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ORIGINAL ARTICLE

Movement Releated Cortical Potentials Obtained by Saccadic Eye Movements In Multiple Sclerosis

Multiple Sklerozda Sakkadik Göz Hareketleri ile elde edilen Devinime İlişkin Kortikal Potansiyeller

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ABSTRACT

Introduction
Movement Related Cortical Potentials (MRCP) are a non-widespread electrophysiological study of clinical use.It demostrates brain mechanisms that appear in cortex during planning and preparing movement by electrophysiologic findings.We aimed to evaluate MRCP that occur due to saccadic eye movement in Multiple Sclerosis (MS).
Material and methods: Twenty-five patients in 18-55 age group and with well cognitive functions who were diagnosed as multiple sclerosis according to Mc Donalds criteria with 0-5 Expanded Disability Status Scala (EDSS) and 20 healthy volunteers in a similar age range were included.
Results: We could not distinguish clearly all the previously reported components of the MRCP in the records.However,it was observed that the latency of the BP group(Bereitshaftpotential, preparation potential) of both groups was longer in the patient group when the latency values were consistent with the values reported in the literature.The amplitude of the PP(peak-pit),which can be regarded as a component of NS(negative slope) and MP(motor potential),is higher in the patient group and may indicate that the target is more difficult in the patient group.
Conclusions: Studies on cognitive impairment in multiple sclerosis have generally been conducted through neuropsychological tests.However,the small number of patients was one of the biggest factors that limited us.The mean EDSS score in our patient group was also low.Although we could not obtain a record that corresponds to the typical MRCP pattern in the literature,we believe that we can make a small contribution by adding new question marks to the MRCP studies with the results we obtained.

Key Words: Movement related cortical potentials, multiple sclerosis, saccadic eye movement, neurology, electrophysiology, cognitive impairement

ÖZ

Amaç: Devinime İlişkin Kortikal Potansiyellerin (DİP) sakkadik göz hareketleriyle Multipl Skleroz' (MS) lu hasta grubunda elde edilmesi amaçlandı.
Gereç ve Yöntem: Çalışma Multiple Skleroz polikliniğinde takipli Mc Donalds kriterlerine uygun olarak multipl skleroz tanısı almış,18-55 yaş aralığında, EDSS 0-5 arasında olan çalışmaya uyum sağlayabileceği düşünülen, bilişsel fonksiyonları iyi olan, 25 MS hastası ve benzer yaş aralığında 20 sağlıklı gönüllü ile yapıldı. Horizontal istemli konjuge bakış ile DİP kayıtlaması ve averajı işlemi Micromed, Brainquick, 32 kanallı EEG cihazında yapıldı.
Bulgular: Hasta ve kontrol grubunda yaptığımız kayıtlamalarda DİP'in daha önce bildirilmiş tüm komponentlerinin net ayrımı yapılamadı. Ancak her iki grubun BP (Bereitshaftpotential, hazırlık potansiyelinin başlangıcı) latans değerleri literatürde bildirilen değerlerle uyumlu bulunduğu halde hasta grubunda latansın daha uzun olduğu gözlendi. NS (Negative slope) ve MP' (Motor potansiyel) in bileşeni olarak kabul edilebilecek olan TÇ' (tepe-çukur) nin amplitüdü ise hasta grubunda daha yüksek bulundu ve hasta grubunda hedefin daha zor bulunduğuna işaret edebileceği düşünüldü.
Sonuç: Multipl sklerozda kognitif bozulma ile ilgili çalışmalar genel olarak nöropsikolojik testler üzerinden yürütülmüştür. Bizim çalışmamız MS tanısı ile takip edilen hastalarda kognitif bozulmayı nörofizyolojik testlerle objektif olarak ortaya koyması bakımından değerlidir ancak daha anlamlı sonuçlar elde edebilmek için yüksek sayıda hasta ve kontrol grubunda, EDSS ile kolerasyonun değerlendirildiği , farklı hareket paternlerine dayanan devinme ilişkin kortikal potansiyel çalışmalarının geliştirilmesi planlanmalıdır.

