

# Cognitive Functions in Hyperthyroid Patients: P300 and Working Memory

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## ABSTRACT

**Background:** Thyroid hormones are quite important for the normal physiological functions and the cognitive functions of brain.

**Objectives:** In the present study, event related potentials (ERPs) have been used to assess the cognitive status of hyperthyroid patients before treatment.

**Methods:** The study was conducted on 26 hyperthyroid patients and 26 healthy volunteers, Plasma levels of fT3, fT4, and TSH were measured pre- and post-treatment in hyperthyroid and control groups. ERPs were recorded with MP150 system using the 10-20 system of electrode placement and the standard auditory “oddball” paradigm, n- back working memory tasks.

**Result:** Prolongation of latencies of P300 was seen in hyperthyroid patients compared to controls ( $p=0.001$ ). P300 amplitudes were also higher in hyperthyroid patients ( $p=0.001$ ). In the euthyroidized patients P300 amplitudes diminished for stimuli 1 and 3 at WM1 and WM2 tasks compared hyperthyroid patients ( $p<0.001$ ).

**Conclusion:** The prolonged P300 latency in hyperthyroid patients that indicated the delayed cognitive information processing and the increased P300 amplitude that was related to the increased activity of cognitive information and attention after the start of treatment in a euthyroid state. This study showed us that the treatment of hyperthyroidism may improve cognitive performance.

**Key words:** *Hyperthyroidism, Working Memory, Evoked Potentials*

## INTRODUCTION

Thyroid hormones act a critical role on the central nervous system as direct neuromodulators and neuroregulators. [1] Cognitive functions of hyperthyroid patients have been evaluated with various psychometric and psychopathological tests in many previous studies. For patients with hyperthyroidism the data are ambiguous, in that cognitive deficits were shown in some studies but not in others. [2,3] This study was performed to analyze quantitatively the cognitive functions of patients with

hyperthyroidism by P300 event related potentials (ERPs) and to evaluate the effect of levothyroxine replacement on the generation of P300 with auditory oddball and WM tasks. In the traditional auditory “oddball” paradigm, the P300 is elicited by an event that is both infrequent and task relevant, and may reflect the activity of neural systems subserving novelty detection, effortful attention (mindfulness) and their interactions. [4]

Working memory (WM) may be the core of many cognitive functions and may

be vital for general human intelligence, it should be investigated whether WM function is affected by hyperthyroidism or not. [5] WM refers to short-term storage and online manipulation of information. [6] The previous studies showed that found a decline WM performance with hyperthyroid. [7,8] This study, WM function was evaluated with a n-back task. A little is known about the neural substrate for the possible influences of thyroid hormone on the cognitive functions of hyperthyroid patients.

In the present study, ERPs have been used to assess the cognitive status of hyperthyroid patients before and after treatment. And the aimed to evaluate the changes in the amplitude and latency of P300 waves in hyperthyroidism in the coding function of the working memory by a new n-back paradigm and Oddball paradigm.

## **MATERIALS AND METHODS**

### **Subjects**

The study was conducted on 26 newly diagnosed hyperthyroid female and male patients with and 26 controls. The participants were studied under three groups. Group I: Healthy control group (n=26, mean age  $39.6 \pm 1.8$  years), Group 2: Hyperthyroid patients group (High thyroid hormone levels, no medication) (n=26, mean age  $42.2 \pm 2.0$  years), Group 3: Euthyroidized patient group (normal thyroid hormone levels, one month drug treatment) (n=15, mean age  $37.6 \pm 2.2$  years). Hyperthyroid patients before treatment were 26 people in the first record, but after treatment were achieved in 15 people (due to the inability of residents came out of the province).

All participants gave informed consent to participate in the study in accordance with the Helsinki declaration. All experiments were performed according to the guidelines of the Erciyes University Ethics Committee (08-236). Patients having hyperthyroid disease were randomly enrolled in the study protocol.

