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# Relationship Between P300 Findings and Neurological Soft Signs in Patients with First Episode Schizophrenia

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**ABSTRACT**

Relationship between P300 findings and neurological soft signs in patients with first episode schizophrenia

**Objective:** In this study, the relationship between neurological soft signs and P300 components was explored in patients with schizophrenia.

**Method:** 22 first-episode schizophrenia patients who were evaluated according to DSM-IV criteria and whose disease lasted at least six months, and a group of 22 healthy controls were included in this study. In both groups, neurophysiological measurements were performed to investigate the P300 potentials and Neurological Evaluation Scale (NES) was applied to detect neurological soft signs. Scale for the Assessment of the Negative Symptoms (SANS) and Scale for the Assessment of the Positive Symptoms (SAPS) were applied only to the schizophrenia group.

**Results:** Results revealed that first episode schizophrenia group had higher NES total and subscale scores, lower P300 amplitude and longer P300 latency compared to healthy controls. NES scores with the highest significant difference from healthy controls were Total NES and NES motor sequencing subscale. When the first-episode schizophrenia group is compared with the control group by the P300 components, difference of P300 amplitude was more significant than difference of P300 latency. It was also found that NES scores and P300 values were not correlated with clinical variables in the patient group.

**Conclusion:** These findings indicate that pathology of these biological markers was found at the beginning of the disease and was not effected by clinical variables. This result can be interpreted as the pathologies exhibited with NES and P300 measurements could not be state but trait characteristics. Within soft neurological signs the most pathological results were obtained from motor sequencing subscale and its relationship with P300 amplitude was statistically significant. These findings indicate that the high scores of motor sequencing subscale which is thought to be sign of prefrontal pathology can be better explained with problems about attention.

**Key words:** Schizophrenia, neurological soft signs, P300

**ÖZET**

Şizofreni hastalarında ilk atakta P300 bulguları ile nörolojik silik işaretler arasındaki ilişki

**Amaç:** Bu çalışmada, şizofreni hastalarında nörolojik silik işaretler ile P300 değerlerinin arasındaki ilişki araştırılmıştır.

**Yöntem:** Çalışmaya, DSM-IV'e göre ilk atak şizofreni tanı ölçütlerini karşılayan, hastalığı en az 6 ay sürmüş olan 22 olgu ve kontrol grubu olarak 22 sağlıklı birey dahil edilmiştir. Olgulara, uyarılmış potansiyellerin P300 komponentini araştırmak için nörofizyolojik ölçümler ve nörolojik silik işaretleri saptamak için Nörolojik Değerlendirme Ölçeği (NES) uygulanmıştır. Şizofreni grubunun klinik özellikleri için Negatif Belirtileri Değerlendirme Ölçeği (SANS) ve Pozitif Belirtileri Değerlendirme Ölçeği (SAPS) uygulanmıştır.

**Bulgular:** Çalışmanın sonucunda, ilk atak şizofreni grubunun, sağlıklı kontrol grubuna göre NES toplam ve alt ölçek puanlarının daha yüksek, P300 amplitüdünün daha düşük ve P300 latansının daha uzun olduğu bulunmuştur. Sağlıklı kontrol grubuna göre, anlamlı farklılığın en fazla olduğu NES alt ölçekleri, Karmaşık Motor Eylemler Dizisi (KMED) ve toplam puan olarak saptanmıştır. İlk atak şizofreni olgularında P300 amplitüd farklılığının daha anlamlı olduğu sonucuna varılmıştır. Hasta grubunda, NES puanları ve P300 değerlerinin klinik değişkenlerle ilişkisinin olmadığı görülmüştür.

