Psychophysiological Characteristics of Aggression Associated with Depression before and after Successful Treatment with Sertraline: A Clinical Trial Study

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Running title: Psychophysiological Characteristics of Aggression Associated with Depression

Abstract

Background: Depression associated with aggression can lead to violent behaviors. The present study was aimed to determine how sertraline, a standard medication for depression treatment, can efficiently decrease aggression and affect psychophysiological parameters in patients with depression.

Methods: Patients with depression and aggression were included in a six-week trial with sertraline (50-100 mg/day). Depression diagnosis was confirmed by the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, Text Revision (DSM-IV-TR). Depression severity before and after treatment was assessed using Beck Depression Inventory (BDI). Aggression was evaluated by Spielberger's State-Trait Anger Expression Inventory-2 (STAXI-II). The BDI and STAXI-II were finally applied to evaluate the effectiveness of treatment. For each patient, peripheral and central psychophysiological parameters were recorded using peripheral biofeedback apparatus and electroencephalogram in the initial and final stages of treatment. These recordings were attempted to assess variations of the autonomic nervous system and electrocortical activity in response to treatment.

Results: Depressive and aggressive symptoms decreased significantly over the six-week treatment period, as measured by BDI and STAXI-II. Significant changes in some of the peripheral and central psychophysiological variables were observed. Sensorimotor rhythm (SMR)/theta ratio ($p=0.01$) have decreased during a task, delta ($p=0.02$) and theta ($p=0.008$) wave activity and theta/alpha ratio ($p=0.01$) have increased during task, and theta/beta ratio has increased during both rest and task ($p=0.02$ for both). Among peripheral psychophysiological variables, skin conductance during task decreased significantly ($p=0.03$).

Conclusion: Several numbers of psychophysiological parameters were influenced significantly after successful pharmacotherapy of aggressiveness in patients with depression.

Keywords: Aggression; Depression; Biofeedback; Neurofeedback; Sertraline

Introduction

In recent decades, psychiatry in both research and clinical practice is moving away from a mere representative of categories toward understanding the neural and biological basis of behaviors and dimensions of the psychopathology of psychiatric disorders, to provide more effective treatments. Thereupon, there is an outstanding advance in the field of neuropsychiatry, exploring the psychophysiological processes of psychiatric disorders.[1]

The current investigation is an attempt for describing the neuropsychiatry of aggressive behaviors associated with depression. Aggression associated with depression occurs prevalently and their relation was investigated and emphasized repeatedly.[2] High levels of aggression have been demonstrated in the depressed population.[3] From a psychoanalytic view, internally directed aggression leads to depression and a feeling of guilt. Based on biochemical evidence, serotonin disturbances were proposed as a potential reason.[4] Serotonin-related anxiety/aggression-driven depression was defined for this purpose as a new subtype of depression. It was also suggested that aggression is a precursor symptom for depressive phase and plays a role in the development of depression.[4,5] With the introduction of selective serotonin reuptake inhibitors (SSRIs), they have become the primary drug therapy for depression. It has been well studied by several meta-analyses in several clinical trials.[6] Among the SSRI drug class, sertraline was favored over other agents due to its more efficacy, availability, and less withdrawal rates.[7] Effectiveness of serotonergic agents in the treatment of patients with depression-associated aggression was an expected prediction supported by evidence.[8,9]

On the other hand, the relationship between aggression and autonomic and electrocortical activity (ECA) have been investigated and reported previously. Resting heart rates (HR), heart rate variability (HRV) and skin conductance (SC) are known as important predictors of

antisocial behavior and aggressiveness.[10-12] General enhancement in slow wave ECA,[11] cortical hyperarousal and reduction in fast wave EEG power have been shown by studies.[13]

The aim of this study was to evaluate the psychophysiological characteristics of patients with depression and aggression before and after successful treatment with sertraline, a standard treatment.

