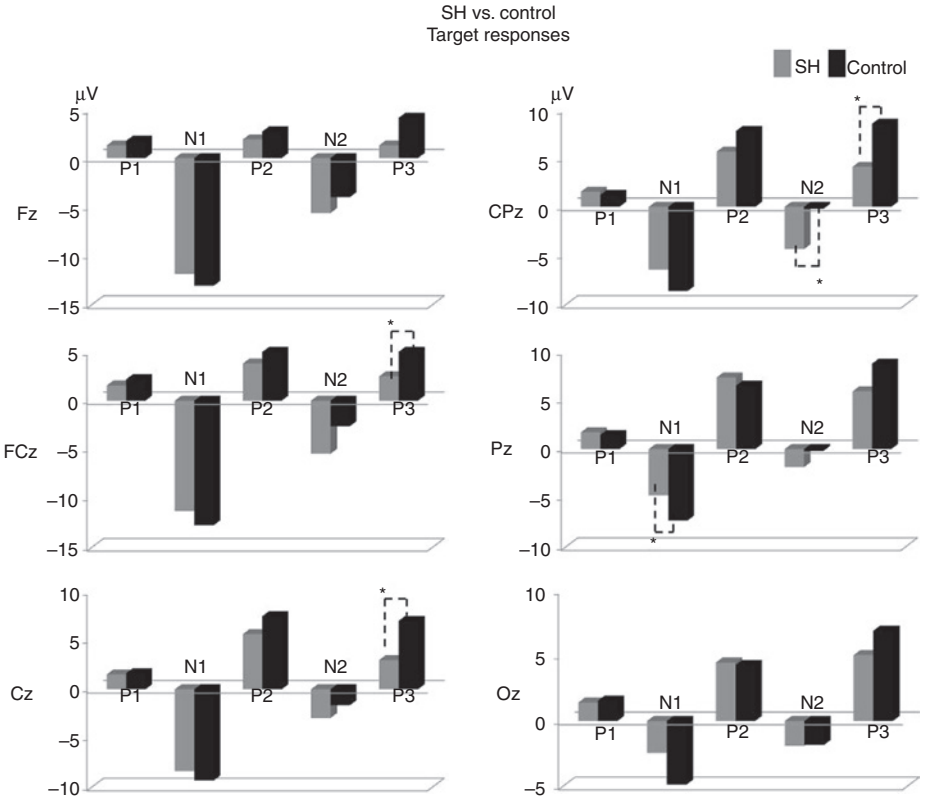

Figure 3: The AERP components (P1, N1, P2, N2 and P3) obtained from central line electrodes are displayed, for the SH (gray) and control (black) groups, on the amplitude-time graph.
The dashed lines above the columns show statistical significance of the difference between the two values.

Table 1: Neuropsychological test results for the SH and control groups.

	SH	Control
Simple RT, ms	409.60 ± 125.36	409.42 ± 86.88
Simple RT test correct response number	33.91 ± 7.10	33.72 ± 7.44
Simple RT test commission error number	1.56 ± 1.56	1.94 ± 2.04
Recognition RT, ms	383.27 ± 68.26	382.85 ± 43.22
Recognition RT correct response number	106.13 ± 6.26	108.61 ± 5.48
Target accuracy rate	0.94 ± 0.05	0.97 ± 0.02
Foil accuracy rate	0.37 ± 0.19	0.40 ± 0.21
Choice RT, ms	538.12 ± 162.89	527.88 ± 112.91
Correct resistance to the interference response rate	123.61 ± 13.50	123.61 ± 10.88
DS standard score	10.00 ± 3.57	9.78 ± 3.82

DS, digit span; RT, reaction times; SD, standard deviation; SH, subclinical hypothyroidism. Data are presented as mean ± SD ($p > 0.05$ for each parameter).

Discussion

The major finding of our study is that there are important differences between children in the SH and control groups with respect to AERP responses, but no difference between the groups were reflected on the neuropsychological tests.

This difference in AERP responses was observed most prominently in the P3 amplitude. When amplitudes of P3 responses to T and NT stimuli were examined, T P3 amplitudes were observed to be significantly higher than NT P3 amplitudes in all channels among the control group children, whereas this difference was not observed among children with SH in any of the channels except the CPz channel

(Figure 1). P3 amplitudes in response to T stimuli among the SH group children stood out to be lower in comparison to those obtained in the control group children (Figure 3). Additionally, although the difference was not statistically significant, the N1 and P2 amplitudes in response to T stimuli were observed to be smaller in the SH group than in the control group (Figure 3). When the P1-N1 and N1-P2 peak-to-peak amplitude values were measured, the difference between the SH and control groups was prominent, and was found to be significantly smaller in SH (Figure 2).

