T.C.
FATIH UNIVERSITY
INSTITUTE OF BIOMEDICAL ENGINEERING

ANALYSIS OF CARDIAC HEALTH IN PATIENTS SUFFER FROM MAJOR DEPRESSIVE DISORDER

ZEYNEP BEYZA ZİLELİ

MSc THESIS
BIOMEDICAL ENGINEERING PROGRAMME

İSTANBUL, AUGUST / 2013 (DEFENSE)

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İSTANBUL, AUGUST / 2013 (DEFENSE)

T.C.
FATİH ÜNİVESİTESİ
BİYOMEDİKAL MÜHENDİSLİK ENSTİTÜSÜ

MAJÖR DEPRESYONU OLAN HASTALARIN KALP SAĞLIKLARININ ANALİZİ

ZEYNEP BEYZA ZİLELİ

YÜKSEK LİSANS TEZİ
BİYOMEDİKAL MÜHENDİSLİĞİ PROGRAMI

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Zeynep Beyza ZİLELİ, a **MSc** student of Fatih University **Institute of Biomedical Engineering** student ID **52011198**, successfully defended the **thesis/dissertation** entitled "**Analysis of Cardiac Health in Patients Suffer from Major Depressive Disorder**", which she prepared after fulfilling the requirements specified in the associated legislations, before the jury whose signatures are below.

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To my lovely mother and my brother,

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August 2013 Zeynep Beyza ZİLELİ

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LIST OF SYMBOLS

Hz	Hertz
$\delta(t)$	Impulse function
μ	Mean
σ	Standart Deviation
$\sum$	Sum
V	Voltage

ABBREVIATIONS

5-HIAA: 5-hydroxyindoleacetic acid
5-hydroxytryptamine, 5-HT: Serotonin
ACS: Acute Coronary Syndrome
ACTH: Adrenocorticotropic Hormone
ANS: Autonomic Nervous System
BAI: Beck Anxiety Inventory
BPM: Beats per Minutes
BVP: Blood Volume Pulse
CAD: Coronary Artery Disease
CBT: Cognitive Behavioral Therapy
CRH: Corticotropin-Releasing Hormone
CRP: C-reactive Protein
CSF: Cerebrospinal Fluid
CT: Continuous-Time
CVD: Cardiovascular Disease
DA: Dopamine
DFT: Discrete Fourier Transform
DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders
DT: Discrete-Time
DTFT: Discrete-Time Fourier Transform
ECG: Electrocardiogram
ECT: Electroconvulsive Therapy
EDA: Electrodermal Activity
EDR: Electrodermal Response
FFT: Fast Fourier Transform
GSR: Galvanic Skin Response
HDRS- 17, also HAM-D: Hamilton Depression Rating Scale- 17 item
HF: Heart Failure
HF: High Frequency
HPA: Hypothalamic-Pituitary-Adrenal Axis
HRV: Heart Rate Variability
ICD-10: International Classification for Diseases and Related Disorders
IL-1: Interleukin-1
IL-6: Interleukin-6

IRS: Inflammatory Response System
LH: Low Frequency
M1: First Auditory Stimuli
M2: Second Auditory Stimuli
MAOIs: Monoamine Oxidase Inhibitors
MDD: Major Depressive Disorder
MHPG: 3-methoxy-4-hydroxy-phenylethylene glycol
MI: Myocardial Infraction
MSE: Mental Status Examination
NA: Noradrenalin
PET: Positron Emission Tomography
PGR: Psychogalvanic Reflex
PNS: Parasympathetic Nervous Systems
PPG: Photoplethysmogram
PSD: Power Spectral Density
R1: First Resting State
R2: Second Resting State
R3: Third Resting State
SC: Skin Conductance
SCL: Skin Conductance Level
SCR: Skin Conductance Response
SNS: Sympathetic Nervous System
SSR: sympathetic skin response
SSRIs: Selective Serotonin Re-uptake Inhibitors
ST: Skin Temperature
TCAs: Tricyclic Antidepressants
TMS: Transcranial Magnetic Stimulation
TNF-α: Tumor Necrosis Factor
VNS: Vagus Nerve Stimulation
WHO: World Health Organization

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SUMMARY

ANALYSIS OF CARDIAC HEALTH IN PATIENTS SUFFER FROM MAJOR DEPRESSIVE DISORDER

Zeynep Beyza ZİLELİ

Biomedical Engineering Programme

MSc Thesis

Advisor: Prof. Dr. Sadık KARA

Co-Advisor: Assist. Prof. Dr. Saime AKDEMİR AKAR

The purpose of this study was to investigate the autonomous cardiac activity in mental disorder patient with physiological parameters and to determine the connection between mental disorder and cardiovascular diseases. In this study, skin temperature, galvanic skin response and blood volume pulse signals were recorded from major depressive disorder patients and healthy individuals during resting, active and calm auditory stimulation periods. Recorded signals were analyzed with signal processing method and the results were compared with each other to demonstrate the differences between major depressive disorder patients and healthy subjects. This study can be considered ss a first study that these signals were collected simultaneously with different auditory stimuli at different time periods.

Keywords: Major depressive disorder, heart rate variability, blood volume pulse, galvanic skin response, power spectral density.