Patients and Methods

Study design

This study was a six-week clinical trial conducted in a psychiatric hospital between October 2015 and March 2017. Patients were treated with 50-100 mg/day sertraline (KRKA, Novo Mesto, Slovenia) film-coated tablets. All patients were prescribed 50 mg daily sertraline for one week and increased to 100 mg daily for the rest of the six-week period. Patients were followed up weekly in the outpatient clinic for evaluation of the patient's condition and taking medication regularly. Before and after treatment, psychophysiological variables were recorded using the bio-neurofeedback apparatus during rest and while a standard stressing task as mental arithmetic while the subjects were seated on a comfortable chair. To avoid environmental confounding factors, both primary and secondary assessments were done in a single shielded room that was light- and sound-attenuated. Before participation, the study procedure was explained to the subjects, written informed consent was provided for all of them and before their consent it was ensured that the consent was completely comprehended. The study protocol was approved by the Ethics Committee of Tabriz University of Medical Sciences (Reference number: IR.TBZMED.REC.1393.93196) and Iranian Registry of Clinical Trials (IRCT registration number: IRCT201411122999N4), which meets the criteria of world health organization.

Participants

A total of 50 patients with depression who claimed to suffer from aggression and irritability accepted to participate in the trial. Patients were recruited to the study from an outpatient psychiatric clinic of Razi Hospital of Tabriz University of Medical Sciences. Twelve patients did not attend in primary assessment session due to different reasons (e.g. wrong numbers, personal or household matters, spouse disagreement). After considering inclusion/exclusion criteria, from rest of the 38 patients, 23 patients including nine males and 14 females with depression diagnosis were aggressive who successfully treated, enrolled in the trial (Figure 1). Clinical interview was used for depression and aggression diagnosis and validated Persian translation of structured clinical interview for DSM-IV (SCID) [14-16] was completed by a trained psychiatrist for all patients to confirm the diagnosis of depression. The Persian version of Beck depression inventory (BDI) validated by previous studies was applied to assess the severity of depression before and after treatment.[17,18] Aggression diagnosis was made based on Spielberger's State-Trait Anger Expression Inventory-2 (STAXI-II) and patients who scored 8 to 32 were included in the experiment. For aggressive patients pre- and post-treatment STAXI-II scores were compared. Significant reduction in each of STAXI-II subscales interpreted as successful pharmacotherapy of aggression. Another inclusion criterion was no previous antidepressive treatment. Patients with the following conditions were excluded from the study: history of psychiatric disorders other than depression, consumption of drugs affecting central nervous system (CNS) or peripheral nervous system, history of diseases with CNS involvement, cardiovascular diseases, respiratory diseases, endocrine abnormalities, malnutrition, alcohol and/or drug abuse disorders, premenstrual syndrome and reduction in BDI scores lower than 50%.

Measurements

SCID-DSM-IV

The Persian translation of the SCID for DSM-IV was administered to make a reliable diagnosis of major depression disorders. This tool is a semi-structured interview and has been developed based on the DSM-IV criteria for psychiatric diagnosis. Since SCID requires to be performed by a trained interviewer, psychiatry residents or attending psychiatrists evaluated our subjects using this tool. The Clinical version of SCID-I that was applied in this study is a type of SCID for the assessment of DSM-IV Axis I major disorders. It takes a 45 to 90 minutes session.[19]

BDI

The BDI is a well-known psychometric test used for the measurement of depression severity. The second version of the DBI (BDI-II) is revised based on the DSM-IV criteria for major depression. It is designed for patients aged 13 and more. It consists of 21 items, each has 4 possible questions being scored 0 to 3 based on the severity of symptoms.[17] The Persian version of BDI-II was administered in this study that has been indicated to have sufficient validity and reliability.[18]

STAXI-II

Farsi version of STAXI-II was applied to assess aggression in the subjects. According to studies, this version has acceptable validity and reliability and has preserved the features of the English version.[20] In a 12 to 15 minutes session patients answer 57 items to become evaluated for the experience, expression and control of their anger.[21]

