

## P50 Sensory Gating Deficit in Obese Individuals

### Obez Kişilerde P50 Duyusal Kapılama Defisiti

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#### ABSTRACT

**Objective:** Obesity may cause cognitive dysfunctions such as attention, processing speed, memory, and executive functioning. However, little is known about how obesity can affect cognitive functions in obese individuals. Sensory gating shows the early pre-attention period in information processing and is accepted to be the result of the integration of multi-step procedures that can be tested with the double click P50 paradigm. The aim of this study is to investigate changes in cognitive functions with sensory gating in obese individuals.

**Methods:** A total of 31 obese individuals and age- and sex-matched healthy 24 control subjects were included in the study. The latencies and amplitude P50 waves were measured in the healthy controls and obese individuals. Also the P50 sensory gating was calculated.

**Results:** We found a significant difference between the obese group and controls regarding the amplitude of the first P50 wave ( $p<0.048$ ). The obese group showed reduced P50 sensory gating as compared to controls ( $p<0.004$ ).

**Conclusion:** The findings suggest that obese individuals have a sensory gating abnormality seems to be a result of cholinergic dysfunction. This results may help explain cognitive impairment in obese individuals.

**Key Words:** Obesity, sensory gating, cholinergic dysfunction, cognition.

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#### ÖZET

**Amaç:** Obezitenin dikkat, bilgi işleme hızı, bellek ve eksekütif fonksiyonlar gibi kognitif alanlarda fonksiyon bozukluklarına neden olabileceği bilinmesine rağmen, bu fonksiyonları nasıl etkilediği çok az bilinmektedir. Duyusal kapılama; bilgi işleme süreçlerinin dikkat öncesi döneminin göstergesidir ve çift uyarımlı P50 paradigması kullanılarak test edilebilen, çok basamaklı işlemlerin entegrasyonu sonucunda ortaya çıktığı kabul edilir. Bu çalışmanın amacı obez kişilerde kognitif fonksiyonlardaki değişiklikleri duyuşsal kapılama aracılığıyla araştırmaktır.

**Yöntemler:** Çalışmaya 31 obez kişi ve 24 yaş, cinsiyet açısından eşleştirilmiş sağlıklı kontrol dahil edildi. Her iki grubun P50 latans ve amplitüd ölçümleri yapıldı ve aynı zamanda duyuşsal kapılamaları hesaplandı.

**Bulgular:** İlk P50 dalga amplitüdü ile ilgili obez kişilerde kontrol grubu arasında anlamlı farklılık saptandı ( $p<0.048$ ). Kontrol grubu ile karşılaştırıldığında obez grubun P50 duyuşsal kapılaması daha düşük saptandı ( $p<0.004$ ).

**Sonuç:** Bu bulgular, obez kişilerde kolinerjik sistem disfonksiyonu sonucu olarak duyuşsal kapılama anormalliklerinin olduğunu ortaya koymaktadır. Bu durum obez bireylerdeki kognitif fonksiyon bozukluğunu açıklamaya yardımcı olabilir.

**Anahtar Sözcükler:** Obezite, duyuşsal kapılama, kolinerjik disfonksiyon, kognisyon

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## INTRODUCTION

The rapid increase in the obesity prevalence in western societies is related to changes in the culture of eating (1). Obesity substantially increases the risk of morbidity for conditions such as premature type II diabetes mellitus, hypertension, cancer, stroke, and obstructive sleep apnea (2). Obesity may be also related to cognitive dysfunction in adolescents and adults. Fergenbaum et al. investigated the association between obesity and cognitive functions. They found that obese individuals are at an approximately fourfold increased risk of lowered cognitive performance as compared to controls (3, 4).

Some studies showed that patients with medical diagnoses including hypertension, diabetes and obstructive sleep apnea have a variety of cognitive deficits, including attention, processing speed, memory, and executive functioning in neuropsychological investigations (5-8). While these medical conditions are often resulting from obesity or excess body weight, recent findings indicate that the compromised neurocognition in obese individuals may be present independently of these medical conditions (9,10). However, little is known about how obesity can affect cognitive functions in these patients.

Sensory gating is an important neurocognitive function associated with the early pre-attention period in information processing, working memory, processing speed, executive functions. It is a natural response of the brain that protects upper cortical structures from the effects of excessive stimulation by blocking unnecessary and irrelevant sensory stimuli (11).

Sensory gating is typically tested with the double click P50 paradigm. The P50 evoked potential is a pre-attentive positive wave and appears approximately 50 ms after an auditory stimulus. In the double click paradigm, the amplitude of the P50 wave appearing after the first stimulus (S1) is larger than that of the second stimulus (S2) when two stimuli with a 500 ms interval are used. This result is thought to be due to inhibitor mechanisms activated by the first stimulus, inhibiting the second response (12). A S2/S1 amplitude ratio below 50% is the usual definition of the normal sensory gating (13).