Anahtar Kelimeler: Hareketle ilgili kortikal potansiyeller, multipl skleroz, sakkadik göz hareketi, nöroloji, elektrofizyoloji, bilişsel bozukluk

Introduction

Undoubtedly, the most important quality that leads humans to science is curiosity. Despite all the advances in technology, our knowledge about the central nervous system (CNS), especially the brain and its functioning, is still limited. An electrophysiological technology that has recently gained momentum is the measurement of movement-related cortical potentials (MRCPs), even though clinical use is not widespread. (1-3)

MRCPs can be noninvasively recorded from the scalp using a recording device that is triggered by the initiation of the EMG activity that occurs before and during voluntary movement. MRCPs can be used to investigate the neural mechanisms associated with motion and to reveal the connections within the motor system. For this reason, MRCPs are measured in studies of movement disorders and cognitive disorders

because they allow insight into the preparation phase prior to the onset of movement and therefore represent cognitive potential. There are also MRCP studies involving patients with Parkinson's disease and Alzheimer's disease reported in the literature.(1,2)

Studies have shown arm, foot, and saccadic eye movements are generated by MRCPs.(3) However, the majority of the MRCP studies in the literature have been conducted using hand or finger movements. Here, we studied the potentials related to revolution, which are evoked potentials of interest in both neurology and psychiatry. Unlike previous studies, we planned to record MRCPs using saccadic eye movements, rather than limb movements, in patients with multiple sclerosis (MS) to determine whether the MRCPs reveal cognitive impairment, which is suggested in the early stages of the disease. In other words, we wished to investigate whether the disease is reflected in the MRCPs and whether the widespread demyelination affects the regions responsible for saccadic eye movements in the brain.

MS is a chronic, inflammatory disease characterized by focal demyelinated plaques primarily in the CNS that may also affect the cortex and deep gray matter.(4) MS is the prototype of demyelinating diseases and is the leading cause of disability in young adults.(5) In addition to demyelination, developing axonal degeneration is accepted as the main cause of irreversible neurological disability in the course of the disease.(4) The etiology of MS has not been elucidated, but it is thought that in individuals who are genetically predisposed, a trigger encountered in early life causes demyelination by stimulating the autoimmune mechanism over time.(6)

Symptoms usually begin in young adulthood, between the ages of 20 and 40 years.(7) Inflammation may occur anywhere in the brain, spinal cord, and optic nerve and may be clinically relevant with any symptom of the CNS depending on the site involved. Objective examination findings are often accompanied by fatigue, depression, and cognitive impairment and constitute an important part of patients' complaints. (8) Although the presence of mental symptoms in MS has been known for a long time, studies in this area have increased in recent years.(9) It is thought that MS, which has been defined as a white-matter disease for many years, also causes cortical atrophy of gray matter, resulting in cognitive impairment.(10)

The aim of this study was to examine the electrophysiological background in MS by recording, interpreting, and comparing the MRCP in patients with MS and in healthy individuals. The MRCPs were recorded using saccadic eye movements.

Patients and Methods

This study was approved by the Necmettin Erbakan University Meram Faculty of Medicine Clinical Research Ethics Committee on 27/01/2011 (2010/009). Twenty-five patients aged 18–55 years with good cognitive functions who were diagnosed with MS according to the McDonald criteria in the MS outpatient clinic and scored 0–5 on the Expanded Disability Status Scale (EDSS) were included. Twenty healthy volunteers in a similar age range also participated in the study.

Informed consent was obtained from all subjects before the study, and all patients underwent neurological examination. Patients who had cognitive disorders, marked vision loss, impaired eye movement, nystagmus, titodation, and other involuntary movements were excluded from the study. In the patient and control groups, no alcohol or sedative drugs that negatively affect eye movements and cognitive functions were used in the last 72 hours.

Voluntary horizontal conjugate gaze and MRCPs were recorded and averaged using a Micromed Brainquick 32 channel EEG device in the Neurosensory Laboratory at the Neurology Department of the Meram Faculty of Medicine Hospital at Necmettin Erbakan University. During the recording, the subjects were seated in a comfortable chair in a quiet environment, and the optimum conditions were ensured by avoiding head movements during recording.

The subjects were placed at a fixed distance of 120 cm and positioned at a 20-degree angle from signs placed horizontally on a wall. Subjects were informed about the procedure. When the subject was seated, the opposite point was the primary position, the sign on the right was the right point of view, and the side on the left was the left point of view. The subject was told to fix his or her eyes on a specified target and not make any eye movement until the next instruction was given.