ÖZET

MAJOR DEPRESYONU OLAN HASTALARIN KALP SAĞLIKLARININ ANALİZİ

Zeynep Beyza ZİLELİ

Biyomedikal Mühendisliği Programı

Yüksek Lisans Tezi

Danışman: Prof. Dr. Sadık KARA

Eş-danışman: Yrd. Doç. Dr. Saime AKDEMİR AKAR

Bu çalışmanın amacı, psikiyatrik rahatsızlıkları olan kişilerde otonom kardiyak aktivitenin fizyolojik parametrelerle incelenmesi ve psikiyatrik rahatsızlıklar ile kardiyovasküler hastalıklar arasındaki ilişkinin belirlenmesidir. Bu çalışmada vücut sıcaklığı, deri iletkenliği yanıtı ve kan hacmi sinyalleri sessizlik, hareketli ve sakin işitsel uyaran periyotlarında majör depresyon hastaları ve sağlıklı kişilerden kaydedilmiştir. Kaydedilen sinyaller sinyal işleme metoduyla incelenmiş ve sonuçlar majör depresyon hastaları ile sağlıklı kişiler arasındaki farklılıkları göstermek için birbirleriyle karşılaştırılmıştır. Bu çalışma, bahsedilen sinyallerin farklı uyaranlarla birlikte faklı periyotlarda, eş zamanlı olarak kaydedildiği ilk çalışma olarak değerlendirilebilir.

Anahtar kelimeler: Majör depresyon, kalp atış değişkeni, kan hacmi, deri iletkenliği yanıtı, güç spektral yoğunluğu.

CHAPTER 1

INTRODUCTION

Psychiatric disorders are one of the major diseases in worldwide and mood disorders are the most well-known psychiatric disorders. Major depressive disorder (MDD) has high prevalence in general population [1].

1.1 Literature Survey

Many studies were done to examine the relationship between MDD and cardiovascular diseases. One of the studies was showed that depressed people had lower Valsalva ratio than control group [2] and another study was investigated MDD patients before SSRI or SNRI treatment and predominance of sympathetic activation was observed. After antidepressant treatment, this imbalance was increased [3]. In another study proved that vagal control are negatively correlated with depression severity [4] but other research no correlation was found between them [5]. However another study was about hypotension and MDD relationship and it was proved that hypotension is also risk for MDD patient [6]. Increased skin response was recorded in two different electrical stimuli patients but pain perception was decreased. Sympathetic activation increment is not directly related to perceived pain [7].

1.2 Purpose of the Thesis

The purpose of this thesis was to compare physiological parameters that were recorded from major depressive disorder patients and healthy subjects with resting and auditory stimulation periods for showing relationship between major depression and autonomous

activity. The differences of autonomous nerve system response to resting, active and calm auditory stimulation periods in both patient and healthy group and how these changes occur from resting state to active and to calm auditory stimuli periods will be investigated. Correlation between psychiatric scaling and extracted features of recorded signals and will also be examined.

1.3 Hypothesis

The active auditory stimuli will increase heartbeat due to increased sympathetic nerve system activation while the calm auditory will decrease heartbeat because of reverse of this process in people. If major depression affects autonomous nerve system activation then there will be no significant difference between periods in patient group's physiological signals and significant difference in records of control group between auditory stimulation and resting state. Comparison between depression patients and healthy controls will result significant difference.

CHAPTER 2

MAJOR DEPRESSIVE DISORDER

In this chapter information about sign and symptoms, diagnosis, epidemiology, etiology and treatment of major depressive disorder (MDD) and the relationship between MDD and cardiovascular diseases have been discussed. Effects of MDD on heart rate variability and galvanic skin response were reported. Psychiatric disorders are extensive group of illness and cause disability to people. Most prevalent members of this illness are mood disorders.

2.1 Mood disorder

Mood disorder is a mental illness that affective experience, a complaint defined by operational criteria. In mood disorder, disturbance of mood state is main factor of illness [8]. Two main types of mood disorder are recognized. Bipolar disorder, as known as manic depression, has manic episodes that show fluctuations between increased energy and activity (mania) and low mood state and decreased energy and activity (depression) [9-10]. Another main type of mood disorder is MDD, commonly called major depression, clinical depression or depression. MDD has only one polar of mood state which is depressive state [11]. Other subtypes of mood disorders are seasonal affective disorder, dysthymia (atypical depression), psychotic depression, pediatric mood disorders, and geriatric mood disorders (Figure 2.1) [8, 11].

2.1.1 Major Depressive Disorder

MDD is described by a single or periodic major depressive episode(s); most people with MDD will experience periodic episodes [12]. The categories of MDD are mild,

moderate and severe depressive episodes. Differentiation between the categories is identified by the number, type, and severity of symptoms that present in patient [11].

