Cortical Excitability and Aggressive Behavior in Post-Traumatic Stress Disorder

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ABSTRACT

Introduction: Hyperarousal and alertness play an important role in the clinical presentation of Post-traumatic stress disorder (PTSD). Strenuous effort has been made to shed light on the mechanisms that cause these symptoms of patients. Based on the claim that there is a relationship between some subtypes of hyperarousal symptoms and aggression in patients with PTSD, we aimed to examine the relationship between electrophysiological measurements that was measured through transcranial magnetic stimulation (TMS) and aggression scale scores of PTSD patients in this study.

Methods: The study included 37 patients with a diagnosis of PTSD according to DSM-IV criteria and 25 healthy volunteers. Electrophysiological measurements of participants were made with TMS. The Buss Perry Aggression Questionnaires was administered to patients and control group.

Results: In the patient group, a positive correlation was found between scores of aggression and arousal symptoms. Motor excitability threshold, one of TMS measurements, which is a sign of cortical excitability, was significantly lower in the patient group than the control group. There was a negative correlation between aggression scale scores and the parameters of motor excitability threshold and cortical silent period which both shows cortical excitability of the patients.

Conclusion: We concluded that there was an increase in cortical excitability in PTSD patients and we suggest that this increase might be associated with hyperarousal symptoms and aggressive behavior.

Keywords: Aggression, cortical excitability, PTSD, TMS

INTRODUCTION

Post-traumatic stress disorder (PTSD) is a psychiatric disorder that emerges after a life-threatening traumatic experience and lasts more than a month. This disorder is characterized with symptoms such as hyperarousal, re-experiencing, avoidance, decreased interest to the outside world, reduction in reactions, and alienation. PTSD causes clinically significant distress and impairments in social, occupational, or other areas of functioning (1). It is estimated that approximately 80%–100 % of people are exposed to at least one traumatic event throughout their lives (2). PTSD develops in 5%–9% of people who are exposed to trauma, depending on the nature of the trauma (3).

A set of three main symptoms draw attention in PTSD patients. The first one is constant avoidance from the stimuli associated with trauma and reduction in the level of common response. The second one is re-experiencing the event because of stimuli that remind of the trauma, dreams associated with the trauma, dissociative experiences, and giving psychological and physiological responses. The third one is the symptom of hyperarousal. Hyperarousal is the most common cluster of symptoms in PTSD. In this regard, state of alertness irritability, outbursts of anger, and exaggerated startle response are the prominent symptoms (4). These symptoms are manifested in the form of excessive anger and aggression. Outbursts of anger and impulsive behaviors are the hyperarousal symptoms of PTSD. These symptoms are associated with aggression, and they are a serious problem both for the patient and close vicinity of the patients. The presence of aggressive behaviors in PTSD patients plays an important role in treatment (5,6,7).

Outbursts of anger, impulsivity, and aggressive behaviors are associated with anatomical structures such as the brain stem, hypothalamus, limbic system, and frontal lobe (orbitofrontal cortex–neocortex) (8,9). It is thought that impulsive and aggressive behaviors emerge with the impairment of inhibitory control after the effect of a series of information processing, such as activation of threat response system, failure of the limbic system (hippocampus, amygdala) to comply with regulatory functions, and failure of the frontal cortex with inhibitory functions (10). Aggressive and impulsive behaviors have been demonstrated to be associated with an increase in the release of acetylcholine and dopamine and a decrease in the release of norepinephrine, gamma-aminobutyric acid (GABA), and serotonin (11,12,13,14,15,16).

Electrical motor evoked potentials (MEPs) are recorded from peripheral nerves or striated muscles through the stimulation of the motor cortex or motor pathways in the central nervous system by the transcranial magnetic stimulation (TMS), which is one of the neuro-

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physiological investigation methods. This method enables investigating the mechanism of disease by causing changes in the excitability of cortical motor areas. Similarly, TMS has been used to study the effect of psychotropic drugs on cortical activity and to evaluate the electrophysiological aspects of aggressive behaviors. Studies with TMS showed that GABA-mediated cortical regulation may be impaired in PTSD patients (17). The two relationships that were between impaired TMS measurements of the right hemisphere with the duration of illness and between avoidance symptoms with prolonged right hemisphere response have been determined in PTSD patients. These relationships suggested impaired cortical excitability in PTSD patients. At the same time, the relationships between impaired excitability and illness duration and some symptoms have been shown. Impaired short interval intracortical inhibition (reflecting the GABA_A function) and intracortical facilitation (ICF) (reflecting the glutamatergic function) are obtained from the right hemisphere of PTSD patients in the same study (18).