To measure the horizontal conjugate gaze, 0.5 cm Ag-AgCL superficial disc electrodes were placed in each lateral epicantus, and Cz was recorded as the reference point. High-pass 1 Hz and low-pass 5.300 values were set for the DC 1 channel to detect the onset of deflection of the voluntary horizontal gaze. MRCP recordings were performed using 0.5 cm Ag-AgCL superficial disc electrodes placed on the skin of the scalp, according to the international 10-20 system, to optimize detection of motor potential (MP) from the contralateral motor cortex. The earth electrode was connected to the Fpz point using a superficial disc electrode. A high-pass value of 10 Hz and a low-pass value of 1.000 Hz were set for the C3-C4 channels. After the electrophysiological adjustment of the device, recording was performed when the subject was asked to look at the right and then at the left. Taking into account the bias that might occur during the test, the first command was selected randomly to be "look to the right" or "look at the left", followed by the opposite command. Commands were given at an average of 2–2.5 s intervals. When the commands were not immediately followed, the subject was distracted, or the muscles of the eye were noticeably tired, the subject was allowed to rest. Each outlook EEG (not less

than 100) was recorded at the device memory and used to calculate the average.

After the recordings, the average starting point of the horizontal eye movement was marked with a vertical cursor as the 0 point. The analysis time was adjusted to be the place where the cursor cuts the DIP potentials recorded from C3-C4 points, and it was 3000 milliseconds backwards from the start of the motion, and 1000 milliseconds forwards, with a total of 4 seconds by back-averaging method.

It was observed that the traces of the C3 and C4 recording channels, which were noteworthy as the common feature, approached and moved away from the isoelectric line. After the registration process was completed, the MRCP wave traces were analyzed individually. Initially, the aim was to measure the amplitude of the peak of the wave before the EMG activity (i.e., the starting (N0) latency of the cortical negativity) in ms and then the MP (M1) in microvolts (μV) before the EMG activity. However, the exact distinction of the negative slope (NS) from the MP component could not be performed because the MRCP pattern obtained after augmentation was different from the MRCP pattern reported in the literature. As a clearly identifiable point, the T (Top)-point, which is the most extreme point of negativity, was marked. A relatively sharp transition from the T point to positivity was suitable for reporting in the literature, and the point of this positivity was called the D (Deep)-point. The TD amplitude was measured as amplitude.

The SPSS 15.0 program was used for all statistical analyses. Since the data did not show parametric distribution, mean, median, and minimum-maximum values were calculated. The Wilcoxon test was used for intragroup comparison, and the Mann Whitney U Test was used for intergroup comparisons.

Results

A total of 25 patients with MS participated in the study; the mean age was 28 ± 10.07 years, and the range was 18–52 years. Of the 25 patients, 24 were right-hand dominant and one was left-hand dominant. Four of the patients had a concomitant disease, two had completed treatment for depression and were in the follow-up period without medication, one had familial Mediterranean fever, and one had a history of thalassemia minor. The EDSS mean value was 0.5 ± 0.5. The majority (n = 24) of the patients were experiencing relapsing-remitting MS (RRMS), and one had primary-progressive MS (PPMS). The mean number of attacks was 2 ± 2.91, the mean duration of disease was 4 ± 4.69 years, and the lower and upper limits were one and 21 years, respectively. While 15 patients did not use interval therapy for various reasons, 10 had immunomodulatory therapy and one had immunosuppressant treatment. After the average, 24 of 25 patients had movement related potentials.

The patients' characteristics (i.e., age, number of episodes, years of disease, and EDSS score) are shown in Table 1. The mean BP and TD values recorded from active and passive hemspheres in the patients and control groups are shown in Table 2.

Table 1. Demographic properties of the patients.

	Patients
Age (mean, std dev)	28.00 (10.08)
Number of episodes	2.00 (2.92)
EDSS scores	1.00 (0.97)
Years of disease	4.00 (4.69)

Table 2. The mean BP and TC values recorded from active and passive hemspheres in the patients and control groups

	Patients (n:)	Controls (n:)
Active BP lat. (msn) mean (std dev.)	1870 (258)	1625 (133)
Passive BP lat. (msn) mean (std dev.)	1850 (260)	1688 (137)
Active TC lat. (msn) mean (std dev.)	247 (143)	237 (21)
Passive TC lat. (msn) mean (std dev.)	227 (55)	253 (19)
Active BP amp. (μV) mean (std dev.)	2.66 (1.15)	2.89 (1.43)
Passive BP amp. (μV) mean (std dev.)	2.40 (1.27)	2.21 (1.1.14)
Active TC amp. (μV) mean (std dev.)	4.31 (1.62)	3.40 (1.40)
Passive TC amp. (μV) mean (std dev.)	4.21 (1.42)	1.68 (2.22)

TC: BP:? Lat: latency, amp: amplitude, μV: mikrovolt; std dev: standart deviation

When active and passive hemispheres were compared in the patient group, the BP latency in the active hemisphere was 20 ms longer than that in the passive hemisphere, and this difference was statistically significant (P = 0.008). There was no statistically significant difference between the BP amplitudes (P = 0.996), TD latencies (P = 0.126), and TD amplitudes (P = 0.364).