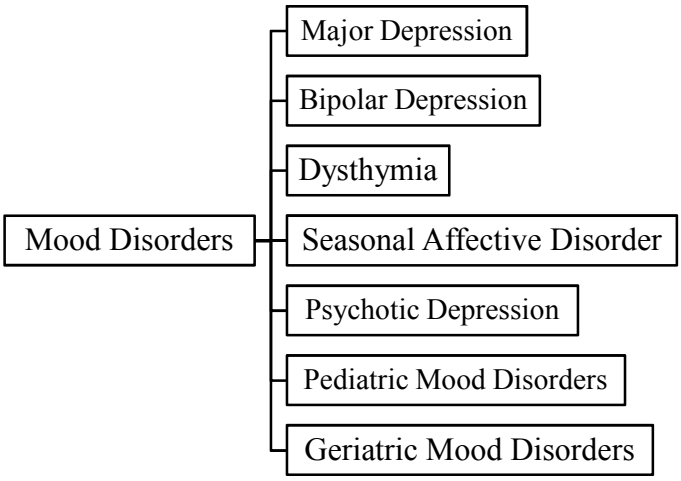


Figure 2.1 Subtypes of mood disorders

2.1.1.1 Symptoms and Signs

Two major symptoms that are usually exhibited by depressed people are overwhelming hopelessness and loss of interest or joy in activities that are formerly enjoyable. The major symptoms are combined with another symptoms that patterns individual's clinical level. Other symptoms vary patient to patient. The person who has depression may experience low self-esteem that is feeling of worthlessness, change in sleep pattern, change in appetite and weight that shows itself two ways: some people eat more than their normal limit and others' appetite may be reduced and they lost weight. Ability to tolerate pain may be reduced and the patient may has unexplainable pains. Impaired concentration and memory, slow thinking (retardation), suicidal thoughts, reduced sexual energy, loss of motivation are most common symptoms of major depression [13-15].

Symptoms may not stable during the depressed episode, they may change slightly through the day. Depression usually worsens in the morning and improves as the day goes on. Some patient may experience reverse of it or may be no change in the mood during all day [16].

2.1.1.2 Diagnosis

There is no laboratory tests for diagnose MDD. Mental status examination (MSE) is the important diagnose type of major depression. An observation of patient's appearance, behaviors speech, mood, thinking process, perception by the doctor is combined with patient's biological and family history to diagnose MDD accurately.

The two major classification systems in use today are Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) and The World Health Organization's (WHO) International Classification for Diseases and Related Disorders (ICD-10). Diagnose of MDD based on the presence of basic symptoms with precise duration of time. Basic symptoms are depressed mood, loss of interest or pleasure. In addition, at least five criteria from DSM-IV-TR list have to be present for duration of two weeks. It includes appetite and sleep disturbance, low self-esteem, feeling worthlessness and guilt, suicide thoughts and ideation [8]. ICD-10 describes depressive episodes which include loss of interest in activities, loss of appetite, libido and weight, motor retardation, lack of emotional reactions [17]. These symptoms need to be present duration of two weeks. All these symptoms are listed in Table 2.1 [18].

Depression inventory tests are also used to diagnose and score the major depression. Hamilton Rating Scale for Depression and Beck Depression Inventory tests are widely used psychiatric test for this purpose but there is no single test that it can be apply all populations for rating scale [19].

2.1.1.3 Epidemiology

MDD is the one of the extensive mental disorder in the world and causes loss of life quality and social problems in patient's life. In a study results show that depression is the fourth leading cause of disease burden in the world accounting 4, 4% of total disability adjusted life years [20] and another investigation shows that MDD is the first reason of years lost due to disability [21]. The prevalence of MDD in the USA population was 16, 2% in the lifetime and 6, 6% in 12-months prevalence [21]. The WHO has been reported depression caused 12, 4 years lived with disability [22]. Depression has higher ranks in females than males [23-24], affects up women 50% higher than men in general population [8] but there are no gender difference in prevalence of depression in prepubescent boys and girls [25]. These differences are explained by hormonal differences and exposure stressful life events. The suicide

Table 2.1 Criteria for depressive episode [18]

DSM-III-R/DSM-IV	ICD-10
Symptoms present nearly every day in same 2-week period	Episode must have lasted at least 2 weeks with symptoms nearly every day
Change from normal functioning Key symptoms (n=2)	Change from normal functioning Key symptoms (n=3)
Depressed mood	Depressed mood
Anhedonia	Anhedonia
	Fatigue/loss of energy
Ancillary Symptoms (n=7)	Ancillary symptoms (n=7)
Fatigue/loss of energy	Weight and appetite change
Weight/apettite loss/gain	Sleep disturbance
Insomnia/hypersomnia	Subjective or objective agitation/retardation
Observed agitation/retardation	Low self-esteem/confidence
Low self-esteem/guilt	Self-reproach/guilt
Impaired thinking/concentration	Impaired thinking/concentration
Suicidal thoughts	Suicidal thoughts
Criteria:	Criteria:
One key, five sysmptoms in total *plus*	Mild episode: two keys, four symptoms in total
Significant distress *or*	Moderate episode: two keys, six symptoms total
Social impairment	Severe episode: three keys, eight symptoms total
Exclusions:	Exclusions:
Not mixed episodes	No history (ever) of manic symptoms
Not substance related	Not substance related
Not organic	Not organic
Not bereavement,	
Not psychotic	

attempt is 25% less in women population than man population [26]. The onset age of major depression is in the mid to late 20s. The median age of onset in MDD is 30 years [24]. Economic status also affects the depression rates. In developed countries, the prevalence of depression in lifetime is 14.6% and in developing countries this result is 11.1% according to WHO survey". It is estimated that 350 million people are affected by depression globally [27].

2.1.1.4 Etiology

The etiology of depression is multifactorial and incompletely understood. Abnormalities in hypothalamic-pituitary-adrenal (HPA) axis response to stress and is affective in pathophysiology of depression. Investigations between patient and healthy group clearly showed some neurochemical imbalances in patient's neurotransmitter systems and neuromodulators. The studies suggest monoamine hypothesis that MDD is caused by monoamine transmitter system abnormalities at one or more brain sites. Three monoamines are highly related with major depression: Serotonin (5-hydroxytryptamine; 5-HT), noradrenaline, and dopamine [12].