Age- and sex-matched volunteers were taken as controls. The controls were healthy volunteers without any clinical evidence of thyroid dysfunction. Department of Psychiatry examined the subjects for psychiatric examination before being taken their electrophysiological records. Patients with the diagnosis of hyperthyroidism directed were diagnosed as anxiety and depressive disorder, besides this subjects suffering from any hearing impairment, systemic disease or any history of drug abuse (alcohol, opium etc.) and pregnant females were excluded from the study. The patients belonged to the middle socioeconomic status. Intelligence was not evaluated in this study, but all participants had completed high school. They also presented with hyperthyroid symptoms. The average interval between the diagnosis and start of symptoms was about 6-12 months.

The diagnosis of hyperthyroidism was based on thyroid function tests including free T3 (fT3), free T4 (fT4), and TSH levels, thyroid ultrasonography, and thyroid scintigraphy. Control group's venous blood samples were taken for the measurement of basal hormone levels, immediately followed ERP measurement. Serum concentrations of hormones were determined by immunoradiometric assay with reagents from Diagnostic Product Corporation. Euthyroidism was defined by normal plasma T3 (2.5-3.9 pg/ml), T4 (6.1-11.2 pg/ml), and TSH (0.35-5.5  $\mu$ u/ml) levels.

### **Psychiatric Assessment**

Patients were examined by a psychiatrist and the Hamilton Depression Rating Scale (HDRS) [9,10] and Hamilton Anxiety Rating Scale (HARS) [11,12] were performed to assess the severity of anxiety and depression. Standardized Mini-Mental Examination (SMMSE) [13,14] was also performed to assess the cognitive functions of patients. Patients that were determined any psychiatric disorder in psychiatric examination and patients with scores of 24

and less in MMSE were excluded from the study.

### Recording procedure

The study was conducted in the Electrophysiology Laboratory of the Department of Physiology, Erciyes University, Medical Faculty. Patients and controls were tested under similar laboratory conditions after becoming familiarized with them. The recording of ERP for the controls and the hyperthyroid patients was done once.

During the recording session, subjects were seated in a comfortable chair in a half supine position in a sound and light attenuated examination room. They were instructed to sit quiet with open eyes and to follow the stimuli carefully, to try to detect target tones of 1500 Hz frequency. Prior to the experiments 20 tones with altering frequencies (2000 and 1500 Hz) were demonstrated to the subjects. They were also asked not to move or speak, or to blink too much, and to look at a fixed point.

### Recording of ERPs

ERPs were recorded with the use of 8 EEG100C amplifier modules that were attached to the MP150 acquisition system (Biopac Systems Inc.), using an Electrocap with electrodes positioned according to the International 10–20 method of electrode placement. Electrodes of interest were frontal (Fz, Fp1, Fp2), central (Cz), parietal (Pz, P3, P4) and occipital (Oz). The ground electrode was placed on right ear, whereas the reference electrode was placed on the left ear. All electrode impedances were under 5 k $\Omega$ . and homologous sites had impedances that were within close range relative to each other. Eye movements were also recorded in order to facilitate artifact scoring of the EEG.

Subjects pressed a button in response to the target stimulus. The ERP peak latencies were evaluated from stimulus onset (stimulus artifact) to onset of the particular wave (P300), i.e. point of largest amplitude. [15] The P300 amplitude was

evaluated by first marking a baseline determination from the pre-stimulus baseline analysis time, and the amplitude was the distance of the corresponding peak measured from the baseline. [15] The auditory ERPs were recorded using the 'oddball' paradigm in which two stimuli (target and non-target) and 1-back task were presented in a random order by headphones.

