



Effects of Smoking on P50 Waveform in Schizophrenic Patients

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ÖZET:

Sigaranın şizofrenili hastalarda P50 dalgası üzerine etkileri

Amaç: Genel popülasyonla karşılaştırıldığında sigara içimi şizofrenik hastalarda çok yaygındır. Nikotinin şizofrenide görülen işitsel duyuşsal kapılama yetersizliğinin normalleştirilmesindeki rolüne ek olarak bilişsel bozuklukları iyileştirdiği düşünülmektedir.

P50, uyarının başlangıcından itibaren yaklaşık 50 milisaniye sonra pozitif sapma olarak ortaya çıkan işitsel uyarılmış bir potansiyeldir ve nöral cevabı yansıtır. Bu pozitif dalga şekli duyuşsal kapılama mekanizmasını göstermek için kullanılır. Şizofrenide bu mekanizmadaki yetersizliğe bağlı olarak P50'nin baskılanmadığı bulunmuştur.

Bu çalışmada kronik sigara içen ve sigara içmeyen şizofrenik hastalarda sigaranın P50 bileşeni üzerine olan etkisinin ve bu etkinin şizofreni hastalarındaki muhtemel bilişsel bozulma ile bağlantısının incelenmesi amaçlanmıştır.

Yöntemler: Şizofreni için DSM-IV tanı kriterlerini tam olarak karşılayan hastanede yatmakta olan 43 şizofrenik hasta ve 44 sağlıklı kontrol çalışmaya dahil edildi. Dokuz hasta herhangi bir ilaç kullanmıyordu. Yirmi dört hasta atipik antipsikotik ve 10 hasta ise tipik antipsikotik kullanıyordu. Hastalar ve kontroller sigara içenler ve içmeyenler olmak üzere iki gruba ayrıldı. Sigara içen hastalardan ve kontrollerden gece yarısından sonra sigara içmemeleri istendi. Ertesi sabah P50 işlemi uygulandı. İlk ölçümden sonra, sigara içen deneklerin her zamanki içtikleri sigara miktarını tüketmelerine izin verildi. Otuz dakikalık sigara içiminden sonra P50 ölçümü tekrar edildi. Wechsler Sayı Menzili Testi sigara içme esnasında ve sigaranın kısıtlanmasının bitiminde uygulandı. İşlem sigara içmeyen deneklerde yalnızca bir kez uygulandı.

Bulgular: Dört grup arasında P50 oranları açısından anlamlı fark vardı ($F=19.01$, $p<0.001$). Sigara içen hastalar sigaranın kısıtlanmasından sonra (sigara içmeden önce) ve sigara içmeyen hastalar, sigara içen ve sigara içmeyen kontrollerinkinden anlamlı derecede yüksek P50 oranlarına sahipti (karşılaştırmaların tümü için $p<0.001$). Sigara içen hastaların P50 oranı sigara içmeden öncekiyle karşılaştırıldığında 30 dakikalık sigara içiminden sonra azalmıştı ($t=7.07$, $p<0.001$) ve kontrollerinkine benzer hale gelmişti ($t=1.96$, $p>0.05$). Sigara içen hastaların sigara içiminden sonraki P50 oranı sigara içmeyen hastalarinkinden aynı zamanda daha düşüktü ($t=3.32$, $p<0.005$). Hastalar 'ilaç kullanmayan' ($n=9$), 'atipik antipsikotik kullananlar' ($n=24$) veya 'tipik antipsikotik kullananlar' ($n=10$) olarak alt gruplara ayrıldıklarında, alt gruplar arasında P50 oranları açısından anlamlı fark yoktu, ancak tüm hastaların P50 oranları kontrollerinkinden daha yüksekti (sırasıyla $p<0.05$, $p<0.001$, $p<0.001$). Sayı menzili testi puanları açısından sigara içen ve içmeyen hastalar ve sigara içen ve içmeyen kontroller arasında fark bulunmadı.