Serotonin is important to regulate HPA axis that adjusts serotonergic activity [28]. Synthesis of serotonin in the brain needs a precursor amino acid, L-tryptophan. In a study plasma tryptophan level of untreated depressed patients are found lower than healthy group [29, 30]. Another research proved that reduced cerebrospinal fluid (CSF) concentrations of 5-hydroxyindoleacetic acid (5-HIAA) which is the main metabolite of serotonin formed in the brain, in depressed people who made a suicide attempt [31].

There are no direct evidence about noradrenaline or its major metabolite 3-methoxy-4-hydroxy-phenylethylene glycol (MHPG) levels in the CSF concentration levels [32] but in a study a1-adrenoceptor that is one of the subclass of noradrenaline receptors has lowered binding in some brain regions [33]. Noradrenaline function increasing elevates plasma concentrations of adrenocorticotropic hormone (ACTH), cortisol, and growth hormone. Growth hormone affects noradrenaline re-uptake inhibitor desipramine and the noradrenaline receptor agonist clonidine and levels of these in plasma are reduced in depressed patients [34]. Activation of glucocorticoid corticosteroid receptors mediates cortisol levels with corticotrophin (ACTH) release at pituitary gland. Adrenal gland enlargement affects ACTH release and it cause hypersecretion of corticotropin-releasing hormone (CRH) in the hypothalamus that is affect cortisol release [35]. Dopamine and

norepinephrine both modulate stress and plays important role in motivation and hedonic response [36] and acquisition of emotionally arousing memory [39]. Subjects who have tyrosine and phenylalanine reduction in their dopamine and norepinephrine system feel less glad and more prone to emotionally negative words [37].

The hippocampus is also important in HPA axis regulation that links hippocampal dysfunction and abnormal HPA axis regulation. Enlarged lateral ventricles, volume loss in frontal and temporal lobes, decreased hippocampal volume and volume of basal ganglia structures are proved in studies [38]. Decrease in brain volume in depressed people is showed as long-term consequences of depression due to hypersecretion of cortisol [14] but another study suggest that decrease in hippocampal volume may be present early in depression [39]. In PET investigations, lowered prefrontal perfusion is observed and it is linked decrease in grey matter volume of subgenual prefrontal cortex [40]. Reduced glial cells in post-mortem studies are also evidence for decreased volume of the brain [40-41]. In another research, cerebral blood flow and metabolism is altered in prefrontal cortex, anterior cingulate cortex, amygdala and thalamus [42].

Increased production of proinflammatory cytokines effects regulation of stress reactive neuroendocrine and central neurotransmitter changes and this increment is evidence of activation of the inflammatory response system (IRS) [43].

2.1.1.5 Treatment

Major depression is more plausible than other mental disorders. Psychotherapeutic and pharmacological approaches are effective in treatment of major depression. Pharmacological treatments are depended on monoamine hypothesis and aims monoaminergic transmission [12]. Tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) are used in treatment of MDD but they have more severe side effects such as anticholigenic symptoms and sedation than other drugs [44-45]. Selective serotonin re-uptake inhibitors (SSRIs) are more specific than TCAs and MAOIs and side effects are less but they are slower than other drugs [46]. Other antidepressants are more specific than TCAs, MAOIs and SSRI and used treatment of treatment-resistive depressed patient with trial-and-error method to find effective treatment type. These antidepressants are shown in Table 2.2 [18].

Table 2.2 Commonly used antidepressant in depression treatment [18]

Class of antidepressant	Monoamine affected	Mode of action	Other notes
Tricyclics antidepressants (TCAs)	Noradrenaline (NA) and serotonin (5-HT)	Reuptake inhibition	Individual TCAs vary in the proportion of NA and 5-HT reuptake
			Larger number of side effects
			May be more effective in severe depression
SRIs	Mainly 5-HT but can have NA and Dopamine (DA) effects	Reuptake inhibition	Now used as first-line treatment
			More selective action than TCAs
			Generally fewer side effects than TCAs, and better tolarated
5-HT and NA-RIs (Venlafaxine)	5-HT and NA, at higher doses possibly DA	Reuptake inhibition	At lower doses mainly 5-HT action
			At moderate doses NA action
			Pronounced withdrawal effects
NA-RIs	NA	Reuptake inhibition	Increased risk of seizure
Monoamines Oxidase Inhibitors	NA, 5-HT and DA	Prevent synaptic breakdown of NA and 5-HT	Tranycypromine is activating
			Tyramine low-diet required
5-HT_2 antagonists + reuptake inhibitors (Trazodone)	5-HT and NA	Block post synaptic 5-HT_2 receptors	Acts both pre- and post-synaptically
			Belief that both components are important for therapeutic effect
Mianserin, Mirtazepin	NA and 5-HT	Block pre-synaptic α_2-receptors	Pre-synaptic α_2-receptors usually inhibit release of NA and 5-HT
			Blocking these receptors stops the inhibition
Lithium	5-HT and other		Possibly influences post synaptic 2nd messenger system once receptor is activated
NA and DA reuptake inhibitor	NA and DA	Reuptake Inhibition	Only licensed in USA

Psychotherapy is successful in every age of patient groups. Cognitive behavioral therapy (CBT) and interpersonal therapy are an effective treatment for major depressive disorder [47-48]. Electroconvulsive therapy (ECT) is used for severe major depression patients who have no respond to antidepressant treatment [40]. Transcranial magnetic stimulation (TMS) is another treatment way of depression that is alternative for ECT and antidepressant treatment [49]. Vagus nerve stimulation (VNS) are also useful in recurrent or chronic and treatment resistive depression [43] but side effects of treatment has to research for future use [51].