In the control group, there was no statistical difference between the BP latency values of the active and passive hemispheres (P = 0.1515). There was no

statistical difference between the BP amplitude values of the active and passive hemispheres (P = 0.1029). The TD latency recorded from the active hemisphere was statistically significantly shorter than that recorded from the passive hemisphere (P = 0.001). The TD amplitude of the active hemisphere was found statistically smaller than that recorded from the passive hemisphere (P = 0.0075).

When the patient and control groups were compared, the BP latency in the active hemisphere of the patient group was 245 ms longer than that in the control group, and this difference was statistically significant (P < 0.001). There was no statistically significant difference between the BP amplitudes of the active hemispheres (P = 0.301) and the TD latencies of the active hemispheres (P = 0.614). The TD amplitude in the active hemisphere of the patient group was found higher than in the control group, and this difference was statistically significant (P = 0.037). The BP latency in the passive hemisphere of the patient group was 190 ms longer than in the control group, and this difference was statistically significant (P = 0.006). The BP amplitude in the passive hemisphere of the patient group was higher than in the control group, and this difference was statistically significant (P = 0.034). The TD latency in the passive hemisphere of the patient group was found to be 27 ms shorter than that in the control group, and this difference was statistically significant (P = 0.001). In the passive hemisphere of the patient group, the TD amplitude was higher than in the control group, and this difference was statistically significant (P < 0.001).

Figure 1 demonstrates BP (early negative slope of the Bereitschaftspotential), NS (late negative slope), MP (motor potential) and Figure 2 shows a right point-of-view patient sample, and a right point-of-view control sample.

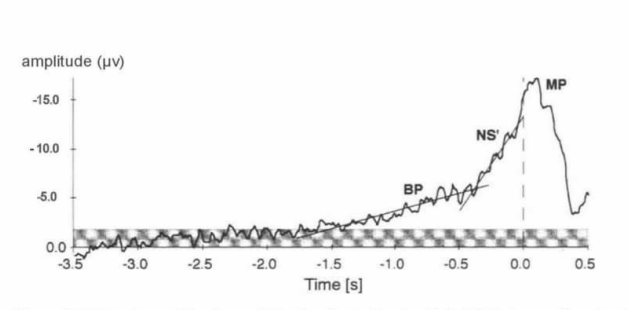


Figure 1: BP (early negative slope of the Bereitschaftspotential), NS' (late negative slope), MP (motor potential)

Discussion

Neurology is a science that applies the principle of cause and effect; when a physician evaluates a patient, they not only make a diagnosis and prescribe treatment, but they also question why and how the clinical picture has occurred. At this point, neurophysiology is a considerable resource for physicians.