### Oddball Task

Non-target (2000 Hz) and target (1500 Hz) auditory stimuli were presented in a random order with duration of 1000 ms (Superlab 4.0). Interstimulus interval was 2 sec. The target stimulus was a 2- kHz click sound with 20% occurrence and a non-target beep sound of 1 kHz with 80% occurrence. The auditory stimuli had a 10-ms rise/fall time, 100-ms duration and intensity of 60 dB above the hearing threshold. Prior to the first run of the oddball task, the subjects were told that they would need to attend to a defined auditory target stimulus (1500 Hz), presented through headphones, and to respond by pressing a button. [16]

After the oddball task, subjects were interrupted by a 3 min break, during which instructions were repeated for WM paradigm, patient-seating position could be slightly changed and the positioning of the electrodes was controlled.

### WM paradigms

The WM paradigm used consists of two tasks. All two tasks are physically the same. There are three different auditory stimuli (stimuli 1, 2, and 3). One hundred fifty-six auditory stimuli were applied with interstimuli interval of 3000 msec at control and easy WM tasks. These stimuli were presented in a semi-random sequence. Stimuli 1 (short stimuli, 50 msec, 1500 Hz), stimuli 2 (middle stimuli, 200 msec, 1000 Hz), and stimuli 3 (long stimuli, 400 msec, 1500 Hz) occur 63, 62 and 31 times with 90 dB SPL, respectively. The difference between the individual tasks lies in the rule that prescribes responses to each stimulus (Table 1). Response is always a button

pressed on the left or the right side. The side of the button pressed depends on the given for the task. The rules of the WM task require the subjects to keep in mind the last movement executed by them. Thus, the WM content relates to execute movements.

In analysis of P300 latency and amplitude in ERPs during an oddball

paradigm and WM tasks in groups, the target stimuli were evaluated during oddball paradigm. In WM task, responses for stimuli 2 and stimuli 1, 3 (we analyzed these stimuli together) were analyzed.

**Table 1. Task specific response rules**

	Stimulus 1	Stimulus 2	Stimulus 3
Control task (WM1)	Right hand	Left hand	Right hand
Easy WM task (WM2)	Repeat on same side	Change side	Repeat on same side

**Statistical Analysis**

The data are expressed as mean ± standard error (SE). The statistical analysis for the comparison between controls and hyperthyroid patients for the eight electrode montages were done using ANOVA followed by Post-hoc Scheffe test.

P300 wave’s amplitudes and latencies of groups compared with independence Student’s t test. For compare task effect within groups, ANOVA followed by Post-hoc Scheffe test was used. Spearman’s rho correlation was applied to see the correlation of the P300 amplitude and latency with TSH, fT3, and fT4.

Differences were considered significant when p<0.05.

**RESULTS**

**Comparison of serum levels of TSH, fT3, fT4**

Twenty six patients passed the clinical study according to the protocol. There was no significant difference for mean ages between the groups (p>0.05). The mean values of fT3, fT4, TSH, and age in control group and hyperthyroid patients before and after treatment are given in Table 2. The fT3, fT4 levels were statistically higher and TSH level was lower in Group II (p<0.05).

**Table 2. Comparison of serum levels of TSH, fT3, fT4 and age in subjects of groups**

	Group I (n=26)	Group II (n=26)	Group III (n=15)	F	p
Age	39.6 ± 1.8	42.2 ± 2.0	37.6 ± 2.2	1.15	0.32
sT3 (pg/ml)	3.13 ± 0.07*	4.38 ± 0.2 <sup>#</sup>	3.3 ± 0.8	14.79	0.000
sT4 (pg/ml)	8.19 ± 0.21*	16.49 ± 1.0 <sup>#</sup>	8.52 ± 0.4	43.75	0.000
TSH (µu/ml)	2.6 ± 0.1* <sup>#</sup>	0.05 ± 0.2 <sup>#</sup>	2.04 ± 0.1	111.01	0.000

Group I: healthy controls; Group II: Hyperthyroid patients group; Group III: Euthyroidized patients group. Normal range: free T3 (fT3): 2.5-3.9 pg/ml, free T4 (fT4): 6.1-11.2 pg/ml, Thyroid stimulating hormone (TSH): 0.35-5.5 µu/ml \*; different from Group II,<sup>#</sup>; different from Group III. Data are expressed as mean ± SD.