2.2 Major Depressive Disorder and the Heart

Cardiovascular disease (CVD) and coronary artery disease (CAD) is the leading cause of death in worldwide and depression is the leading cause of disability [52]. Similar symptoms of MDD and CVD draw attention to the relationship between these two important and prevalent diseases. The studies showed that prevalence of depression in myocardial infraction (MI) population is 5% higher than general population [53] and 48% of 155 heart failure (HF) patients diagnosed as depression [54]. In another longitudinal study reported relative risk of cardiac mortality of 1.6 for people with depressive signs and symptoms and 3.8 for those with clinically diagnosed depression [55]. These suggested that depression may be cause to develop CVD and may be a risk factor for patients with CVD and CAD [56].

Beginning of the disease is still unclear. Depression leads to CVD development and accelerate CVD risk and progression due to risk factors of depression. Another possibility is that person is already CVD patient and changes in behavioral and biological changes cause depression. Changes in major biological pathway of the body may cause both depression and CVD is the third possibility between depression and CVD [57].

The connection between depression and cardiovascular disease is explained by behavioral and psychological factors. The loss of interest in basic life needs like eating meals or physical activity cause poor lifestyle habits and these non-healthy habits and motivation lost do not help patients stop smoking, make a well-balanced diet or do regular physical activity and this leads to develop CVD or worsen CVD [58-59].

The biological factors between depression and CVD are explained by several mechanisms. Platelets contain serotonin receptor and are effective in coronary

vasoconstriction. Psychological stress triggers acute hemostasis responses and this responses effects platelet function both healthy individuals and CVD patients [60]. Studies with depressed people demonstrated that increased platelet reactivity, increased and decreased reactivity of platelet to serotonin, decreased platelet reactivity to adenosine diphosphate [61-62] and increased sympathetic nervous activity was also evaluated [62]. Increased platelet activation has relationship with increased endothelial dysfunction and inflammatory activity [63]. Brachial artery flow-mediated vasodilation of MDD patients without CAD and control subjects is compared and endothelial dysfunction is observed in MDD patients [64]. Inflammatory activation blood markers such as C-reactive protein (CRP), interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor (TNF-α) induce acute coronary events and these markers have been found in high concentrations in blood in both MDD and CVD patients [65]. In Figure 2.2 these mechanisms are shown [66].

2.3 Major Depressive Disorder and Heart Rate Variability

Heart rate variability (HRV) is the variation in R-R intervals of the electrocardiogram (ECG) signals and represents the balance between two branches of autonomic nervous system (ANS), sympathetic and parasympathetic nervous systems (SNS and PNS), in the heart rate regulation. HRV analysis is noninvasive, quick and reproducible method to examine cardiac autonomic regulation. It is an important parameter for prognosis the myocardial infraction, left ventricular dysfunction and frequency of arrhythmia [67]. Hypothalamus, as well as HPA axis, is involved in autonomous system regulation, influencing brain stem autonomic nuclei. The hypothalamus receives inputs from limbic system which works close coordination with prefrontal neocortex to integrate emotional and motivational behaviors. Dysregulation of ANS may generate CVD and MDD. Several studies reported increased sympathetic vascular resistance [68], decreased parasympathetic/vagal control of cardiac activity [69], decreased baroreflex sensitivity [70], higher values of autonomic index LH/HF due to dominance of sympathetic to parasympathetic control. In a study, HRV of unmedicated depressed adolescent girls was examined and increased sympathetic activation was observed [71]. Another research, short-term HRV of acute coronary syndrome (ACS) patients was examined to exhibit relationship between HRV and inflammatory markers. HRV were significantly and negatively associated with inflammatory markers but no difference between

depressed and non-depressed ACS patients [72]. Lesser Valsalva ratio, increased sympathetic activity due to decreased parasympathetic activity and altered sympathovagal balance was also reported with research[73].