**Sonuç:** Sonuçlar, bu biyolojik belirteçlerle ilgili bozukluğun hastalığın başlangıcında da bulunduğuna ve klinik değişkenlerden etkilenmediğine işaret etmektedir. Yine bu sonuçlar, P300 ve NES değerlendirme ölçeğiyle gösterilen bozuklukların durumsal değil, yatkınlaştırıcı/yapısal özellikler olabileceği şeklinde yorumlanabilir. Ayrıca nörolojik silik işaretlerle ilgili olarak ise, daha çok karmaşık motor eylemlerin sıraya konulmasında problem olduğu ve bunun P300 amplitüdü ile ilişkisinin anlamlı olduğu saptanmıştır. Bu durum, prefrontal bölge patolojilerine işaret ettiği değerlendirilen KMED alt ölçeğindeki yüksek puanların, daha çok dikkat alanındaki problemlerle açıklanabileceğine işaret etmektedir.

**Anahtar kelimeler:** Şizofreni, nörolojik silik işaretler, P300

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## INTRODUCTION

Schizophrenia affects about 1% of the general population, usually begins before the age of 25, continues throughout life and occurs in people of all social classes. The basic feature of schizophrenia is the loss of reality testing ability. This manifests as a clinical situation by, delusions, hallucinations and disorganized behavior which indicate the cause-effect relationships. Although schizophrenia is discussed as a single disease, diagnostic category includes a group of disorders with probably a heterogeneous etiology and similar behavioral symptoms. Technological developments in the second half of the twentieth century accelerated the studies on the role of biological factors as of the causes of psychotic disorders. Neurochemical and neuroendocrinologic studies focusing to the etiology permitted to achieve the important steps (1).

In the studies on hemispherical properties of behavior a variety of methods have been used. It has been reported that these methods were the behavioral evaluation, electrophysiological studies (EEG, ERP); brain imaging studies (PET, fMRI) and divided visual field experiments involving dichotic listening in a variety of regional brain-injured patients (2). By means of advanced neuroimaging techniques, the changes of neuronal activity in the brains of people with schizophrenia can be measured directly. However, as a relatively older and consistent finding, the reduced P300 amplitude is still the main evidence for the change of normal neuronal physiology in schizophrenia (3).

P300 is a positive potential having a peak after 300 ms of the target stimulus and showing maximum amplitude in the parietal and central areas. It has been suggested that the many of the brain areas can be a source for P300 component. In healthy subjects, it has been considered that two primary brain regions give rise to P300 wave. These regions are the posterior parietal and the frontal cortical regions. This is because, while an unexpected stimulus directed to the passive recognition process during the scattered attention gives rise to P300 wave in the frontal region, the same stimulus directed to the active recognition process forms P300 wave in the posterior parietal region. Reduced P300 amplitude is a strong finding in patients with schizophrenia; in first-episode patients, after one year of the schizophrenia onset a test repetition has been shown to be consistent (4-7). Mathalon et al (8) in their longitudinal study showed that P300 amplitude were lower than controls even in the best clinical situations of the patients. In schizophrenia, the P300 latency is one of the values which were also investigated. While in most studies showed that the P300 latency is normal, others found delayed latency (9-10).

Many of studies pointed out the relationship between of neurological soft signs (NSI) and the schizophrenia pathophysiology. NSI incidence is about 60% of patients with schizophrenia (11). Compared with controls, high NSI rates were found in first-episode patients who were on treatment or not (12, 13).

As we explained above, with various theories the attempts aiming to fill the gap between biological changes and clinical experiences were made. Generally in the studies on schizophrenia patients, prolonged latency and decreased amplitude of P300 suggesting cortical hypofunction were found (14). Studies investigated on which neural circuits were in association with the neurological soft signs found that the sequential movements and complex motor actions were related to the frontal region and the other brain regions such as bilateral sensory motor, left parietal, and the right cerebellum were involved in more complex tasks (15).

In this study, the changes in the electrophysiological measuring method P300 and the relationship with NSI in schizophrenia have been aimed to be illuminated.