The P3 component reflects cognitive processes during complex memory tasks and is related to focused attention, working memory, signal detection and decision-making processes [26–28]. The P3 amplitude is known to be positively correlated to attention, stimulus recognition and working memory performance, while an increase in the P3 latency is related to task difficulty [29, 30]. Increased attention produces increased P3 amplitudes. Latencies are generally interpreted to reflect the stimulus classification speed [31]. The decrease in the P3 amplitude is posited to be related to diminished attention and cognitive impairment and can be used as a neural marker [32]. This assumption receives support from studies with Alzheimer patients. Decrease in the P3 amplitude and increase in latency with cognitive impairment have been shown in many studies with Alzheimer patients [33–35]. Apart from this, a decrease in the P3 amplitude was reported in patients with mild cognitive impairment and Parkinson's [36, 37].

There are studies reporting increase in P3 latency and decrease in its amplitude among adults with hypothyroid and SH [38–41]. Decreases in amplitude and increases in latency of the P3 component in both clinical and subclinical hypothyroid cases imply that cognitive functions are negatively affected in hypothyroidism including subclinical cases [41]. Jensovsky et al. [42] reported that P3 latency of SH patients were significantly larger than the control individuals. Besides, P3 latencies were normalized after TSH normalization. There are not many studies investigating the effect of SH on cognitive functions in children and adolescents. In a study by Sangün et al. [12], there was reported to be no difference with respect to ERP responses between children with SH receiving 6 months of L-T4 treatment and healthy controls both before and after treatment. In our study, prominent differences were found between the SH and control group children especially with respect to P3 amplitudes and P1-N1 and N1-P2 peak-to-peak measures in response to T stimuli. The controversy among studies with regard to different ERP responses may be accounted for by variances in recording and signal averaging methods. Besides, the duration of the disease may be the underlying cause of diverse psychophysiological findings [42]. In our study, the absence of significant differences between responses to T and NT stimuli in children with SH and lower P3 amplitudes in response to T stimuli in comparison to the control group children indicates that cognitive functions such as attention and working memory are affected in these children.

Furthermore, the lower P1-N1 and N1-P2 peak-to-peak amplitude values obtained for T stimuli in SH children in comparison to healthy controls presented in this study may be considered to imply that attentional processes are affected. The P1, N1 and P2 early ERP components can be affected by the characteristics of the stimuli and are likely to affect the consecutive processes of information processing. They reflect filtering mechanisms related to the triggering and focusing of attention [30, 43–45]. Lowered amplitudes in these potentials have been demonstrated to be correlated to P3 amplitudes, and thus these early AERP responses have been posited to be related to attention and learning [45]. In light of previous ERP studies, the smaller P1-N1 and N1-P2 peak-to-peak amplitudes found in children with SH in our study may be reflecting impairments in attention triggering and orienting and thus may be considered to be underlying the weakening of the P3 amplitude.

Attentional deficiencies in children with SH have been detected via neurocognitive function tests [4, 11, 12]. SH cases were reported to perform poorly in attention tasks in comparison to control cases [11]. In a study by Sangün et al. [12], verbal memory and recall scores were reported to be significantly lower in the SH group compared to the control group before treatment and to present no significant difference after treatment. As a consequence, it was concluded that SH affected cognition in children, and L-T4 replacement treatment normalized cognitive functions. In our study, children with SH did not differ from healthy controls with respect to their scores on neuropsychological tests evaluating psychovigilance, alertness, sustained and selective attention, inhibition, resistance to interference, and short-term working memory functions. This result could imply that SH has no effect on cognitive processes. However, neuropsychological tests may be incapable of detecting very weak impairments in cognition due to mild thyroid dysfunction. Furthermore, neuropsychological tests are behavioral assessment tools, and scores may be affected by many factors such as stress, enthusiasm, task engagement and motivation, as well as environmental factors [46–50]. Therefore, these factors and the children's motivational attitudes during assessment may greatly affect the scores. The difference between our study and other studies with respect to neuropsychological test results may be accounted for by these factors. Furthermore, these factors may also have dampened the neuropsychological test's already limited ability to detect very mild

changes that may exist in cognitive functions related to SH, which may be detected by more objective or neurophysiological tools.

The joint evaluation of neuropsychological test results together with an objectively reliable and sensitive parameter such as ERP results will enable a more objective evaluation of cognitive faculties. In this perspective, the results of our study show that the cognitive effects of SH are not to a scale that can be detected by neuropsychological tests but are reflected in AERP responses in the form of neuroelectrical variances. Due to its effects on the central nervous system, the presence of SH in childhood is of vital importance and needs further investigation.

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