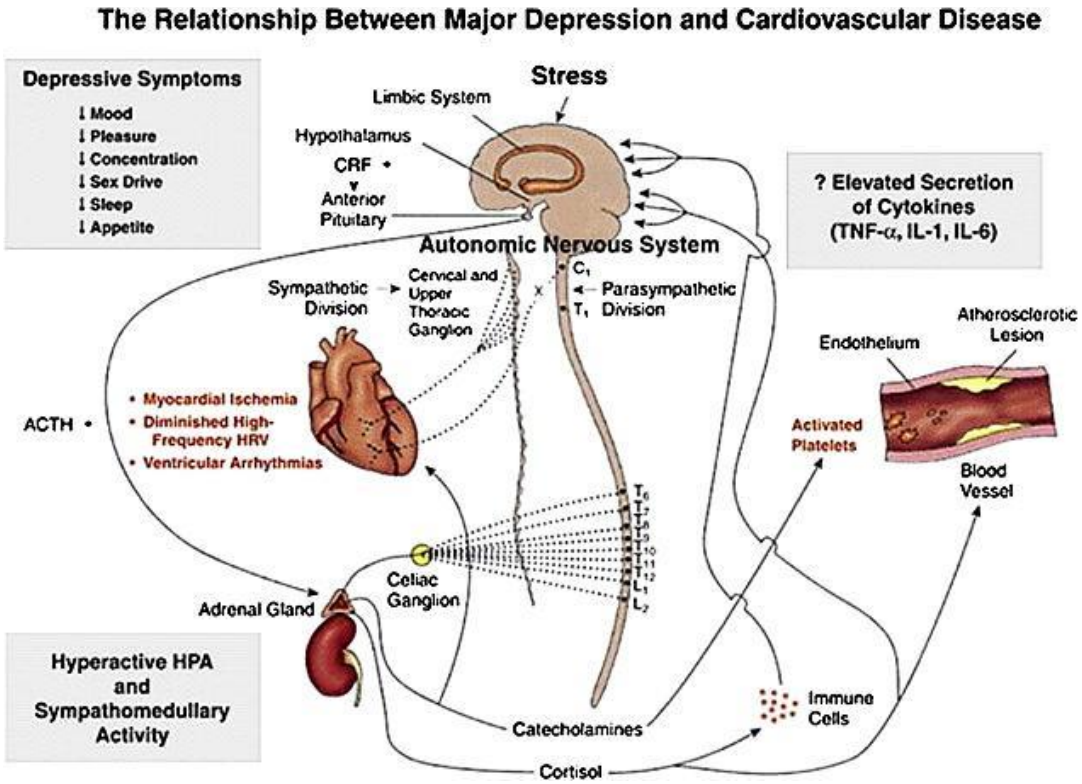


Figure 2.2 Several biological mechanisms [66]

2.4 Major Depressive Disorder and Galvanic Skin Response

Internal or external stimuli change the electrical conductance of the skin with moisture level of the skin and this change is measured as galvanic skin response (GSR). This change is regulated by sweat glands, which are controlled by SNS, so gives an evidence for person's mood and state. Due to SNS activation, the researchers hypothesized reduced pain perception to external stimuli in depressed patients and proved this hypothesis [74]. Another study is also showed latencies of GSR were reduced in MDD patients [75].

CHAPTER 3

MATERIALS AND METHODS

Information about the subjects, the procedure of research, the physiological signals that were investigated in the research, the measurement system that used to gathering signal and signal processing methods constitutes this chapter.

3.1 Subjects

Patients were taken from Bezmialem Vakıf University Faculty of Medicine Department of Psychiatry and controls were taken from janitors of Fatih University. The study was proven by both hospital and university ethics committee. Fifteen drug-naïve MDD patients and fifteen age-matched control subjects were involved the study. The procedure was explained verbally to participants and written informed consent was obtained from all them.

Table 3.1 Demographics, clinics and self-report measures of subjects

	MDD Patients	Controls
Number	15	15
Male/Female	4 / 11	6 / 9
Age	37.66 ± 13.4	39.8 ± 10.87
Dominant Hand	All right-handed	All right-handed
HAMD Score	20.5±7.18	-
BAI Score	13.73 ± 6.14	-
Smoker/ Non Smoker	5 / 10	6 / 9

The patients were diagnosed as a moderate depression according to DSM- IV- TR criteria by physician. Severity of depression was obtained by Hamilton Depression Rating Scale- 17 item (HDRS- 17, also HAM-D) and between 18 –25 was considered to be moderate depression. Beck Anxiety Inventory (BAI) was also performed to participants (Table 3.1). Patients were chosen by some inclusion and exclusion criteria.

Inclusion Criteria:

- Between 18 – 65 years old
- Diagnosed with MDD according to DSM-IV
- HDRS score between 18-25
- Giving written, informed consent

Exclusion Criteria:

- Having any other mental disorders except major depressive disorder (comorbidity)
- Having pathological, endocrinological, cardiovascular disorders
- Psychotropic medication usage
- Cardiovascular medication usage
- Having head trauma or other neurological disorder
- Having cardiac pacemaker or any device that affect cardiac autonomic function
- Having substance abuse disorders (including alcohol abuse)
- Having vandalism risk
- Having hearing loss
- Being pregnant or lactation period in females

It was noticed that the chosen patient has no pathological, endocrinological, neurological and cardiovascular disorders and comorbidity. Cardiac pacemaker users and patient who uses hypertension, anticoagulant, cholesterol lowering, antiarrhythmics, vasodilators or any medication that is effective in cardiac function were excluded. In control group, users of these medications were also excluded.

3.2 Procedure and Auditory Stimuli

The signals were recorded between 9.00 AM and 12.00 PM in quiet and illuminated room at Bezmialem Hospital, Department of Psychiatry. The subjects were quietly sitting on chair in relaxed position, did not moved until end of the recording and their eyes were closed during recording.

Galvanic skin response (GSR), photoplethysmogram (PPG) and skin temperature (ST) signals were recorded simultaneously during 10 minutes from each subject. Recorded signal was consisted of 5 equal periods. First period was resting period with 2 minutes duration and labeled with R1. Second period was first auditory stimuli period and lasted 2 minutes. In this period, active music was preferred as auditory stimuli to fasten heartbeat. "Symphony No. 10 in E minor (Op. 93) by Dmitri Shostakovich 2nd movement" was chosen. The main symphony has 4 movements: First movement is moderato (86-97 BPM), second movement is allegro (109-132 BPM), third movement is allegretto (98-109 BPM) and fourth movement is andante-allegro (73-77 BPM and 109-132 BPM) [76]. Second movement of the symphony was most appropriate part of the symphony to increase heart rate [77]. Third period was resting period (R2) and there was no auditory stimuli. Fourth period was the second auditory stimuli period and sedative music was chosen for decrease heartbeat. Instrumental "Gamzedeyim Deva Bulmam" by Başar Dikici from classical Turkish music which is composed by Tatyos Ekserciyan was used as sedative auditory stimuli [78]. Its makam (mode) was Uşşak makam and this makam brings happiness to listeners according to Turkish philosopher Farabi. Lastly the recording ended up with 2 minutes resting period (R3) (Figure 3.1). Subjects listened the auditory stimuli via headphones.