Psychophysiological characteristics are regulated essentially by the autonomic nervous system (ANS). The instruments for the peripheral biofeedback assess the tone of ANS by measuring variables such as SC, respiratory rate, HR, and HRV. A computer-based device was used in this study. The instruments for central biofeedback i.e. electroencephalogram (EEG) biofeedback or the neurofeedback examine the electrical activities of the brain as EEG recorded

by a few specific channels. Brain waves were obtained by a single specialist as a single-channel EEG recording by the neurofeedback apparatus (Thought Technology Ltd., Montreal, Canada) while the active electrode was placed on the vertex (Cz point in the 10-20 International system for electrode placement). All rest and task examinations performed in a stable state with the open-eye condition. Brain wave analysis to determine the frequency bands and related parameters was performed by the BioGraph software (Thought Technology Ltd., Montreal, Canada). Brain waves have different frequencies and amplitudes. They are categorized into delta (<4 Hz), theta (4-8 Hz), alpha (8-13 Hz), beta (13-30 Hz) and gamma (30-100 Hz). These frequency bands in various brain locations are associated with different functions of the brain.[22]

Data analysis

Data were analyzed using Statistical Package for Social Sciences software for windows version 16.0 (SPSS, Chicago, IL, USA). A statistical significance level of ≤0.05 was applied. Descriptive statistics were used to investigate basic features of the data, including mean, standard deviation (SD), frequency and percentage. To examine data normality, the Kolmogorov-Smirnov test was applied. The paired t-test for normally distributed data and the Wilcoxon test for non-normally distributed data were used to examine the variables before and after intervention.

Results

The mean±SD age of the subjects was 33.91±8.41 years old. The youngest and oldest patients were 21 and 58 years old, respectively. The mean age in women was 34.63±8.06 and in men was 30.5±8.81. Age and gender analysis did not indicate any significant difference between genders (P=0.44, P=0.21, respectively). All the subjects were literate and there was no significant difference in the level of education between genders (P=0.06).

BDI scores after treatment (Mean changes= -6.96±0.02) showed a significant decrease compared to initial scores (P=0.003) and more than 50% reduction in BDI scores which confirmed a successful treatment of depression.

Some of the subscales of STAXI-II including state anger (Mean change= -8.61±0.73, P=0.003), feeling angry (Mean change= -3.39±0.12, P<0.001), and feel like expressing anger verbally (Mean changes= -3.52±0.6, p=0.01) decreased significantly and external (Mean change= 4.57±0.32, P<0.001) and internal (Mean change= 5.44±0.22, P=0.001) control of anger increased significantly after pharmacotherapy, which was interpreted as an effective treatment of aggression.

Table 1 demonstrates baseline and post-treatment values of peripheral psychophysiological variables. The variables are shown during rest and while performing a simple task. All normally distributed variables in this table were analyzed using paired t-tests that showed no significant difference after treatment.

The baseline and post-treatment values of EEG variables are depicted in Table 2. Paired t-tests for normally distributed parameters showed that following successful treatment delta and theta wave activity have increased significantly during task (P=0.02 ,and P=0.008, respectively). Significant changes were seen in theta/alpha, theta/beta and sensorimotor rhythm (SMR)/theta ratios while performing task (P=0.01, P=0.02 and P=0.01, respectively). Theta/beta ratio has also shown significant change during rest (P=0.02).

In table 3, the rest of the variables are shown that did not distribute normally according to the Kolmogorov-Smirnov test and they were analyzed using the Wilcoxon test. Except for SC during task (P=0.03), none of the other variables showed statistically significant changes.

Discussion

This study has examined psychophysiological correlates of aggressive patients with depression during rest and task, before and after successful treatment of both conditions. There were two main objectives: The first one was to examine the efficacy of sertraline in aggressive patients with depression. The second one was to evaluate the psychophysiological changes before and after treatment.