Sonuçlar: Bu çalışma şizofrenideki bilişsel bozuklukların bir yansıması olan P50'deki baskılanmamayı desteklemektedir. Bununla birlikte, şizofrenik hastalarda bir gecelik yoksunlukta sonra sigara içme P50 defisitini düzeltmektedir. Antipsikotikler ve bilinen diğer tedavilerin bilişsel semptomları iyileştirmede yetersiz kalması nedeniyle şizofrenik hastalar bilişsel semptomlarını sigara içerek tedavi etmeye çalışıyor olabilir. Bu sorunu çözmek için uzun ömürlü nikotin benzeri ilaçların geliştirilmesi daha iyi olacaktır.

Anahtar sözcükler: Sigara içme, nikotin, P50, şizofreni, duyuşsal kapılama

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ABSTRACT:

Effects of smoking on P50 waveform in schizophrenic patients

Objective: Smoking is very common in schizophrenic patients compared to general population. It is considered that nicotine improves cognitive disturbances in addition to its role in normalization of auditory sensory gating deficit in schizophrenia.

P50 is an auditory evoked potential that appears about 50 msec as a positive deflexion after stimulus onset and reflects neural response. This positive waveform is used to show sensory gating mechanism. In schizophrenia P50 is found to be non-suppressed due to the insufficiency of this mechanism.

In this study we aimed to investigate the effects of smoking on P50 and the relationship of this effect on probable cognitive impairment in chronic schizophrenic patients.

Methods: Forty-three schizophrenic inpatients who fully met the DSM-IV criteria for schizophrenia and forty-four healthy controls were included in the study. Nine of the patients were not taking any drug. Twenty-four of them were on atypical antipsychotics and 10 patients were on typical antipsychotics. The patients and controls were divided into two groups; smokers and non-smokers. Smoker patients and controls were asked to refrain from smoking after midnight. P50 measurement was performed the following morning. Smoker subjects were allowed to consume their usual amount of cigarettes for 30 minutes after the first measurement. Then P50 measurement was repeated. The Wechsler Digit Span Task was performed while smoking and at the end of the restriction of smoking. In non-smokers the procedure was performed only once.

Results: There was a significant difference in P50 ratios between the four groups ($F=19.01$, $p<0.001$). Smoker patients after smoking restriction (before smoking) and non-smoker patients had significantly high P50 ratios than smoker and non-smoker controls ($p<0.001$ for all of the comparisons). P50 ratio of smoker patients decreased after 30 minutes' smoking compared to that before smoking ($t=7.07$, $p<0.001$) and became similar to that of the controls ($t=1.96$, $p>0.05$). P50 ratio of smoker patients after smoking was also lower than that of nonsmoker patients ($t=3.32$, $p<0.005$). When the patients were divided into subgroups as "no drug" ($n=9$), "atypical antipsychotics" ($n=24$) or "typical antipsychotic" ($n=10$), there was no significant difference in P50 ratios among subgroups, but all patient groups had higher P50 ratios than the controls ($p<0.05$, $p<0.001$, $p<0.001$; respectively). It was found that digit span scores were not different between the smoker and nonsmoker patients and between the smoker and nonsmoker controls.

Conclusion: This study supports P50 non-suppression which is a reflection of cognitive disturbances in schizophrenia. However, in schizophrenic patients smoking after overnight abstinence improves P50 deficit. Schizophrenic patients may be trying to treat their cognitive symptoms by smoking since antipsychotics and other known treatments are insufficient to ameliorate cognitive symptoms. It will be better to develop long-half life nicotine-like drugs to solve this problem.

Key words: Smoking, nicotine, P50, schizophrenia, sensory gating.

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INTRODUCTION

It is known that schizophrenic patients smoke more than general population. Although smoking frequency decreases in the general population, in schizophrenic patients it remains high (1). Though the reasons, why schizophrenic patients are heavy smokers, are not clear, one of the suggestions is that nicotine improves cognitive disturbances (2) and normalizes auditory sensory gating deficit in schizophrenic patients (3). Moreover, nicotine may decrease side effects of neuroleptics (4).