## METHOD

In this study, 22 male patients diagnosed with schizophrenia in the diagnostic process following a psychotic disorder and a control group including 22 healthy male without any psychiatric diagnosis were included. All patients had admitted to Psychiatry Department of Gulhane Military Medical Academy and accepted to participate in the study by themselves or their caregivers. The healthy males were selected by random sampling method and matched for age and education level. Psychotic disorder and schizophrenia

were diagnosed according to DSM-IV criteria. Those with a history of medical or psychiatric illness and those with a history of substance use were excluded. While psychiatric evaluation of the patients and the control group were performed by a psychiatrist, neurological evaluation and P300 application were performed by a neurologist. Following assessments were performed for the patients and the control group:

**Structured Diagnostic Interview for DSM-IV Axis I (SCID-I):** A semi-structured assessment scale developed by First et al. (16). Turkish version of the scale of which the validity and reliability have been studied was used.

**Scale for the Assessment of Negative Symptoms (SANS)** was developed in 1983 by Andreasen and the validity and reliability study was carried out by Erkoç et al (17) after the translation in Turkish. It consists of five subscales, including affective flattening or blunting, alogia, avolition-apathy, anhedonia-asociality and attention.

**Scale for the Assessment of Positive Symptoms (SAPS):** was developed in 1984 by Andreasen and the validity and reliability study was carried out by Erkoç et al (18) after the translation in Turkish. It consists of five subscales, including hallucinations, delusions, bizarre behavior, positive formal thought disorder and inappropriate affect.

**Neurological Evaluation Scale (NES)** was developed in 1989 by Buchanon and Heinrichs (19). Disorders in three different functional area is evaluated; 1. Sensory integration dysfunction (SID): extinction, graphesthesia, stereognozis, right-left confusion, impaired auditory-visual integrity, 2. Motor coordination disorder (MCD): consecutive walk, uncontrolled movements, finger-nose test, finger-thumb reciprocity test, 3. Complex motor sequencing (frontal neurological signs) (CMS): Fist-ring test, fist edge-palm test, Ozeretski test, rhythm test. In addition, abnormalities in eye movements (convergence, continuity point of view), short-and long-term memory and developmental reflexes are also evaluated.

**P300:** The P300 component, often obtained by called "staggered stimuli" (oddball paradigm). In this mechanism, two stimuli which one of them appears infrequent than other are applied randomly. While the frequent stimuli are called as standard, infrequent stimuli are called "deviant". When the subject is asked to count infrequent or stimuli, or to respond to these stimuli, the N200 and P300 responses occur with the target stimulus but these responses are not derived from the standard stimuli. Evaluation was performed in a well-lit and quite room using 4-channel Esaote (Italy) EMG-EP device and ERP were recorded. Impedances were kept below 5 kΩ. Auditory stimuli in both ears were used with hearing threshold intensity value above 60 dB. Frequency was determined as 1800 Hz and 2800 Hz for non-target and target stimuli, respectively. The stimulus frequency was 0.7/s, the screen width (sweep) was 500 ms; "prestimulus delay" was given as 200 ms. Subjects were asked to count the random target stimuli occurring with 20% frequency among non-target stimuli repeated with 80% frequency. Recording was continued until obtaining 40 target stimuli. Recordings were repeated two times. During the data analysis, the point Cz which was the best record was taken into consideration. Because the difference was not statistically significant, the other records were not evaluated.

### Statistical Analysis

In this study, statistical analysis was performed by using JMP statistical program. To assess the data, the descriptive statistical methods (mean, standard deviation), as well as Kruskal-Wallis test for comparisons between groups, Pearson, Spearman and Kendall correlation tests for the relationship between variables and Roc Curve analysis for evaluation of the method diagnostic benefit were used. The results are assessed at the $p < 0.05$ level of the significance.

## RESULTS

Socio-demographic characteristics of patients and control group included in the study are given in Table 1 (Table 1). All patients were male. The mean age 22.77±1.06, the average education level was 10.14±1.31 years. The mean age of the control group 22.32±1.30,

the average education level was 10.18±1.27 years. In terms of age and education level between cases and control group no statistically significant differences were found (p>0.05).