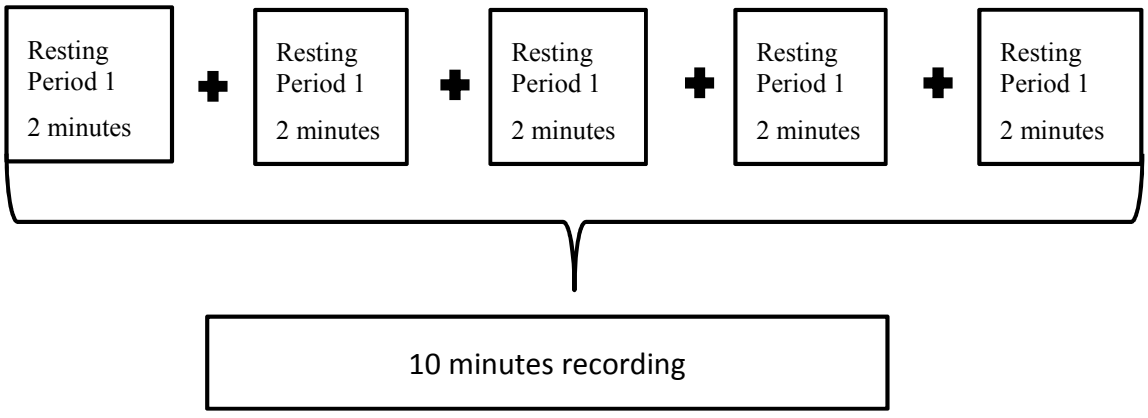


Figure 3.1 Total lenght of signal recording

3.3 Physiological Signals and Data Recording Unit

BIOPAC System Inc. MP150WSW data acquisition system was used to record GSR, PPG and ST signals (Figure 3.2) [79].

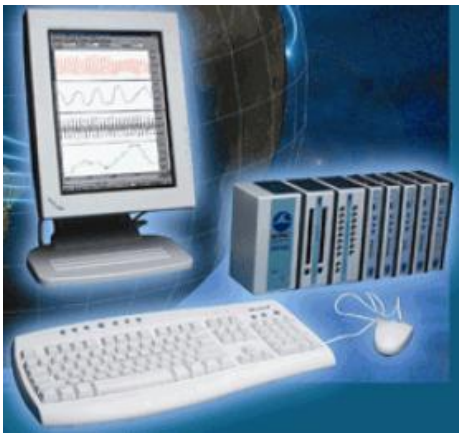


Figure 3.2 BIOPAC MP150WSW data acquisition system [79]

3.3.1 Galvanic Skin Response (GSR)

GSR is also known as skin conductance (SC), electrodermal response (EDR), electrodermal activity (EDA), psychogalvanic reflex (PGR), skin conductance response (SCR), skin conductance level (SCL), sympathetic skin response (SSR) is a psychological measurement that indicates emotional changes due to affective stimuli. This change is regulated by sweat gland and sweat glands' activation and secretion is controlled by sympathetic nervous system (SNS). SNS is one of branches of autonomic nervous system (ANS) which regulated involuntary effectors and cardiac muscle. Parasympathetic nervous system (PNS) is another component of ANS and it works coordinately with SNS (Figure3.3) [80]. SNS is responsible from "fight-or-flight" reactions that occur in stressful events and increases heart rate, blood pressure, urinary bladder while PNS produce "rest and digestion" response due to fight-or-flight response and decreases heart rate, blood pressure, urinary bladder. Sweating is also regulated with SNS but PNS has no effect on this action [81]. When a person feels fear, anger or excitement SNS activates sweat glands and this activation appears as a sweating. Increased humidity on skin by sweating increases conductance of the skin.