P50 is one of the midlatency auditory evoked potentials that appear about 50 msec as a positive deflexion after stimulus onset and reflect neural response. When paired click stimuli (conditioning and testing) are presented, second stimulus evokes a smaller P50, i.e.e.g. P50 suppression occurs. P50 is thought to reflect a sensory gating mechanism and prevent information overload in humans (5). P50 wave is posited to have origins in hippocampus (6,7). This gating mechanism seems to be insufficient in schizophrenic patients. It means that schizophrenic patients are unable to filter out extraneous noise from meaningful sensory inputs. This deficit may cause sensory overload and may explain cognitive disturbances in schizophrenic patients. Some authors have found decreased P50 suppression in schizophrenic patients (8,9). Some symptoms in schizophrenia may be due to poor P50 suppression (8,10). Typical antipsychotics do not improve this defect. It means that sensory gating deficits exhibited in schizophrenic patients are independent of dopaminergic neurotransmission. Of atypical antipsychotics only clozapine improves this deficit by indirectly increasing cholinergic neurotransmission (11).

About half of the first-degree relatives of schizophrenic patients also demonstrate P50 deficit (12). This defect may reflect genetic risk for schizophrenia. The P50 deficit in schizophrenia has been genetically linked to a locus at 15q14 (13) that contains the low affinity $\alpha 7$ nAChR gene. De Luca et al (14) reported that there might be an association between smoking and $\alpha 7$ nicotinic receptor subunit gene in schizophrenic patients. Expression of the $\alpha 7$ receptor, which binds to nicotine with low affinity, is reduced in the hippocampus of schizophrenics (15). A marker of the gene for the $\alpha 7$ nicotinic receptor is linked to schizophrenia and P50

abnormalities (13). Albuquerque et al (16) suggest that in the human cerebral cortex and in the rat hippocampus, neuronal nAChRs are involved in inhibitory (a disinhibitory) ? mechanisms. The cholinergic system plays an important role in regulating the diminished response to repeated stimuli, which is not seen in schizophrenic patients, through stimulation of the $\alpha 7$ nicotinic receptors (7). In a study it was found that a nicotinic acetylcholine receptor antagonist mecamylamine produced a dose-dependent reduction smoking cue reactivity in schizophrenic smokers compared with placebo. This finding may have been due to the reduced nAChR levels in the brains of schizophrenic patients (17).

To our knowledge, there are a few studies in the literature which have assessed the effects of smoking on P50 component in schizophrenic patients. Adler et al (3) found that smoking can transiently normalize P50 deficit in schizophrenic patients. They suggested that nicotine may be normalizing defects in cholinergic neurotransmission in schizophrenic patients. Normalized P50 deficits seem to be consistent with normalized cholinergic neurotransmission in schizophrenic patients.

In this study it was aimed to investigate the effects of smoking on P50 component and the relationship of this effect on probable cognitive impairment in chronic schizophrenic patients. With this goalaim, non-smoking schizophrenic patients and smoking and non-smoking healthy subjects were included in the study along with the smoker schizophrenic patients. In the present study we also investigated acute effects of smoking on P50 component.

METHOD

Subjects

Forty-three inpatients (mean age \pm SD: 32.53 \pm 10.12, range: 18-55, 21 males 22 females) who fully met the fourth Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria (18) for schizophrenia were included in the study. The DSM-IV diagnosis of schizophrenia was determined via clinical interviews by two psychiatrists independently. The patients were selected in the order of hospitalization from the inpatient population of Psychiatry Clinic of Erciyes University Medical School.

Exclusion criteria for patients were: i) having any current or past psychiatric disorder other than schizophrenia, ii) having substance use disorder except cigarette smoking, iii) having any significant neurological disorder and head trauma history, vi) taking ECT during or within the previous 6 months before the study.

The patients remained hospitalised for the full duration of the study. The patients were in the acute exacerbation period of the illness. Nine of the patients were not taking any drug yet. Twenty-four of them were receiving on atypical antipsychotic (18 patients on risperidone, three on olanzapine, two on quetiapine, and one on clozapine) and 10 were taking typical antipsychotics (6 patients haloperidol, three zuclopenthixol, and one flupenthixol). Eight patients had a family history of schizophrenia. According to the presence of cigarette smoking, the patients were divided into two groups; smokers who had been smoking for at least one year (n=23) and nonsmokers (n=20).