The clinical characteristics of the patients are given in Table 2 (Table 2). The mean SANS score and SAPS score were 46.45±10.49 and 29.95±7.22, respectively. Mean age of the disease onset was 22.77±1.06. Rate of the schizophrenic patients in the family was 0,045 (n=1) and 0.090 (n=2) in control group and the patient group, respectively. But the difference was not significant ($\chi^2$=0.364, p=0.5462).

The P300 results of the cases are given in Table 3 (Table 3). The average amplitude and average latency of the patients were 2.78±0.93 μV and 342±12.51 ms, respectively. The average amplitude and average latency of the healthy control group were 17.99±4.64 μV and 312±7.19 ms, respectively. Compared with the healthy control group, patients had significantly lower P300 amplitudes and longer latencies (based on Kruskal-Wallis test, p<0.001).

NES results of the patients are given in Table 4

**Table 1: Socio-demographic characteristics of the study population**

| | Group | | |
|---|---|---|---|
| **Parameter** | **Schizophrenia (n=22)** | **Control (n=22)** | **Statistical analysis (t,df,p)** |
| Age, mean±S.D | 22.77±1.06 | 22.32±1.30 | t=2.080, df=21, p=0.814 |
| Duration of the education, mean±S.D. | 10.14±1.31 | 10.18±1.27 | t=2.080, df=21, p=0.544 |

t: Student t test, S.D.: Standard Deviation

**Table 2: Clinical characteristics of the study population**

| | Group | | |
|---|---|---|---|
| **Parameter** | **Schizophrenia (n=22)** | **Control (n=22)** | **Statistical analysis** |
| SAPS: mean±S.D. | 29.95±7.22 | - | - |
| SANS: mean±S.D. | 46.45±10.49 | - | - |
| Age of disease onset: mean±S.D. | 22.77±1.06 | - | - |
| Family history: | 0.090 | 0.045 | $\chi^2$=0.364, p=0.54 |

$\chi^2$: Ki kare test, SAPS: Scale for the Assessment of Positive Symptoms; SANS: Scale for the Assessment of Negative Symptoms, S.D.: Standard Deviation

**Table 3: P300 results of the study population**

| | Group | | | |
|---|---|---|---|---|
| **Parameter** | **Schizophrenia (n=22)** | **Control (n=22)** | **t** | **p** |
| P300 amplitude (μV): mean±S.D. | 2.78±0.93 | 17.99±4.64 | 2.080 | <0.001 |
| P300 latency (ms): mean±S.D. | 342±12.51 | 312±7.19 | 2.080 | <0.001 |

t: Student t test, S.D.: Standard Deviation

**Table 4: NES results of the study population**

| | Group | | | |
|---|---|---|---|---|
| **Parameter** | **Schizophrenia (n=22)** | **Control (n=22)** | **t** | **p** |
| SID: mean±S.D. | 4.05±1.00 | 1.14±0.46 | 2.080 | 0.052 |
| CMS: mean±S.D. | 4.77±0.88 | 1.18±0.49 | 2.080 | 0.0001 |
| MCD: mean±S.D. | 2.27±0.83 | 0.41±0.22 | 2.080 | 0.125 |
| NES total: mean±S.D. | 21.27±2.77 | 4.18±1.29 | 2.080 | <0.0001 |

SID: Sensory Integration Dysfunction, CMS: Complex Motor Sequencing,
MCD: Motor Coordination Disorder, NES: Neurological Evaluation Scale
t: Student t test, S.D.: Standard Deviation

(Table 4). The significant difference between the patients and controls was found in mean total NES and CMS scores ($p<0.001$). When the relationship between the CMS and SANS/SAPS scores was assessed, CMS correlation coefficients for both variables had no statistically significant difference ($p=0.88$ and $p=0.92$). When the relationship between the total NES and SANS/SAPS scores was assessed, it was observed that correlation coefficients of total NES score for both variables had no statistically significant difference ($p=0.91$ and $p=0.68$, respectively).