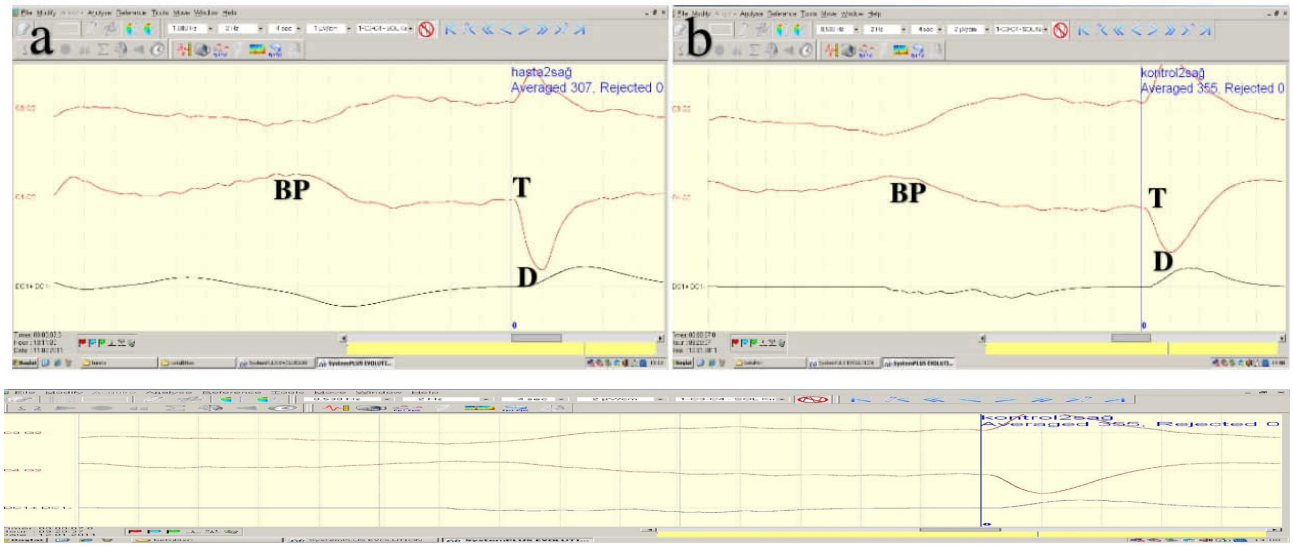
Event-related cortical potentials reflect the electrical activity in the brain during information processing. Event-related potentials resulting from visual, auditory, or bodily stimulation are detected using an EEG-like recording method; however, the signals are smaller than background EEG signals. Therefore, signals are recorded by applying successive stimuli to increase the signal-to-noise ratio. The evoked potential recorded as a result of a simple sensory stimulation is called an event-related (endogenous, cognitive) potential if the person has a cognitive function in response to the stimulation. The resulting potentials are named after the type of stimulation, depending on the time of emergence and the positive or negative deviation in the recording.(11)

Among the cortical potentials, the most commonly studied are P300 and CNV; although, recently, there has been an increase in the number of MRCP-related studies.(2) The MRCP is considered to be a cognitive potential because it is obtained by the backward averaging technique and reflects the preparation phase prior to the onset of movement. In various studies, although the number of components varies depending on the method applied, the general approach is that the MRCP consists of three components: BP, NS, and MP. When the values are measured in ms and the continuity of the components is retained (they are not separated from the net), the source of the differences in the nomenclature can be understood.

The two components of MRCP, pre-motion BP and NS, are thought to reflect cortical activity for the planning and preparation of voluntary movements, respectively.(12) The negativity in the amplitude is considered an indicator of the amount of effort and energy needed to plan the action.(13) Similarly, MRCP may indicate the time required to plan and prepare a movement.(14)

It is reported in the literature that BP occurs approximately 1.500–2.000 ms after EMG activity. The late component NS of the MRCP starts approximately 400–600 ms before the onset of movement, rises rapidly, and ends about 90 ms before the movement. MP starts about 10–20 ms before the onset of the movement, and after the onset of EMG activity, and the maximal amplitude reaches 50–60 ms.(15)

In this study, we planned to obtain MRCPs with eye movements in patients with MS and a healthy control group. In our study, although the MRCP pattern was obtained, despite the EEG average of more than 300 samples, all of its components could not be clearly distinguished. Similarly, the inability to clearly distinguish the components in both the patient and control groups was interpreted in favor of attributing this to physiological causes rather than disease-specific pathology. The main reason for this may be the use of conjugated eye movements in our study.



Conjugated eye movements are complex; For each eye, oculomotor, trochlear and abducens nerves and their central-peripheral connections, frontal conjugated gaze center (contralateral conjugated gaze), parapontine reticular formation (ipsilateral conjugated gaze center), occipital connections, which are important in saccadic and rolling eye movements, cerebellar, vestibular and deep sense connections are provided in cooperation. Due to the complex connections, the conjugated gaze centers continue to operate even if the eyes are in the midline, so the transition from the resting state to voluntary movement required for MRCP cannot be fully met. This may be a reason why we could not make a clear distinction between all components of MRCP in our study.

In MRCP studies, choosing limbs with a larger area in motor homonculus such as hands and feet and movements managed by physiologically simpler pathways may be beneficial in terms of revealing all components.