All patients were assessed with the Brief Psychiatric Rating Scale (BPRS) (19) for the severity of clinical symptoms, Scale for the Assessment of Positive Symptoms (SAPS) (20) for the severity of positive symptoms, and Scale for the Assessment of Negative Symptoms (SANS) (20) for the severity of negative symptoms. Udvalg for Kliniske Undersøgelser (UKU) side effect rating scale (21) was performed to assess the severity of side effects (psychological, neurological and autonomic and others) related to antipsychotic drug.

Forty-four physically and mentally healthy persons (mean age: 34.20 ± 7.92 , range: 18-55, 24 males, 20 females) who were recruited voluntarily from hospital staff members participated in the study as controls. Exclusion criteria for controls were having a psychiatric disorder in themselves or in their family, having alcohol or other substance use disorder except smoking cigarettes, having any significant neurological disorder and head trauma history. According to the presence of cigarette smoking, the controls also were divided into two groups; smokers who had been smoking for at least one year (n=21) and non-smokers (n=23).

Patients and controls were all right-handed. Demographical and clinical features of the patients and controls were demonstrated in table 1.

This study was carried out in accordance with the Helsinki Declaration of the World Medical Association

and was approved by the local Ethics Committee. Written informed consent was obtained from each patient after providing standard information about the description of the study.

Procedures

Smoker patients and controls were asked to refrain from smoking after midnight. P50 measurement was performed at 09:00 AM in the following morning. After the first measurement, subjects were allowed to consume their usual amount of cigarettes for 30 minutes. Then P50 measurement was repeated. The Wechsler Digit Span Task (22) was performed while smoking and at the end of the restriction of smoking. This task has two components; one is forward digit span task, a measure of general attention, and the second is backward digit span task, a measure of verbal working memory. In nonsmoking subjects the procedure was performed only once.

P50 procedure

Subjects were relaxed, awake and seated upright with eyes open in an acoustically isolated room during the recording session. Standard Ag/AgCl electrodes in plastic cups were used for monopolar EEG derivations. They were attached with electrode paste and tape at Cz (vertex) according to the 10-20 system. Linked right ear electrodes were used as references and the ground electrode was attached to the left earlobe. Electrode resistance was less than 10 kohm. The signals from the electrodes were amplified, and filtered by a Nihon Kohden amplifier (AB-621G) and sent to analogue inputs of a computer for on-line analogue-digital conversion. Sampling rate was 1000 Hz. The electrooculogram (EOG) from the superior orbital references to the lateral canthus was also recorded. Individual trials were rejected if the EOG and EEG activity was greater than 50 μV , which indicated movement artifact.

Auditory stimuli were presented in pairs in a conditioning-testing (C-T) design with a 0.5-second intrapair interval and a 10-second interstimulus interval by the Brain Data Acquisition System, and were delivered through a headphone. Peak intensity was 70-dB sound-pressure level above normal thresholds. Each average consisted of the responses to 32 pairs of stimuli (3). Data were collected for 100 ms following the click stimulus for

all interpair intervals. Our subjects were instructed to keep their eyes open and still. Subjects were monitored by the technician via video camera given a short break halfway through each C-T protocol. During these short breaks, subjects remained in the recording chamber but were allowed to stretch and blink their eyes.

The P50 wave was identified and measured in each set of averages by using a previously described computer algorithm. The algorithm identified the conditioning P50 wave as the most positive peak between 40 and 80 msec after the first stimulus. P50 amplitude was measured relative to the preceding negativity, and a conditioning wave amplitude of at least 0.5 μ V was required. The test P50 wave was identified as the most positive peak with a latency from the test stimulus within 10 ms of the latency of the conditioning P50 response.

The amplitude of the test P50 wave divided by the amplitude of the conditioning P50 wave, multiplied by 100 (P50 ratio=(test amplitude/conditioning amplitude) x100) and referred to here as the P50 ratio, was used as a measure of auditory gating (23).

Statistical Analysis

The distributions of all variables were checked by Kolmogorov-Smirnov test. Demographical and clinical characteristics and P50 latencies, amplitudes, and P50 ratios of the patients and controls were compared by using independent sample t-test between the two groups, and one-way ANOVA between the four groups (smoker and nonsmoker patients and controls) (post-hoc Bonferroni's test). Gender ratio in patients and controls were compared

using chi-square test. To compare the scores of repeated clinical scales and P50 amplitudes, latencies, and P50 ratios within the groups, paired samples t test was used. Correlations between clinical variables and P50 values were investigated by using Pearson's correlation test.