Sensory gating is modulated and regulated by neural cholinergic circuits, the cholinergic arousal system and basal forebrain neurons. Impaired sensory gating is therefore associated with a cholinergic deficit (14,15). Neural cholinergic circuits also have key roles in regulation of food intake and energy expenditure. Decreased cholinergic activity results in significant and sustained hyperphagia and weight gain. On the other hand, the increased cholinergic activity results in hypophagia and weight loss (16,17).

The relationship between obesity and sensory gating has not been studied previously. We tested whether there was a difference in sensory gating between obese individuals and healthy controls using the P50 paradigm.

## MATERIALS AND METHODS

We included 31 people who presented at the Inonu University Medical Faculty as obesity outpatients between December 2011 and April 2012 with a BMI over 30 kg/m<sup>2</sup> and no endocrine disorder. All participants were given detailed information about the action, and signed informed consent forms. Body mass index (BMI) was calculated as weight/height<sup>2</sup>, and is stated in kg/m<sup>2</sup>. Neurological and psychiatric evaluations of obese participants and healthy controls were performed by specialists, and those who had personality or psychiatric disorders according to the SCID II (18) or a neurological disease were excluded. Obese participations and healthy controls refrained from tea and caffeine in the morning of the EEG. Those who smoked or had a relative with psychosis were also excluded. Controls were chosen from healthy subjects working in our hospital with a BMI of 18.5-24.9 kg/m<sup>2</sup>. In total, 24 healthy controls were included. All subjects were informed about the aim and methods of the study and provided written informed consent.

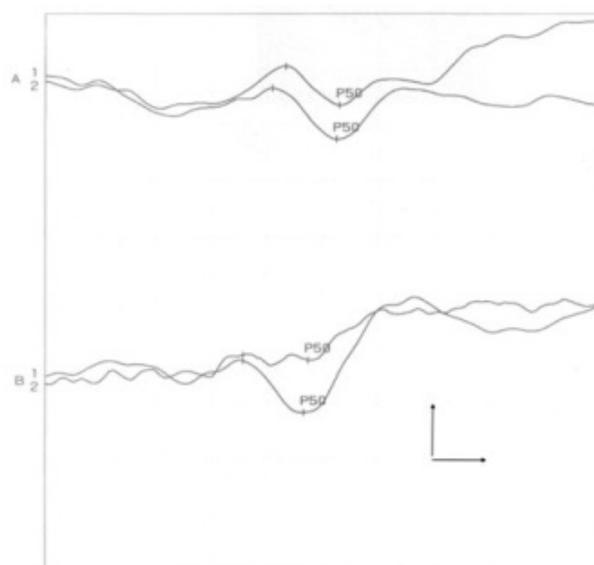
### P50 measurements

The method for electrophysiological recordings was based on protocols described previously, with slight modifications (19). Electrophysiological examinations were performed at the Laboratory of Clinical Neurophysiology at the Department of Neurology, University of Inonu, only during the morning hours (at the same time of the day for all subjects). Subjects were seated in a comfortable chair in a sound- and light-attenuated, electrically shielded room. Subjects were instructed to relax with eyes open and to fixate on a point straight ahead to avoid eye motion artifacts.

The EEG was recorded with a MEM-4200K evoked potential recorder (Nihon Kohden, Japan) system in four channels, which recorded evoked responses integrated with an auditory stimulator. Electroencephalographic activity was recorded from a disk electrode affixed to the vertex (Cz) and referenced to the left mastoid (A2). The mean signal was registered in two channels, and amplified 20,000 times with a band-pass filter between 1 and

100 Hz and a 50 Hz notch filter. Impedance was kept < 0.5 kOhm. EEG data were collected for 1000 ms for each paired stimulus presented.

Additional channels were used to record the electro-oculogram (EOG) between the superior orbita and lateral canthus. Ten minutes of continuous 'resting state' EEG was recorded prior to the auditory double-click paradigm. The test stimulus, a click sound of 0.1 s duration set at 60 dB above the auditory threshold with a rarefaction output phase, was presented binaurally through earphones. The auditory threshold of each subject was measured 15 min before the recordings through earphones. The interval between the first and second clicks (interstimulusinterval = ISI) was 500 ms, and the interval between two pairs of clicks was 10 s. Trials were rejected automatically by the device if they contained artifacts indicated by a response of  $\pm 70 \mu\text{V}$  over the area of P50 for evoked potentials or the EOG recordings. Thirty non-rejected waves were added together to give an average signal, which was used for analysis. The averages of S1 waves and of S2 waves were collected in sequence. The S1 and S2 wave averages were then considered separately for analysis. The wave peaks were determined visually and the latencies and amplitudes were marked manually. The most positive peak, between 40 and 80 ms after the conditioning stimulus, was selected as the P50 final latency and the wave amplitude (S1) was measured relative to the preceding negativity. The second wave (S2) was determined using the corresponding peak between S1  $\pm 10$  ms away from latency of the first waveform (conditioning) and its amplitude was also measured relative to the preceding negativity (Figure 1).