The effectiveness of sertraline in treating aggression was confirmed based on the significant reduction in some of the subscales of STAXI-II. This was expected based on the studies that showed a positive relation between aggressive behavior and the serotonergic system.[23] SSRIs have been examined and shown to be effective in the treatment of aggression. Placebo-treated patients were four times more likely to show aggression than patients treated with fluoxetine, a SSRI, in a meta-analysis of 6000 depressed patients.[24] Fluoxetine treatment also reduced anger attacks in 71% of unipolar depressive patients. Patients with major depression following mild traumatic brain injury revealed reduction in both depression and aggression after 8 weeks of sertraline.[25] Sertraline was also shown to reduce aggression and impulsive behavior among patients with personality disorders.[26] It has also decreased anger attacks in 53% of depressed and dysthymic patients.[27]

Regarding the second goal of this study, i.e. to find changes in psychophysiological correlates before and after treatment, our analysis showed that task SC was the only peripheral variable that reduced significantly. It did not change significantly during rest. No other alterations were observed among peripheral variables. The autonomic nervous system that controls the peripheral variables has been considered related to both depression and aggression.[11,28]Studies with children and adolescent subjects have consistently shown lower resting autonomic activity during stressful situations. It should be emphasized that to our knowledge this is the first study to date that has measured psychophysiological variables associated with aggression in patients with depression during a period of pharmacotherapy. As

a result of this novelty comparing our results with previous reports that compared baseline variables with a control group would be challenging. However, a review of previous studies has been provided to show whether significant variations that occurred after sertraline therapy in this study were the same as the previous reports. Regarding the autonomic variables, most studies that were investigated in meta-analyses have focused on HR and electrodermal activity.[11,29,30] One of these studies reported increased reactivity in HR and SC in aggressive adults.[11] Lower resting HR but higher reactivity in resting HR and electrodermal activity were related to aggression in another meta-analysis.[29] Based on the other meta-analysis composed of 40 studies, slow HR, during a stressor or rest, has a strong negative association with antisocial behavior in children and adolescents.[30] Although a link between HR, HRV and SC with aggression has been reported in several studies but they did not show consistency and ~~increased systolic and diastolic blood pressure have been reported several times,~~ lower resting both hyper- and hyporeactivity were reported.[31] Insignificant change in all peripheral variables in this study, excluding task SC, highlights this point that psychophysiological characteristics of this type of aggression are distinct.

Concerning the ECA, our results showed several significant changes. Delta and theta waves, and theta/alpha and theta/beta ratios indicated an increase while the SMR/theta ratio showed decreased activity after treatment. According to previous studies, enhanced slow-wave activity, particularly delta wave, is a reliable finding in aggressive individuals.[11] Based on this report, delta wave activity is expected to decrease after clinical improvement in aggression while our results showed the opposite direction i.e. an increase in delta wave activity. Results of a pilot study of individuals with dysfunctional anger have shown increased resting beta and frontal cortical activity (i.e. alpha activity) comparing with the control group.[32] Enhanced frontotemporal beta activity and generally increased beta power while facing unpleasant pictures were also reported.[33] Sertraline therapy did not change beta and alpha activity in our

patients. A meta-analysis of studies about the ECA in externalizing behaviors has reported a generally cortical hyperarousal. Comparing ECA of externalizers and controls has revealed higher delta and theta and lower alpha power with eyes closed, higher alpha power with eyes open and a general decrease in fast-wave EEG power (i.e. beta and gamma) incompatible with the results of our study in which no change has been shown following treatment.[13]

As mentioned above, all inconsistencies that were observed between our results and previous studies might have originated from the fact that this study has focused on aggression in patients with depression. Psychophysiological variables of our aggressive subjects might have affected by depression that was associated with changes in both ECA[34] and ANS regulation[28]. It was suggested that by reducing parasympathetic and/or increasing sympathetic tone, depression affects ANS.[28]

This study had some obvious limitations such as lack of blinding and control group. Hence, a placebo-treated trial with an appropriate number of subjects is needed to perform in the future to delineate the changes related to treatment and enable us to generalize the results to this population.