RESULTS

There was no statistical difference between the age and the gender distribution of the patients and controls. Smoker and nonsmoker patients had similar psychometric scores and clinical features. There were no differences in smoking features (duration of smoking, daily consumption and number of abstinence) between the smoker patients and controls (Table 1).

Effect of smoking on P50 waveform

In both smoker patients and smoker controls, P50 amplitudes and latencies were not statistically different between before and after smoking. There was significant difference only in test latencies between the four groups compared with one way ANOVA. No difference was found by post hoc Bonferroni test between the groups. However, nonsmoker patients had statistically lower test latency and amplitude than those of both smoker and nonsmoker controls comparing independent samples t test as in two groups ($t=3.21$, $p<0.005$; $t=2.09$, $p<0.05$; $t=2.68$, $p<0.05$; $t=2.55$, $p<0.05$, respectively) (Table 2).

There was significant difference in P50 ratio between among the four groups compared with one way ANOVA ($F=19.01$, $p<0.001$). Smoker patients after the restriction

Table 1: Demographical and clinical features of the patients and controls.

Demographical and clinical variables	PATIENTS		CONTROLS	
	Smokers n=23 Mean \pm SD	Nonsmokers n=20 Mean \pm SD	Smokers n=21 Mean \pm SD	Nonsmokers n=23 Mean \pm SD
Age	35.39 \pm 10.78	29.25 \pm 8.40	35.95 \pm 8.24	32.60 \pm 7.44
Male/female ratio	13/10	8/12	13/8	11/12
Duration of smoking (year)	14.59 \pm 11.17	-	14.40 \pm 8.62	-
Daily consumption of cigarette	22.28 \pm 9.49	-	17.75 \pm 8.65	-
Number of abstinence	2.09 \pm 5.97	-	1.38 \pm 4.11	-
Duration of illness (year)	9.63 \pm 6.43	6.55 \pm 3.31	-	-
Age of illness onset	27.15 \pm 8.81	23.80 \pm 8.79	-	-
Number of hospitalization	3.85 \pm 3.46	2.31 \pm 1.63	-	-
SANS score	51.33 \pm 12.15	55.35 \pm 13.93	-	-
SAPS score	33.04 \pm 20.60	35.75 \pm 13.30	-	-
BPRS score	22.33 \pm 10.12	22.30 \pm 7.93	-	-
HAM-D score	8.80 \pm 4.37	6.70 \pm 3.18	-	-
UKU score	5.26 \pm 4.60	5.17 \pm 3.87	-	-

Table 2: P50 amplitudes and latencies of the patients and controls.

	PATIENTS		CONTROLS				
	Smokers n=23 Mean±SD		Nonsmokers n=20 Mean±SD	Smokers n=21 Mean±SD		Nonsmokers n=23 Mean±SD	
	Before smoking	After smoking		Before smoking	After smoking		
Condition latency (ms)	56.65±4.68	53.68±6.83	55.12±4.50	56.17±5.45	54.70±3.90	56.44±8.06	
Condition amplitude (µV)	-1.04±8.35	-1.45±6.30	-2.46±6.45	-4.68±10.08	-3.55±6.54	-1.49±5.72	
Test latency (ms)	55.90±7.58	54.21±6.94	51.75±4.83*	57.35±5.14	58.29±4.60	57.55±7.33	
Test amplitude (µV)	-1.63±7.88	-0.77±2.31	-2.36±5.54*	0.56±1.53	1.25±2.37	1.05±1.19	
P50 ratio	104.75±61.82†	14.17±41.91‡	112.11±120.37§	8.94±23.30	10.05±30.22	19.19±29.30	

*: Lower than those of both smoker and nonsmoker controls

†: Higher than that of smoker controls

‡: Lower than those of both smoker patients before smoking and nonsmoker patients