**Figure 1:** Characteristic of P50 potential records of obese (A) and control (B) individuals. Calibration bars indicate 5  $\mu\text{V}$  and 1.25 ms. 1 indicate first stimulus, 2 indicate second stimulus. In a control subject (B) the P50 potential in response to first auditory stimulus (1) is shown at peak latency 59 ms and amplitude 4,8  $\mu\text{V}$ . The P50 potential in response to the second auditory stimulus (2) had amplitude of 0,9  $\mu\text{V}$ . The P50 recording from obese individuals showed 61 ms latency to the peak of the first P50 potential amplitude 4.6  $\mu\text{V}$  second P50 was 3.5  $\mu\text{V}$ . The sensory gating ratio for control volunteers is %81, for obese individuals is %24.

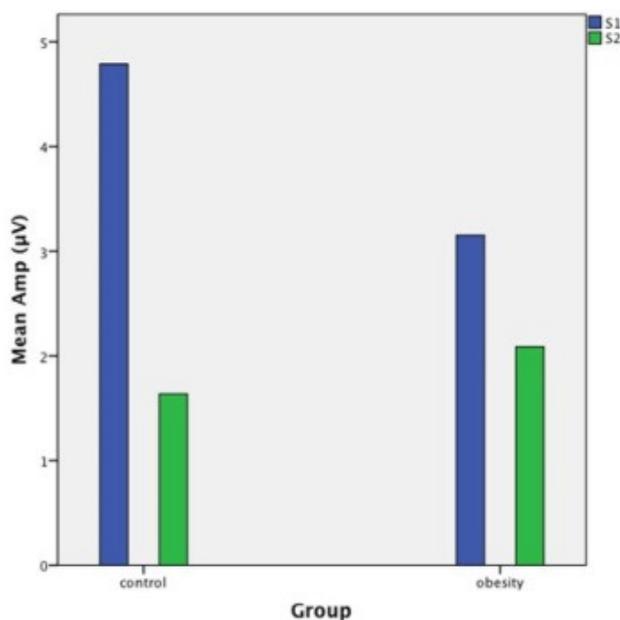
Data were collected by one investigator and analyzed by an independent, trained evaluator blinded to the state of the subjects. Averages with no discernible conditioning P50 waves were excluded from the analysis and the analysis was repeated in four subjects concerned. The percentage of P50 suppression was calculated using the following formula:  $(1 - [\text{second click amplitude}/\text{first click amplitude}]) \times 100$  (20). Results are expressed as median values  $\pm$  standard deviation.

### Statistical methods

Statistical analyses were conducted by using IBM SPSS Statistics software (ver. 20 for Mac). P50 variables of the obese and control groups were compared. All results are presented as means  $\pm$  SD. Student's t-test for independent samples and the Mann-Whitney U-test for non-normal distributions were used to compare the obese and control groups for continuous variables. Categorical variables (gender) were analyzed using chi-squared based tests. P50 amplitudes and latencies and suppression percentages of amplitudes were correlated separately with age and BMI in the obese group (Pearson's correlation coefficient). The criterion for significance was set at  $p < 0.05$  in all tests.

## RESULTS

The gender, age, P50 amplitude and latency, and percentage of P50 suppression in the obese and control groups are presented in Table 1 with the p values. The obese group did not differ significantly from the control group in age or gender ( $p > 0.05$ ). Body mass index (BMI) of the obese group ranged from 30.0 to 57.0 kg/m<sup>2</sup>, with a mean value of 39.3±6.8 kg/m<sup>2</sup>. The obese group showed a lower P50 suppression than the controls ( $p < 0.004$ ). The S2 P50 amplitudes were greater for the obese than for controls, but not in a statistically significant way (Figure 2). S1 P50 amplitudes were significantly lower for the obese than controls ( $p < 0.048$ ). Latencies, S1 and second waves S2 of the P50 component of auditory evoked potentials were not different between the two groups. There was no correlation within the obese group between BMI and the S1 and S2 P50 amplitudes, latencies, or suppression percentage of P50.