In this study, we aimed to investigate the relationship between the aggression level and electrophysiological measurements determined by TMS in PTSD patients.

METHODS

Participants

Thirty-seven male patients who were diagnosed with PTSD and who met the criteria to participate were enrolled in the study. In the study, the patient group was selected from the patients hospitalized in the Gulhane Military Medical Academy Psychiatry clinic between January 2010 and July 2010. The control group constituted 25 healthy volunteers without any major medical or psychiatric illness and who had similar age, education, and socio-economic characteristics with the patient group. The control group was selected from the attendants of the patients who were admitted to the Gulhane Military Medical Academy outpatient psychiatry clinic for examination and who agreed to participate after receiving information about the study. The patients diagnosed with PTSD according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria constituted the patient group. The patients in this group did not suffer from mental retardation or an organic disease after physical, neurological, and psychological examination, and they had at least primary level education and sufficient intellectual capacity to take the tests. They agreed to participate in the study. The participants in the control group did not have any psychiatric disorder according to the Semi-structured Clinical Interview Form I-II (SCID I-II), mental retardation, or an organic disease. They had at least primary level education and sufficient intellectual capacity to take the tests. They agreed to participate in the study. Those who had a history of head trauma resulting in the loss of consciousness, a history of using psychiatric medication for the last month, alcohol or drug abuse, personality disorder, low levels of education to take the tests, and who did not want to participate in the study were excluded. The study was planned as a clinical observation. After the approval of the Gulhane Military Medical Academy local ethics committee dated 08.07.2009 and no. 1491-1057-09/1539, the applications were started in the Department of Neurology and Department of Psychiatry of Gulhane Military Medical Academy. The participants were informed about the study, and written consents were received.

Tools for Data Collection

Socio-Demographic Data Form

This form comprised multiple choice and open-ended questions such as

disease, traumatic life, time, frequency, duration of traumatic life, bodily injury caused by trauma, substance abuse, and history of psychiatric disorder in the family.

SCID-I

SCID-I is a clinical interview scale structured for DSM-IV Axis I disorders. Adaptation and reliability studies for Turkey were conducted by Çoraçioğlu and his colleagues (19).

Buss-Perry Aggression Questionnaire

This scale was developed to be used for assessing the scale of anger and aggression. There are two separate profile forms for youth (9–18 years) and adults. Total physical and verbal subscales take different values according to gender in the profile form, but anger, hostility, and indirect aggression take the same values in both genders. The scale consists of 34 items and 5 sub-scales. Turkish validity and reliability study was conducted (20).

Edinburgh Handedness Inventory

This scale was developed by Oldfield. How often the subjects use their hands was investigated at ten different activities for the determination of the dominant hemisphere in the scale.

TMS Measurements

Maglite model of Dantec magnetic stimulator (Dantec Medical A/S, Skovlunde, Denmark) for magnetic stimulation and Dantec MC-125 circular structured coil (Dantec Medical A/S, Skovlunde, Denmark) with 90-mm inner diameter as a stimulant coil were used. The maximum output of the coil was 1.0 Tesla. Recordings were made by the evolution model of Dantec EMG device. Dantec Ag-CI surface recording electrodes (11-mm diameter) were used for EMG recordings. Applications were carried out at normal room temperature and sitting position in a comfortable chair. The potentials of upper and lower extremities were obtained. Active electrodes were placed on the abductor pollicis brevis (APB) muscle of each hand, and reference electrodes were placed on the dorsal surface of the distal phalanx of the thumb. The ground electrode was attached to the wrist.

MEPs were obtained by cortical magnetic stimulation. Motor output levels that 50 µV potential of MEP responses obtained with 5 of 10 stimuli were determined as the motor threshold (MT). Supramaximal stimulation intensity was used while MEP measurements were conducted. At least five action potentials of the compound muscle were obtained and analyses were conducted based on the average of these responses. The heights between positive and negative peaks (peak to peak) were based on during the amplitude measurements. Contralateral and ipsilateral cortical silent period (CSP) measurements were obtained by the voluntary activity that had been made at 50% intensity of the maximal muscle and by the stimulus given at the intensity of 150% of resting motor threshold. Three CSPs were obtained, and the average of these was used. Latency to MEP response was found by giving the magnetic stimulus from the cervical region, and it was taken off from MEP latency obtained by stimulating the cortical region to determine the central motor transmission time (CMTT).