§: Higher than that of nonsmoker controls

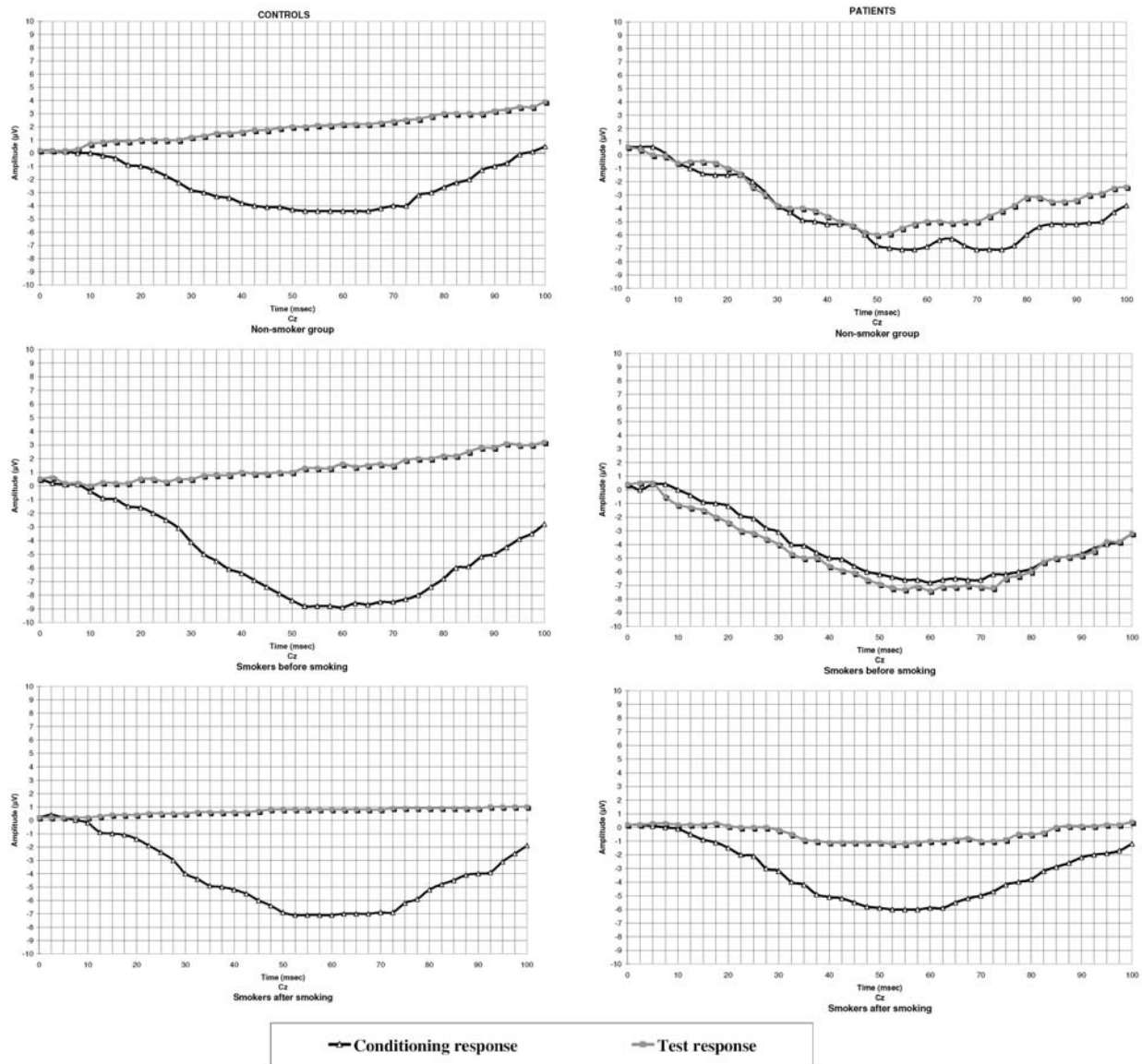


Figure 1: Grand averages of P50 responses of both non-smokers and smokers in patients with schizophrenia and controls, before and after smoking.

Table 3: Effects of smoking on Digit span scores.