In our study there was a statistically significant latency difference between the two groups, and BP latency was longer in the patient group. The fact that the two values that appeared to be similar in the normally accepted range were significantly different shows that measuring in ms is important for accurate recording and interpretation. However, as mentioned earlier, the MRCP is very low in amplitude compared to the EEG signal, and the fact that the initiation of the potential cannot be distinguished from ground activity with certainty means these values are open to interpretation. It has also been shown that different results may occur when different methods are used—even for potentials resulting from the same motion. Satow et al.'s work with hairy skin showed that while the BP latency and hemispheric results did not differ, the BP latencies were variable between the medial and lateral frontal cortex when recorded with subdural electrodes.(16)

In our study, a difference in BP latency was noted between the groups. This latency may reflect a loss of vision that was not noticed by the patient or the physician. It was also not detected during the neurological examination conducted during this study. In the patient group, BP latency measured in the active hemisphere was longer than that measured in the passive hemisphere. In this group of patients, the activity detected in the active hemisphere may reflect the start of the earlier planning phase. It may be a separate discussion, however, whether this 20 ms difference is clinically significant. In addition, the corpus callosum, with its critical role in the transmission of signals between the hemispheres, is one of the regions most affected by demyelination in MS. Although it is not mentioned in the formation of saccadic eye movement, it is worth questioning whether demyelination in the corpus callosum plays a role in the latency difference between the hemispheres. Because hemispheric latency differences are not mentioned in the literature we reviewed, the patients who participated in this study did not undergo magnetic resonance imaging (MRI) to evaluate the corpus callosum, and this lack of data limits the interpretation of the findings.

BP latency is thought to indicate the time required to plan the movement. However, it is difficult to determine what this required time frame is and how it should be interpreted. For example, in patients with schizophrenia, delay in BP latency and amplitude were low, and these findings were associated with coarsening and bullying in patients' movements.(11) In patients with Alzheimer's disease, a delay in BP latency was reported compared to a control group, and it seems more appropriate to associate the delay with cognitive impairment.2 Amplitudes were also found to decrease in MRCP studies in elderly patients and shortening of MRCP latency was reported in patients with frontal lobe dysfunction.(17) However, in another study conducted with athletes, the shortening of BP latency was interpreted as shortening of the

preparation time since the athletes did not need to undertake additional preparation when they were performing movements that were familiar and frequently repeated.(18) Furthermore, significant decreases in amplitude values and the shortening of latency values in rehabilitation patients after the completion of the exercise program were accepted as an indicator of adaptive neuronal changes and rehabilitation efficiency.(19) In this context, the extension of BP latency in our patient group remains open to interpretation. This is another point to be emphasized: this period could signify a slowdown in cognitive functions in terms of extended effort to better plan for the movement or for elongation of the movement.

When the TD values were examined, significant amplitude and latency differences were not observed between the active and passive hemispheres in the patient group; however, the TD amplitude was higher in the patient group than in the control group. As can be seen in Figure 2, it is not possible to differentiate between the NS and MP components in the MRCP pattern we obtained. Compared with the BP component, the starting point can be determined more clearly though, and more precise measurements can be made. It is also feasible to consider this segment as a combination of the NS and MP components, reflecting the preparation and demonstration of the movement.

Deecke and Kornhuber found that the MP amplitudes associated with triggering a small and difficult-to-target motion were lower than those associated with triggering large and easy movements.(20) Although the same target was used, the higher TD amplitude in the control group compared to the patient group with MS could be interpreted as having difficulty in finding the target group.

In fact, rarely is every component detected in a potential's trace.(21- 23) Rektor et al. obtained BP and CNV measurements by inserting multiple electrodes into the basal ganglia of patients undergoing epilepsy surgery and reported the results as a topographical interpretation. One of the striking points of this type of study is the improved capacity to define and measure the potential at the determined points rather than the amplitude and latency when interpreting the data.

As mentioned earlier, it is known that the amplitude and starting time of the pre-movement component of the MRCP varies according to the physical and psychological characteristics of the movement. (18) Considering all these factors, it is reasonable to state that differences can be observed in the MRCP values obtained with different time measures and applications in the same individual.

Conclusions

In the present study, the BP latency obtained in the MS patient group was longer than the control group. It was evaluated that the preparation phase of the movement took longer in the MS patient group. The TD amplitude, which can be regarded as a component of the NS and MP, was higher in the patient group and may indicate that the target movement was more difficult for the patient group.

The inability to clearly distinguish the other components of MRCP despite adequate averaging suggests that conjugated eye movements, which physiologically require the activation of too many anatomical regions, may not be suitable for this examination.

In future MRCP studies, choosing limbs with larger areas in motor homonculus such as hands and feet and movements managed by physiologically simpler pathways may be beneficial in terms of revealing all components.

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