All variables were in the inverse relationship with P300 amplitude. The highest association was with the total NES and CMS. Non-parametric P correlation coefficients of Kendall's and Spearman's were also significant. $p=0.02$ and $p<0.001$ were found for SID and P300 latency variables and for all others, respectively.

The coefficient estimates of the relationship between SANS/SAPS and P300 amplitude values: there was no significant correlation between P300 amplitude with the SAPS. Between the amplitude of the P300 with the SANS there was a more meaningful association compared to SAPS but it had still statistically no significant association ($p=0.35$ and $p=0.78$).

## DISCUSSION

The aim of the study is to investigate the relationship and confirmability between the abnormalities in the event-related potentials (ERP) P300 wave which is alleged as "the biological determinants" and the neurological soft signs in schizophrenia. For this purpose, in first-episode psychosis patients with in the initial stage of the disease, P300 measurement was performed and NES scale was applied to assess neurological soft signs before the treatment. The same measurements were used for the healthy control group to compare and elucidate the differences.

In this study, it was found that the latency of P300 which is one of the late auditory ERP component was delayed and the amplitude of P300 was low. This is compatible with the finding previously reported in schizophrenic patients. Since the first study by Roth and Cannon (20), almost all studies conducting with the evoked potential in schizophrenic patients, confirmed the findings of a prolonged P300 latency and reduced P300 amplitude. Duncan and colleagues (21) demonstrated the prolonged P300 latency and the reduced P300 amplitude in patient with no treatment because of remission. Other two studies showed that P300 values were improved with antipsychotic treatment in patients with schizophrenia, but it could not reach to the level of normal controls (22,23).

In this study, the P300 amplitude was found as statistically significant variable for the disease description. Significantly prolonged P300 latency was found in the patient group compared with controls and proved to have the disease description feature, but it was concluded that this feature was weaker than it was with P300 amplitude.

P300 variables are assessed to have disease description features and this information is consistent with the study results. Differences between the patients and controls in terms of P300 variables may indicate a core disorder regardless of the clinical situation or reflect the clinical symptomatology. In their first study published in 1992 Roth and Cannon (20) stated that the changes in P300 reflect the fluctuations of cognitive functions in schizophrenia and these changes were specific for the period of the active disease. Indeed, P300 is assessed as an indicator of the functions related to cognitive processes in both normal subjects and patients with psychopathology. P300 response reflects the task-related cognitive processes such as attention, expectation and context updating. In other words, the P300 is a measurement of the neuronal activity underlying of the processes of immediate memory and attention addressing. While P300 amplitude is associated with the sources of attention directed to the task, the latency indicates the speed of stimulus classification. Therefore, reduced amplitude and prolonged latency in patients with schizophrenia are compatible with the cognitive function disorders shaping the symptomatology. However, subsequent studies have conflicting results (24).

Higashima and colleagues (25) reached the conclusions supporting that the P300 amplitude recorded from the left hemisphere may be used as a

situational marker reflecting the severity of positive symptoms. Pallanti et al (26) revealed that there was no association between the P300 values and SANS, SAPS and the Brief Psychiatric Rating Scale (BPRS) scores. Frodl et al (27) reported that there was no association between the P300 values and negative symptoms and family history of disease had no effect on P300 values. As it is shown, the different results were found in literature. In our study, it was concluded that the severity or presence of positive or negative symptoms have no association with the P300 amplitude or latency values. The difference in P300 values between the patients and the normal controls values in the beginning of the disease, before the significant progress and destruction, supports the hypothesis of predisposing feature (28). In our study, it was concluded that there was no significant relationship between the P300 values and clinical variables. This result supports the predisposing feature of P300.