Conclusions

This clinical trial highlights that sertraline is an efficient drug in the treatment of aggression in depressed individuals. Regarding the novel aspect of the study i.e. analysis of psychophysiological correlates before and after successful treatment, reduction in task SC, as a peripheral variable, and reduction in task SMR/theta ratio, increase in task delta and theta wave activity and theta/alpha ratio and increase in rest and task theta/beta ratio, as central variables, were observed. There might be no clinical utility for this study at present but it has certainly created a basis for future investigations on this type of aggression. It has enhanced the knowledge about changes in psychophysiological variables after treatment specifically in

aggressive patients with depression. This knowledge will help in the treatment and will potentially assist in predicting treatment response in the future. ~~that can lead to more effective treatment strategies~~.

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Conflict of interest

The authors declare that they have no conflict of interest.

Data Sharing

Applicants can obtain data by contacting the corresponding author

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Table 1. Paired t-test of baseline and post-treatment values of peripheral psychophysiological variables (rest and task)

Physiological variables	Rest			Task		
	Baseline mean ±SD	Post-treatment mean ±SD	P value	Baseline mean ±SD	Post-treatment mean ±SD	P value
Respiratory rate[1]	15.67±1.41	15.52±1.34	0.55	15.29±1.38	15.41±1.43	0.69
Heart rate[2]	74.06±8.85	77.18±11.74	0.22	78.49±9.58	80.68±10.27	0.31
HRV[3]	22.59±10.06	23.78±13.36	0.69	27.89±11.80	29.55±14.28	0.49
Heart rate SD[2]	12.09±4.45	11.96±4.9	0.91	13.60±4.05	14.86±5.56	0.20
Heart rate peak frequency[3]	-	-	-	0.15±0.05	0.13±0.05	0.06
Heart rate LF/HF ratio	0.57±0.10	0.67±0.37	0.21	0.67±0.24	0.66±0.28	0.92
IBI SD[4]	110.40±41.83	101.09±41.76	0.24	111.21±34.54	114.98±48.34	0.65

IBI, Inter-Beat Interval; HF, **High frequency ;** HRV, Heart rate variability; LF, **Low frequency;** SD,

Standard Deviation

[1]Breaths per minute

[2]Beats per minute

[3]Heart rate variation per minute

[4]Milliseconds

Table 2. Paired t-test of baseline and post-treatment values of electroencephalogram

parameters (rest and task)

EEG, Electroencephalogram; SD, Standard Deviation; SMR, Sensorimotor rhythm

EEG parameters	Rest			Task		
	Baseline Mean ±SD	Post-treatment Mean ±SD	*P* value	Baseline Mean ±SD	Post-treatment Mean ±SD	*P* value
Delta[1]	7.44±1.06	7.84±1.38	0.07	8.25±1.21	8.84±1.38	0.02
Theta[1]	7.27±1.58	7.68±1.75	0.13	7.53±1.60	8.44±2.19	0.008
Beta 1[1]	4.92±1.22	4.99±1.41	0.73	4.90±1.36	4.98±1.54	0.73
Beta 2[1]	4.77±0.67	4.64±0.81	0.40	4.79±0.78	4.79±1.07	0.10
Beta 3[1]	3.82±0.63	3.70±0.83	0.47	3.97±0.65	3.80±1.09	0.50
Beta 4[1]	3.41±0.72	3.23±0.93	0.3	-	-	-
Beta 5[1]	4.26±1.03	4.01±1.09	0.35	4.51±1.12	4.31±1.78	0.66
Gamma[1]	2.81±0.78	2.65±0.74	0.41	3.03±0.85	2.91±1.33	0.72
Theta/alpha ratio	0.94±0.22	0.97±0.23	0.26	0.94±0.19	1.02±0.26	0.01
Theta/beta ratio	0.95±0.2	1.01±0.2	0.02*	0.99±0.21	1.1±0.28	0.02
SMR/theta ratio	0.77±0.15	0.74 ±0.16	0.14	0.74±0.14	0.68±0.16	0.01