Digit span scores	PATIENTS		CONTROLS	
	Smokers n=23 Mean±SD	Nonsmokers n=20 Mean±SD	Smokers n=21 Mean±SD	Nonsmokers n=23 Mean±SD
Digit span forward score (while smoking for smokers)	5.19±1.07*	5.05±1.31	6.35±1.49	5.68±1.53
Digit span backward score (while smoking for smokers)	4.33±1.06*	5.45±5.87	5.80±1.64	5.43±1.82
Digit span forward score (after restriction of smoking)	5.09±1.22*	-	6.20±1.64	-
Digit span backward score (after restriction of smoking)	4.19±0.92*	-	5.70±1.59	-

*: Lower than those of smoker controls.

of smoking (before smoking) and non-smoker patients had significantly high P50 ratios than smoker and non-smoker controls according to post hoc Bonferroni test ($p < 0.001$ for all comparisons). Additionally, according to independent samples t test, P50 ratio after smoking restriction in smoker patients was found higher than in smoker controls ($t = 7.15$, $p < 0.001$). Non-smoker patients also had higher P50 ratio than non-smoker controls ($t = 4.48$, $p < 0.001$). P50 ratio of smoker patients decreased after 30 minutes' smoking compared to that before smoking ($t = 7.07$, $p < 0.001$) and became similar to that of the controls ($t = 1.96$, $p > 0.05$). P50 ratio of the smoker patients after smoking was also lower than that of non-smoker patients ($t = 3.32$, $p < 0.005$). There was no significant difference in P50 ratios between before and after smoking in controls (Table 2). Grand averages of test and conditioning responses of patients and controls, before and after smoking, are shown in Figure 1.

Smoking effect on digit span scores

Digit span forward and backward scores of the smoker patients were lower than those of the smoker controls both while smoking and after the restriction of smoking ($t = 2.85$, $p < 0.05$; $t = 3.41$, $p < 0.005$; $t = 2.45$, $p < 0.05$; $t = 3.73$, $p < 0.005$, respectively). There was no effect of smoking restriction on digit span scores. It was found that digit span scores were not different between the smoker and non-smoker patients and between the smoker and non-smoker controls (Table 3).

Treatment effect on P50 ratios

The patients were divided into subgroups according to their treatment status as follows:; Ppatients who received

were on "no drug" ($n = 9$), "on atypical antipsychotics" ($n = 24$) or "on typical antipsychotics" ($n = 10$). There was no significant difference in P50 ratios among subgroups, but all patient groups had higher P50 ratios than the controls ($p < 0.05$, $p < 0.001$, $p < 0.001$; respectively).

When all patients were evaluated, there were strong positive correlations between the condition latency and the test latency and between the condition amplitude and the test amplitude ($r = 0.52$, $p < 0.001$; $r = 0.87$, $p < 0.001$; respectively). In smoker patients, the duration of smoking was negatively correlated with both digit span forward and backward scores while smoking and after the restriction of smoking ($r = 0.51$, $p < 0.05$; $r = 0.55$, $p < 0.01$; $r = 0.47$, $p < 0.05$; $r = 0.65$, $p < 0.005$; respectively). There were positive correlation between P50 ratio and both duration of smoking and number of abstinence attempts in smoker patients before smoking ($r = 0.49$, $p < 0.05$; $r = 0.57$, $p < 0.05$). There was no similar correlation in smoker controls.

DISCUSSION

Consistent with previous research, schizophrenic patients overall exhibited higher P50 ratios than those of the controls in this study. In the smoker patients group, after overnight abstinence from cigarettes, P50 ratio in post-smoking trial decreased significantly and became similar to the value of smoker controls. Additionally, P50 ratios of non-smoker schizophrenic patients were found to be significantly higher than those of non-smoker controls. Taking all these findings together, we can suggest that cigarette smoking transiently normalizes the deficit in the sensory gating mechanism in the schizophrenic patients. However, it seems that continual smoking has no effect on

sensory gating in schizophrenics in the long run.