Neurological soft signs are one of the other factor claiming to be the biological determinant. In this study, the NES was applied to the patients. In various studies, it has been shown that both total and sub-scale scores of complex motor actions were high in patients with schizophrenia than in healthy controls. In this study, as in accordance with the publications, it has been shown that the neurological soft signs were significantly higher in schizophrenic patients than in healthy controls. In particular, the total score and subscales scores of complex motor actions were significantly higher in patients compared with controls.

On the basis of the Neurological Evaluation Scale subscales; while Ismail et al (29) concluded that NES total and MCD subscale scores were significantly higher in patients than in controls, Lawrie et al (30) demonstrated that the NES total and SID subscale scores were more significantly higher in patients. In our study, it was concluded that the NES total and SID subscale scores were significantly higher in the patient group. CMS subscales include fist-edge-palm, fist-ring test, Ozeretski test, go / no go test, keeping the rhythm (with the hands and feet) and show the prefrontal lobe pathology. In general, it is considered that patients with schizophrenia are not able to activate some areas in the prefrontal cortex (31). This was demonstrated in some patients with PET and fMRI. Significantly higher NSS associated with the prefrontal region in the patients group is consistent with the etiologic basis of the disease. There are some studies concluded that the NSS has both situational and predisposing/ structural features in schizophrenia. In the early stages of the disease in which the symptoms fluctuate, the situational characteristics of the active disease process may be dominant (32). We also concluded that there was no significant association between the clinical variables and NSS. This conclusion also supports of the predisposing/ structural nature of NSS.

The presence of both the P300 and NSS pathologies indicates that the schizophrenia is a brain disease having a biologic basis. In addition, the presence of these pathologies reflects the deterioration of cognitive functions and they are considered as biological markers showing cognitive dysfunction in schizophrenia patients. It is thought that P300 and neurological soft signs are formed from the similar brain regions. It has been suggested that many of the brain areas may be source of P300 component. In healthy subjects, it has been considered that two primary brain regions give rise to P300 wave. These regions are the posterior parietal and the frontal cortical regions. Similarly, the findings of examinations in order to evaluate neurological soft signs indicate pathology originated from the frontal and parietal regions. In terms of a relationship between the clinical appearance and P300 pathology and neurological soft signs, studies investigated the relationship between symptomatology and both evaluation method reported different results. In this respect, it seems that it is not possible to use the clear statements about common clinical manifestations of findings in the field of the P300 and NSS.

In terms of cognitive functions, comparison between the patients having P300 pathologies or neurological soft signs, subjects having deviations in both assessment tools indicated neurocognitive problems. While the pathologies in P300 component reflect the disturbances in stimulus evaluation rate, attention and memory; NSS reflect the disturbances in motor coordination, executive function, attention and memory areas.

In the literature, there is no study on the relationship between the P300 values and neurologic soft signs. In this study, it has been found that the P300 amplitude had significant correlation with the scores of the total NES and CMS subscales. Both assessment tools provide information about the cognitive functions particularly in the areas of attention and memory. The parameters evaluated in the CMS subscales are related to the prefrontal area. The working memory and the attention measured by the P300 are the functions of in this field. This is also considered as evidence supporting the relationship between P300 and NSS.

The limitations of this study are the small size of the study population and first-episode patients with severe positive symptoms could not be included in the study. With the follow-up studies observing in the changes in first-episode patients during the remission and drug use will give clear information about the conclusions.

## CONCLUSION

The results of the study can be summarized as follows:

1) In the first-episode schizophrenia which is the recently onset without drug treatment, P300 amplitude was lower and P300 latency was longer than in the normal controls.
2) In the examination of NSS as another biological sign, CMS and total NSS scores were significantly higher in the patient group.
3) P300 amplitude was found to be associated especially with CMS subscale scores of NES.
4) P300 values, and the NES scale scores were not associated with clinical variables.
5) P300 amplitude, the NES total and CMS subscale scores can be used as biological markers to support the diagnosis.

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