Statistical Analysis

Mean±standard deviation values were calculated for continuous variables. Categorical variables were indicated as number and percentage. For the investigation of the differences between the groups, significance of the difference between the two means tests (Student's t-test) was used in continuous variables if normal distribution was provided; Mann-Whitney U-test was used in cases not provided. Chi-square test was used for the investigation of the differences between the two groups in terms of

categorical variables. Because of the failure to comply with the normal distribution, Spearman's correlation test was used for the investigation of the relationships between the aggression level and TMS measurements in both groups. P-values smaller or equal to 0.05 were considered statistically significant.

RESULTS

The analysis of the socio-demographic data of participants who were all male showed that there was no statistically significant difference between the PTSD group, consisting of 37 patients, and the control group, consisting of 25 healthy volunteers, in terms of age, status, education level, and marital status ($p>0.05$) (Table 1).

BAI, CAPS II, and IES-R scale scores of the patients are shown in Table 2. Anxiety symptoms in the patients were found to be severe in the psychometric examination. Hyperarousal and avoidance symptoms were in the severe level (CAPS avoidance=23.66±9.49, IES-R avoidance=20.18±3.99, CAPS hyperarousal=20.96±7.43, IES-R hyperarousal=20.81±5.65) among the PTSD symptoms of the patients measured by both CAPS II and IES-R.

Buss-Perry Aggression Questionnaire total scores and subscale scores (physical aggression, verbal aggression, anger, hostility, and indirect aggression) of the patient group were significantly higher compared with the control group (Table 3).

The comparison of the TMS findings of the patient and control group is shown in Table 4. The mean right and left MT of the patient group was significantly lower than that in the control group (right MT: $Z=3.43$, $p=0.001$; left MT: $Z=4.67$, $p<0.001$). Amplitudes measured from bilateral APB and anterior tibial (AT) muscles in the patient group were lower than those in the control group. Cortical amplitudes measured from the left APB in the patient group were significantly lower than those in the control group ($Z=2.84$, $p=0.005$). All CSP measurements in the patient group were less than those in the control group. Ipsilateral CSP measurements obtained from the right cortical region ($Z=3.11$, $p=0.002$) and left cortical region ($Z=2.78$, $p=0.005$) were significantly lower.

When the relationships between MEP measurements and aggression scale score in the PTSD patients were examined, a negative correlation was found between left MT and physical aggression ($\rho=-0.341$, $p=0.039$) and anger ($\rho=-0.428$, $p=0.008$) subscale scores.

There was a positive correlation between cortical amplitude measured in the right APB and anger subscale scores ($\rho=0.335$, $p=0.043$). A positive correlation was determined between cortical amplitudes measured in the left and right AT and indirect aggression subscale scores (Left AT: $\rho=0.333$, $p=0.044$; right AT: $\rho=0.640$, $p=0.003$).

There was a negative correlation between the right contralateral CSP and subscale scores of physical aggression ($\rho=-0.467$, $p=0.004$), anger ($\rho=-0.511$, $p=0.001$), hostility ($\rho=-0.512$, $p=0.001$), indirect aggression ($\rho=-0.370$, $p=0.024$) and the total scores of aggression scale ($\rho=-0.511$, $p=0.001$). A negative correlation was found between right ipsilateral CSP and physical aggression ($\rho=-0.384$, $p=0.019$), anger ($\rho=-0.377$, $p=0.021$), and hostility ($\rho=-0.422$, $p=0.009$) subscale scores and aggression scale total scores ($\rho=-0.428$, $p=0.008$). A negative correlation was found between left contralateral CSP and physical aggression ($\rho=-0.328$, $p=0.048$), anger ($\rho=-0.425$, $p=0.009$), hostility ($\rho=-0.465$, $p=0.004$), and indirect aggression ($\rho=-0.329$, $p=0.047$) subscale scores. There was

Table 1. Comparison of socio-demographic characteristics of PTSD and the control group

Variable	Group		Statistical analysis
	PTSD (n=37)	Control (n=25)	
Year; mean±SD* (year)	30.45±6.95	32.88±6.97	$t=1.102$; $p>0.05$
Education; mean±SD (year)	12.70±2.30	13.72±1.72	$t=0.674$; $p>0.05$
Marital status; married n (%)	19 (51)	16 (64)	$\chi^2=0.971$; $p>0.05$

*mean±SD=Mean±standard deviation, t: student t test value, χ^2 : Chi-square test value.
PTSD: post-traumatic stress disorder