**Psychiatric ratings: patients versus control subjects**

All ratings were performed immediately before ERPs measurements. The normal controls and hyperthyroid patients exhibited HDRS scores of less than

3, HARS scores of less than 14, SMMSE scores of higher than 24 and were without any current or past personal history of psychiatric disorder.

**Relationship between Psychiatric assessment (HDRS, HARS and SMMSE scores) and thyroid hormone-TSH levels**

For the groups combined, a significant positive correlation was demonstrated between fT4 and HDRS (r=0.55, p=0.26); however, on separate group analysis, there was no significant correlation.

### ERPs results

The data from the target stimuli for latencies and amplitudes of the P300 were measured at Fz, Fp1, Fp2, Cz, Pz, P3, P4, and Oz electrode sites. For the P300 amplitude and latency, in the overall ANOVA, there was no an electrode site effect ( $F=1.22$ ;  $p>0.05$ ). The interaction effect between the group and electrode site was not significant in these analyses, which indicated that the distribution of P300 did not differ between the groups. So, comparison of P300 amplitude and latency between groups were realized only at Fz region. There were significantly differences between groups for all tasks and stimulus.

### Comparison latency and amplitude of P300 according to oddball and WM

Latencies of P300 were prolonged and amplitudes of P300 were higher in hyperthyroid patients than control group ( $p=0.001$ ). Additionally, were found that amplitude of P300 task of WM1 and WM2 stimulus 1-3 in hyperthyroid patients higher than euthyroidized patients ( $p<0.001$ ) (Table 3).

Within group comparison, P300 latencies were compared among the tasks (oddball target, WM1 task; stimulus 2 and stimulus 1-3, WM2 task; stimulus 2 and stimulus 1-3). In healthy control group, P300 amplitudes at WM2 task for stimulus 1, 3 were significantly higher than WM1 stimulus 1-3 ( $t=5.5$ ,  $df=25$ ,  $p<0.001$ ). In hyperthyroid patients, P300 amplitudes WM1 task for stimulus 2 were higher than WM2 stimulus 2 ( $t=1.4$ ,  $df=25$ ,  $p=0.007$ ). In euthyroidized patients, P300 amplitude WM1 stimulus 2 higher than WM2 stimulus 2 ( $t=2.4$ ,  $df=14$ ,  $p=0.02$ ). P300 latency WM2 stimulus 1-3 found higher than WM1 stimulus 1-3 ( $t=2.3$ ,  $df=14$ ,  $p=0.03$ ) (Table 3).

### Relationship between P300 latencies-amplitudes and thyroid hormone-TSH levels

When we performed correlation analysis; there were no significant

correlations between thyroid hormone-TSH levels and P300 latencies-amplitudes ( $p>0.05$ ).

Group I: Healthy controls; Group II: Hyperthyroid patients group; Group III: Euthyroidized patients group. Control task (Working memory-WM1), Easy WM task (WM2).\*; different from Group 1.\*\*; different from Group 3. Within group comparison for P300 amplitude and P300 latency: #; different from WM1 stimulus 1-3, ##; different from WM2 stimulus 2. Data are expressed as mean  $\pm$  SE.

**Table 3. The comparison of P300 latencies (msec) and P300 amplitude ( $\mu$ v) for the "oddball" two-tone discrimination task and working memory n-back task at the frontal (Fz) electrode for all participants.**