**Figure 2:** Mean amplitude of first and second P50 potentials in controls and obese individuals.

**Table 1:** Demographic and neurophysiological findings in the control and obese groups

	Control group (n=19)	Obese group (n=31)	P value
Gender (female/male)	10/9	22/9	NS <sup>b</sup>
Age	32,89±7,77	35,52±10,33	NS <sup>a</sup>
P50 response to first click (S1)			
Amplitude (µV)	4,77±3,89	3,15±1,70	0.048
Latency (ms)	57,36±10,74	51,32±11,00	NS <sup>a</sup>
P50 response to second 2 (S2)			
Amplitude (µV)	1,79±1,83	2,09±1,60	NS <sup>a</sup>
Latency (ms)	56,79±11,05	50,58±12,27	NS <sup>a</sup>
P50 suppression percentage	63,49±19,28	37,02±35,03	0.004

## DISCUSSION

It is not clear what the association between obesity and cognitive functions is, but there are some speculative comments. It is possible that because of a larger body mass requires more blood flow for optimal functioning, the brain is deprived of blood flow (21,22). The other possible mechanism about this situation: is the following. The obese individuals possess more adipokines such as leptin as compared to others and this adipokines can be linked to structural brain abnormalities (23). Leptin can influence neuronal excitability in the brain, and modulate inflammatory signals in microglia. Chronic elevation of leptin in obese individuals probably results in leptin resistance, which is associated with cognitive deficits and inability to regulate weight (24). Besides, studies showed that obesity is correlated with anatomical and functional changes in the brain. BMI is positively related to smaller brain volume in obese adults. The obese adults show atrophy in the frontal lobes, anterior cingulate cortex, hippocampus, and thalamus as compared to normal BMI adults (25).

The relationship between obesity and cognitive decline in the elderly is more complex than in those at mid-life ages. Some differences exist between sexes such that cognitive function can only affect elderly men but not elderly women (26). The complexity may be due to adipose tissue location and cell types, body composition, endocrine adipose (27).

Conversely, some studies of mid-life adiposity have not found an association between elevated adiposity and dementia. Several studies report inverse or non-linear associations between elevated adiposity and dementia. Although postulating that elevated adiposity could be beneficial for cognition seems implausible, the finding that leptin, which is elevated with adiposity, is neuroprotective and associated with lower cognitive decline risk could provide an explanation (28).

The undesirable results caused by obesity may be reversed with exercises. Exercise improves cognitive decline by influencing cognition directly, or indirectly, by reducing obesity. The exercise programs such as aerobic and anaerobic trainings can yield an array of significant benefits (29).

These explanations are only speculative, and it remains unknown whether obesity is a cause or a result of cognitive functions. Nevertheless, an increased number of studies now point to specific cognitive effects of obesity/increased BMI (4,30).

Detailed studies on the neurobiology of being obese and overweight in the fields of neurophysiological studies have concentrated on cognitive processes related to attention (31,32). Sensory gating shows the early pre-attention period in information processing and is accepted to be the result of the integration of multistep cognitive functions. It is known that the sensory gating disorder is related to the inadequate suppression of S2 or decreased S1 P50 amplitude (33). However, we found that the obese individuals had a greater sensory-gating abnormality due to a decrease in S1 amplitude as compared to the controls. S1 P50 auditory information travels through the classical lateral lemniscal pathway from the auditory nerve to the neocortex (34). S1 auditory information also reaches the reticular formation via the nucleus of the lateral lemniscus. At least part of the P50 potential is known to be generated by the output of the pedunculopontine nucleus (PPN) that forms the cholinergic part of the reticular activating system in the brain stem (35). This input activates cholinergic forebrain pathways, which in turn activate nicotinic receptors in hippocampus. Inhibitory hippocampal GABAergic neurons activated by increased cholinergic activity leads to an S2 amplitude suppression (sensory gating) (36,37).

Obesity is also closely related to the cholinergic system, in connection with the hypothalamus. The hypothalamus is a significant central nervous system structure in the regulation of nutrition and appetite. Lesions of the lateral hypothalamus can cause hypophagia and dramatic weight loss while pathologies of the ventromedial hypothalamus can cause hyperphagia and obesity (38,39).

Cholinergic projections to the hypothalamus come from intrinsic and extrinsic sources. The extrinsic cholinergic projections to the hypothalamus come primarily from the PPN and the laterodorsal tegmental nucleus. Nicotinic activity, especially via the alpha 7 nicotinic receptors, in the lateral hypothalamus has been reported to increase GABAergic activity, inhibiting the lateral hypothalamus and causing hypophagia and weight loss (16). Studies have also shown that PPN dysfunction can cause obesity in Prader-Willi syndrome. In contrast a decrease in cholinergic activity leads to overeating and weight gain (40).

## CONCLUSION

We found that obese individuals showed a P50 sensory gating abnormality sensory gating abnormality due to a decrease in S1 amplitude. This seems to be the result of a cholinergic dysfunction. To our knowledge this is the first study to investigate the p50 suppression in obese individuals. This should be considered a preliminary analysis and further studies with a larger number of cases should be carried out.

## Conflict of Interest

No conflict of interest was declared by the authors.

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