Table 2. Clinical scale scores of PTSD patients

Scale	Mean±SD (min-max)
BAI	27.46±14.27 (3-52)
IES-R	
Intrusive	18.75±5.44 (10-31)
Avoidance	20.18±3.99 (10-30)
Hyperarousal	20.81±5.65 (8-27)
Total	59.50±11.98 (35-82)
CAPS II	
Intrusive	15.40±6.24 (7-32)
Avoidance	23.66±9.49 (8-46)
Hyperarousal	20.96±7.43 (8-41)
Total	60.07±22.21 (26-119)

PTSD: post-traumatic stress disorder; BAI: Beck anxiety inventory; IES-R: the impact of event scale

Table 3. Comparison of aggression scores with PTSD and the control group

Scale parameters	Group		Statistical analysis
	PTSD (n=37)	Control (n=25)	
Physical aggression*	28.00±8.26	12.48±3.10	$Z=6.25$; $p<0.001$
Verbal aggression*	19.40±3.63	11.12±2.16	$Z=6.59$; $p<0.001$
Anger*	26.56±5.16	16.08±3.47	$Z=5.79$; $p<0.001$
Hostility*	24.18±5.02	12.00±3.54	$Z=6.36$; $p<0.001$
Indirect aggression*	15.56±4.36	10.08±2.95	$Z=5.10$; $p<0.001$
Aggression scale total*	116.45±24.51	61.76±11.16	$Z=6.41$; $p<0.001$

*mean±SD: mean±standard deviation, Z: Mann-Whitney U test value. PTSD: post-traumatic stress disorder

a negative correlation between left ipsilateral CSP and physical aggression ($\rho=-0.365$, $p=0.026$) subscale scores.

DISCUSSION

The relationships between impulsive and aggressive behaviors, which were the indicators of hyperarousal symptoms and electrophysiological variables in the brain measured by TMS (MEP latency and amplitude, MT, CSP, CMTT), were investigated in this study. Two key findings came to

Table 4. Comparison of TMS findings with PTSD and control group

Variables		Group		Statistical analysis	
		PTSD (n=37)	Control (n=25)	Z	P
MT	Right	49.72±9.78	57.40±3.43	3.43	0.001
	Left	45.54±9.55	57.40±4.11	4.67	<0.001
CL (APB)	Right	20.52±3.41	20.46±1.38	1.91	0.056
	Left	21.07±1.33	20.86±1.42	0.50	0.615
CA (APB)	Right	2.48±1.16	2.69±1.41	0.39	0.693
	Left	2.07±1.05	3.10±1.54	2.84	0.005
CMTT	Right	7.35±1.30	7.50±0.95	0.43	0.661
	Left	7.62±1.10	7.50±0.61	0.20	0.835
CL (AT)	Right	28.28±2.07	29.18±1.19	0.67	0.498
	Left	27.87±2.33	29.16±1.81	1.92	0.054
CA (AT)	Right	1.41±2.10	2.46±2.01	1.51	0.129
	Left	1.22±0.70	2.06±1.43	1.46	0.144
CSP	Right IL	16.22±8.12	21.71±4.90	3.42	0.001
	Left IL	15.79±6.85	22.27±5.68	3.10	0.002
	Right CL	158.78±46.65	159.82±14.98	0.84	0.398
	Left CL	161.37±41.75	164.52±20.48	0.88	0.377

MT: motor threshold; APB: abductor pollicis brevis muscle; CL: cortical latency; CSP: cortical silence period; CA: cortical amplitude; IL: ipsilateral; AT: anterior tibial muscle; CL: contralateral; CMTT: central motor transmission time

the fore among the results. First, MT was lower in the patient group compared with that in the control group, and second, CSP was shorter in the patient group compared with that in the control group. The low MT indicated the increase in cortical excitability. There were two meanings of the shorter of the CSP. These were the increase in cortical excitability and inhibition of cortical dysfunction.

In this study, the low MT was the result of the increased cortical excitability in PTSD patients. GABA/glutamatergic dysfunction involved in the etiology of PTSD was considered to be effective in measuring the low MT. Impaired short latency ICFs in the right hemisphere was the best indicator of this in the studies. There were a very limited number of similar studies in PTSD patients. Nevertheless, TMS parameters changed in other diseases having neuronal impairments were attributed to imbalance between main excitatory neurotransmitter glutamate and main inhibitory neurotransmitter GABA (21,22,23). When the studies investigating cortical excitability in PTSD patients were evaluated, it was seen that there was a change in excitability in these patients but that there was no significant difference in terms of MT (18). MT was reported to be low in some psychiatric disorders (schizophrenia, obsessive-compulsive disorder) because of the deficiency of GABA and was reported to be high in some psychiatric disorders (some of the anxiety disorders comorbid with attention deficit hyperactivity disorder) (24,25). Also, MT was low in disorders characterized by impulsive and aggressive behaviors, such as antisocial personality disorder; because of increased excitability. MT increases by voltage-gated sodium channel blocking drugs. The structure and number of projections on the primary motor cortex and receptor sensitivity in this region also affect MT (26,27,28). In view of these findings, imbalance between GABA and glutamate are likely to have occurred among the trauma cases causing