It is thought that sensory gating abnormalities are associated with cholinergic and cognitive disturbances in schizophrenic patients. Central cholinergic system is known to participate in memory formation and volitional behaviours. Abnormalities in cholinergic system cause some problems in these functions and thus, may be playing an important role in the pathophysiology of schizophrenia (24). Alterations in nicotinic receptors in the hippocampus and cortical regions may be involved in cognitive symptoms of schizophrenia. Expression of the α -7 nicotinic receptor, which binds to nicotine with low affinity, was found to be reduced in the hippocampus of schizophrenics (15). Thus, it can be suggested that schizophrenic patients exert to treat cognitive symptoms by stimulating the nicotinic receptors, which are already decreased, by smoking ie.ge. self medication. However, since the half-life of nicotine is very short; this exertion may be remaining insufficient or transient in improving cognitive symptoms. Probably nicotine ameliorates some symptoms of schizophrenia transiently for a short duration, thus; it may be difficult to observe this effect clinically. Moreover, nicotinic receptors have been reported to show desensitization after long-term exposure to nicotine. Thus, the effect of nicotine on cognitive symptoms decreases in time (25). As a probable result of this, digit span task scores of the patients showed that nicotine is unsuccessful to improve at least some of cognitive symptoms in schizophrenic patients. On the other hand, the finding of 'the duration of smoking was negatively correlated with digit span scores' might be due to the desensitization of nicotinic receptors with time. Additionally, in the study it was found that nicotine abstinence had no effect on digit span scores.

There are inconsistent findings regarding the relationship between smoking and side effects of neuroleptics. In this study we found that smoking status had no effect on the side effects of antipsychotics. Consistently, in a previous study it was demonstrated that heavy smoking was not associated with akathisia in schizophrenia (26). However, in another study it was suggested that smoking reduces antipsychotic induced akathisia in schizophrenic patients (27). In contrast, in another study it was showed that smoking alleviates parkinsonism due to antipsychotics in schizophrenic patients (4) probably via enhancing effect of nicotine on

central dopaminergic activity (28). Altogether, it can be concluded that it is not clear whether smoking relieves extrapyramidal side effects of neuroleptics.

In the present study, it seemed that antipsychotic treatment had no effect on P50 amplitude, no matter which group of neuroleptics, the patients were on has no effect on P50 amplitude. In a previous study it was shown that among atypical medications only clozapine had significant normalizing effect on P50 ratio (11). Interestingly, it was reported that among antipsychotics, only clozapine treatment diminishes smoking behaviour in schizophrenic patients (29). Given these findings together, it may be thought that patients try to ameliorate sensory gate disorder and cognitive disturbance by smoking.

Since nicotinic receptors are reduced in schizophrenia and this reduction is thought to cause cognitive symptoms such as memory and learning deficits (30), recent studies have used galantamine, a cholinesterase inhibitor and allosteric modulator of the α 7 nicotinic receptors, to treat cognitive symptoms in schizophrenia. Indeed, some improvements have been observed in cognitive symptoms of schizophrenic patients in these studies (31,32). Therefore, it can be targeted to develop longer-life agonist agents on α 7 nicotinic receptors to enhance nicotinic activity for cognitive improvement in schizophrenics. At this point there are promising developments such as DMXBBA, a selective partial α 7 nicotinic agonist (33).

In this study, it was found that sensory gating functions and, its reflection, P50 ratio are not different between before and after smoking in the control smokers opposite to the schizophrenic patients. Thus, we can conclude that smoking may have enhancing effect on only defective sensory gating, but not on normal gating; and that a deficit in sensory gating in schizophrenics may be one of the reasons for higher smoking rates in the patients.

To our knowledge this is the first study using both non-smoking control and non-smoking patient groups to compare smoking patients and healthy subjects. This allowed us to evaluate more accurately the sensory gating function of smoking and non-smoking patients, and the effects of acute and long-term effects of smoking in the patients and controls.

In conclusion, the present study supports P50 non-suppression which is a reflection of cognitive disturbances in schizophrenic patients. Acute nicotine usage improves P50 sensory gating deficit in schizophrenic patients. It

may be suggesting the importance of additional nicotinic treatments of cognitive symptoms in schizophrenia. Schizophrenic patients may be trying to treat their cognitive symptoms by smoking since antipsychotics and

other known treatments may not be sufficient to ameliorate cognitive symptoms. At this point, it will be better to develop long half-life nicotine-like drugs to solve this problem.

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