[1]Hertz

Table 3. Wilcoxon signed rank test results for non-normal variables

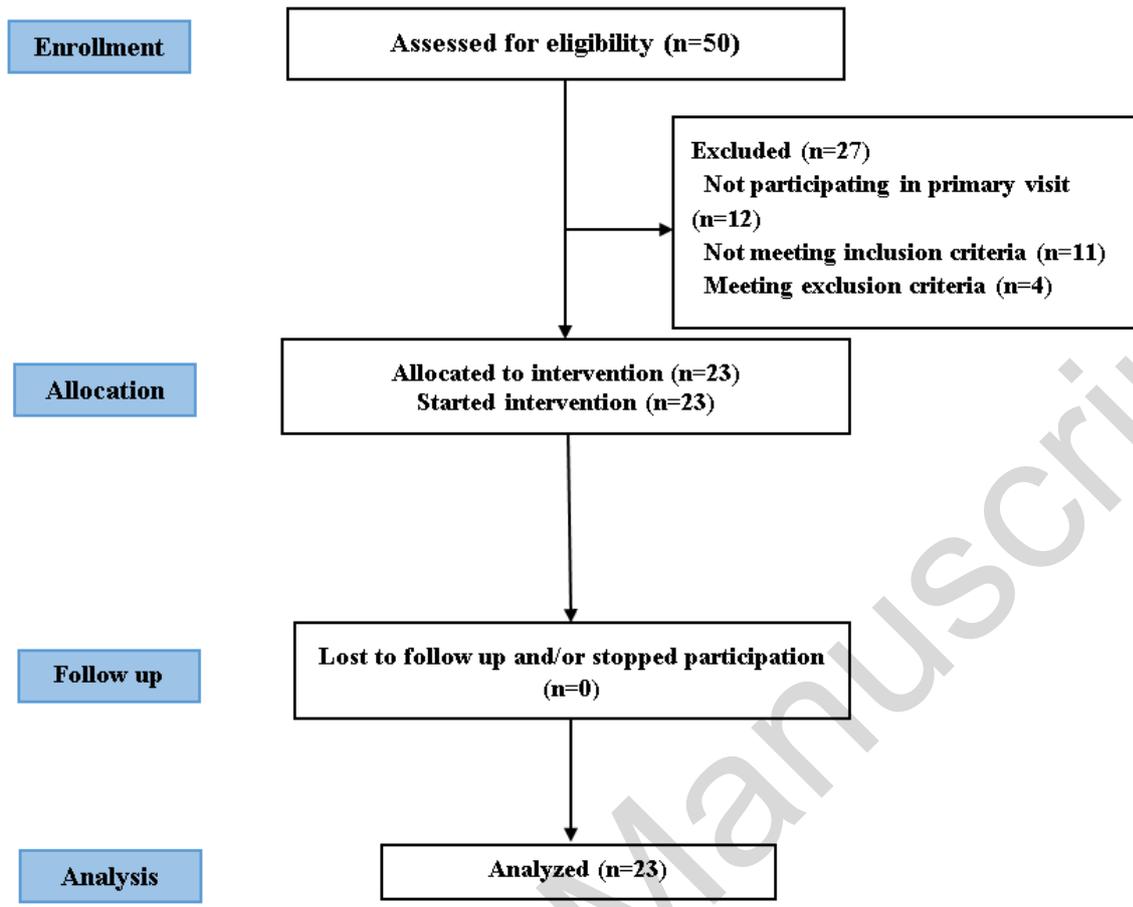| Variables	Rest				Task			
	Negative ranks (Mean rank)	Positive ranks (Mean rank)	Statistics		Negative ranks (Mean rank)	Positive ranks (Mean rank)	Statistics	
			Z	P			Z	P
Heart rate peak frequenc[1]	12.33	11.64	-0.3	0.76	-	-	-	-
SC[2]	11.17	10.93	-1.69	0.09	10.83	12.41	-2.22	0.03
Beta 4[1]	-	-	-	-	8.87	13.38	-1.54	0.12
Alpha[1]	11.46	12.7	-0.34	0.74	12	12	-1.28	0.2
SMR	16	9.87	-0.3	0.76	13.89	10.79	-0.4	0.69

SC, Skin conductance; SMR, sensorimotor rhythm

[1]Hertz

[2]Micro Siemens

Figure 1. Study Flow Diagram