CSP is a duration in case of contraction that EMG activity has been temporarily suppressed after stimulation of the motor cortex with TMS. The neurons that give this inhibitory response are known to use GABA as a neurotransmitter (29,30). In this study, the relationship between PTSD and CSP suggested that not only GABA_A but also GABA_B should draw attention in PTSD. It would be correct to say that the idea that the important role of both the sub-groups of GABA in the pathogenesis of PTSD has been gaining strength with these and similar studies. This hypothesis was supported by reduced allopregnanolone levels in the cerebrospinal fluid of PTSD patients (31) and post traumatic GABA plasma levels as the predictive factor for the development of acute PTSD (32). Differences related with CSP, which was thought to be a phenomenon associated with GABA_B, are not shown in the limited number of studies (30,33). Instead of this, impaired short interval intracortical inhibition (SIII) and decreased plasma levels of GABA are found. In this study, short CSP was considered as a sign of GABA dysfunction based on the belief that the central GABA transmissions are impaired in PTSD patients (18). Possible factors of showing no parallelism with the earlier studies could be the variety of the factors that create trauma, variety of the degree of influence from the trauma despite the homogenous group in terms of trauma type, variety of devices that had been used, possible neural effects (after head trauma) in previous studies, variety of the applications (single-pulse TMS/paired-pulse TMS), and possible use of unrecorded medicines.

There are components of aggression such as fear, anger, impulsivity, and tendency to violence (34). Behaviors including aggression and violent could be a symptom of many psychiatric and neurological disorders, especially antisocial personality disorder. Angry outbursts listed in hyperarousal symptoms, which are one of the main symptoms of PTSD, meet not all but many properties of the major components of the irritability, aggression, and impulsivity concepts. The CSP, MT, and aggression total scores and some subscale scores (physical aggression, anger, and hostility) in PTSD patients suggested the relationship between cortical excitability and aggression behaviors. In PTSD patients, increases in aggressive-impulsive behaviors were seen in parallel with the increases in the excitability.

In literature, there was no study about aggression in PTSD patients. However, a negative correlation was found between MT and aggression scale scores in a study that included patients with antisocial personality disorder. The correlations between aggression scores and parameters indicating increase in excitability (MT, CSP) showed that an indirect relationship could be established between aggression and excitability (35). The relationships between aggression scores and MT, CSP suggested that cortical inhibitory dysfunction and excitability increase play a role in the etiopathogenesis of aggressive behaviors. The idea was put forward that the neuromediators such as GABA, norepinephrine, dopamine, and serotonin in various brain regions could be involved in aggressive behaviors (36). The abnormal activation of slow-wave and slowdown in the theta band were observed in the electroencephalography studies conducted in patients who had aggressive and violent behaviors at an advanced level. Reductions in the activation of P300 in the frontal region are determined in criminals who committed a violent crime, and decreased P300 amplitude and prolonged P300 latency are seen compared with those in the healthy control group (37). In this study, in the associations between some parameters of the scale of aggression and MEP, CSP measurements suggested that dysfunctions of inhibitory neuromediators were related with aggressive behaviors. These results suggested that the over stimulation of related regions in the brain and deficits in the inhibitory control made individuals prone to aggression, impulsiveness, and deficiency in the control of their behaviors.

There were some limitations of this study. While this study had more a broad participation compared with previous studies regarding cortical excitability in PTSD, similar large trials are needed. Measurements could be conducted after the application of a stimulus related to the trauma of patients and could be compared with the situation prior to the stimulus. In the study, the use of the paired-pulse TMS thought to be recognized facility for the measurement of the parameters as SIII and ICF those better reflect the functions of GABA and other neurotransmitters. The patients in our study had a homogeneous feature in terms of experienced trauma. This situation was an advantage for the factors affecting data, but it formed a disadvantage for the representation of the universe.

The clarification of the etiopathogenesis of aggressive behaviors, which are a major problem for both patients and those in the close vicinity of PTSD patients, are thought to be necessary for revealing more effective treatment modalities.

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