	Group I (n=26)	Group II (n=26)	Group III (n=15)
<b>Oddball</b>			
Latency	314.0 $\pm$ 8.06	427.0 $\pm$ 9.02*	416.0 $\pm$ 11.5
Amplitude	13.1 $\pm$ 0.6	27.7 $\pm$ 0.8*	25.3 $\pm$ 2.0
<b>WM1 Stimulus 2</b>			
Latency	348.2 $\pm$ 7.1	422.3 $\pm$ 8.6*	414.6 $\pm$ 7.2
Amplitude	12.6 $\pm$ 0.1	18.9 $\pm$ 0.6*##	18.0 $\pm$ 1.08##
<b>WM1 Stimulus 1-3</b>			
Latency	339.6 $\pm$ 3.3	401.8 $\pm$ 9.6*	393.0 $\pm$ 5.8
Amplitude	13.0 $\pm$ 0.2	26.06 $\pm$ 0.69***	22.66 $\pm$ 1.25
<b>WM 2 Stimulus 2</b>			
Latency	332.5 $\pm$ 6.9	405.3 $\pm$ 11.0*	391.7 $\pm$ 11.9
Amplitude	12.4 $\pm$ 0.2	16.5 $\pm$ 0.3*	15.4 $\pm$ 0.4
<b>WM 2 Stimulus 1-3</b>			
Latency	336.2 $\pm$ 4.9	420.2 $\pm$ 6.9*	417.5 $\pm$ 8.1#
Amplitude	14.8 $\pm$ 0.3#	27.8 $\pm$ 0.8***	23.9 $\pm$ 0.8

### DISCUSSION

The present study revealed significant prolongation of P300 latency and elevation of P300 amplitude in all tasks (oddball and working memory) in hyperthyroid patients as compared to controls. After treatment, there was a shortening in the P300 latencies and a decreasing in the amplitudes, but this condition was not significant at all the electrode sites.

Jensovsky et al. [17] found that the average P300 latency in subclinical hypothyroidism patients was significantly higher than in control subjects, although the

N1, P2, N2 waveforms did not show any significant difference between both groups. They also found that, in patients treated with thyroxine for 6 months, the P3 wave latency decreased significantly from the initial value. In another study Tutuncu et al. [18] documented prolonged P300 latency in both mild and severe hypothyroidism. It was seen that in cases of severe hypothyroidism P300 latency normalized after the first month of euthyroidism, while in mild hypothyroidism normalization was seen after 6 months of euthyroidism. Newly diagnosed clinical hypothyroid patients showed a significant increase in P300 latency compared to control and subclinical cases while there was no significant difference between the P300 latency of subclinical cases and control group. [19] Osterweil et al. [20] found no significant differences in the latency of the auditory ERP component P300. Their study group consisted of elderly (31-99 years) non-demented hypothyroid patients with different degrees of thyroid dysfunction. This neuroregulatory pathway is located in the hypothalamus which is one of the generation sites of ERP waves, especially the P3 wave, ERP latencies might be affected when the TSH level increases leading to an increased latency of ERP waves and amplitude as reported in the present study.

In our study, there was no a correlation of the latencies and amplitudes of P3Fz in all groups with the fT3, fT4, and TSH values. Anjana et al [21] demonstrated that there was a positive correlation of the latencies of P3Fz and P3Cz of hypothyroid patients with the TSH value, which indicates that the higher the value of TSH, the more the cognitive component of ERP is affected. The latencies of P2Fz and P3Fz were negatively correlated with fT4. There was no significant correlation obtained with the TSH or fT3 or fT4 values after treatment, thus suggesting no relation to over-treatment.

Our findings suggest that there is a slowing of cognitive function in hyperthyroid patients, and with treatment

there is improvement in cognitive status as seen by the shortening in latencies and increase in amplitudes emphasizing the importance of thyroid hormones in maintaining cognitive function. Thus this electrophysiological study shows that an optimal amount of thyroid hormones is required for normal sensory and cognitive processing. And we obtained from our results, in the case of hyperthyroidism are affected cognitive function is that the healing effect of anti-thyroid treatment. However, in a one-month treatment, only the P300 amplitudes approached the control values, and there was no change in latency. We think that the psychiatric disorders that occur in the case of hyperthyroidism are caused by the high level of sT4 and that the sT4 levels of these patients should be kept under control and that are needed further studies on this subject.

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