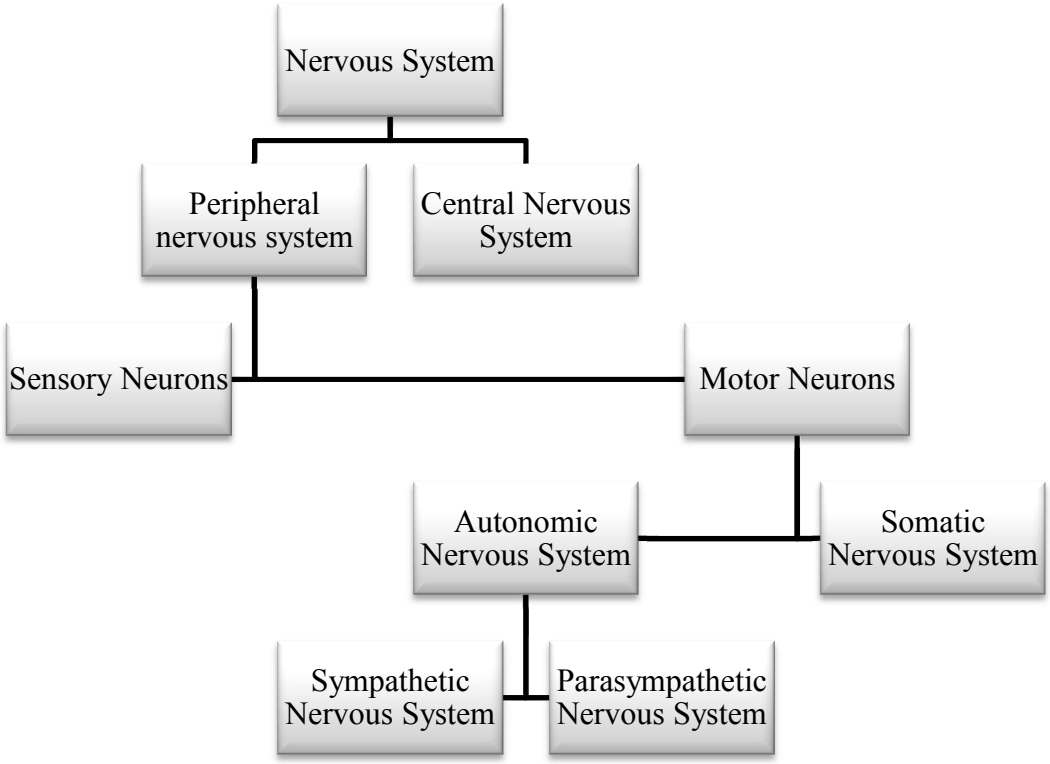


Figure 3.3 Human nervous system [80]

GSR100C amplifier module (Figure 3.4a) [82] which uses 0.5V constant voltage and TSD100C Ag-AgCl non-polarizable electrodes (Figure 3.4b) [83] were used to measure GSR signal. The electrodes were filled with isotonic electrode gel for conduction and bound to the subject's distal phalanx of an index and middle finger of non-dominant hand. The sampling rate was 200 Hz. The GSR signal low pass filtered at 1 Hz and high pass filtered at 0.05 Hz. Table 3.2 and Table 3.3 give information about input conductance range and electrical specifications of GSR100C amplifier.

Table 3.2 Input conductance range of GSR100C amplifier

DC(μmho)	Sensitiviy (μmho/V)
0-200	20
0-100	10
0-50	5
0-20	2

Figure 3.4a) Galvanic Skin Response Amplifier GSR100C [82] and b) TSD203 transducer [83]

Table 3.3 Electrical specifications of GSR100C amplifier

Gain	20, 10, 5, 2 micro-mhos/volt
Output Range	0-10V nominal ±10V full
Low-pass filter	1Hz, 10 Hz,
High-pass filter	DC, 0.005 Hz, 0.5 Hz
Sensitivity	0.7 nano-mhos
Excitation	0.5 VDC (Constant Voltage)

3.3.2 Blood Volume Pulse (BVP)

Blood volume pulse (BVP) is the physiological signal that is obtained by blood volume change due to blood pulsation of the each heartbeat. Measurement of blood volume change in blood vessels is made by method called photoplethysmography and depends on the fact that blood absorbs more infrared light than the surrounding tissues. The PPG transducer has infrared emitter that sends infrared light through the blood vessel and detector that detects transmitted light. PPG is noninvasive and simple method for detecting changes in blood volume and it gives information about autonomic nervous function. RR peaks in electrocardiogram (ECG) are related with PP peaks in PPG signal and PPG signals give information about heart rate and heart rate variability (HRV) (Figure 3.5) [84]. Usually PPG signals are taken from fingers but also ear lobe, nasal

septum and forehead is used to detect signals when the blood circulation is not enough to meaningful signal record [67].

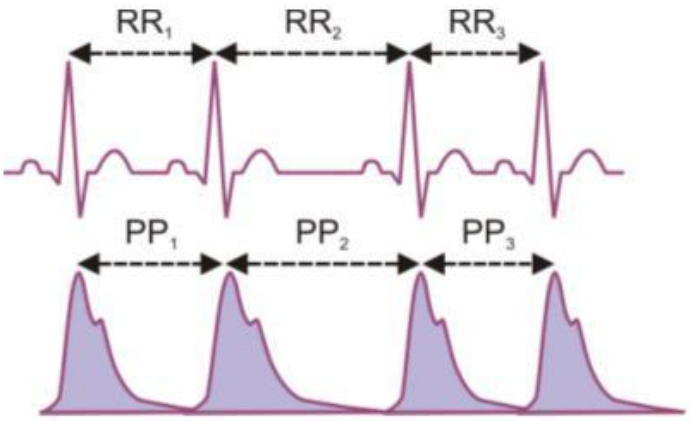


Figure 3.5 The relationship between ECG and PPG signal [84]

For detection PPG signals, PPG100C photoplethysmogram amplifier module (Figure 3.6(a)) [82] and TSD200 photoplethysmogram transducer (Figure 3.6 (b)) [85] which consists of infrared emitter/detector of 860 nm ±60 nm waveleght is used. Transducer was bound to the subject's phalanx of ring finger with the Velcro straps. PPG signal low pass filtered at 10 Hz and high pass filtered at 0.05 Hz. The gain was set at 100 and sampling freqency was 200 Hz. Electrical specifications of PPG100C amplifier module is given in Table 3.4.

Table 3.4 Electrical specifications of PPG100C amplifier

Gain	100, 50, 20, 10
Output Range	±10 V (analog)
Low-pass filter	3 Hz, 10 Hz,
High-pass filter	DC, 0.005 Hz, 0.5 Hz
Noise voltage	0.5 μV (rms)
Excitation	6 V

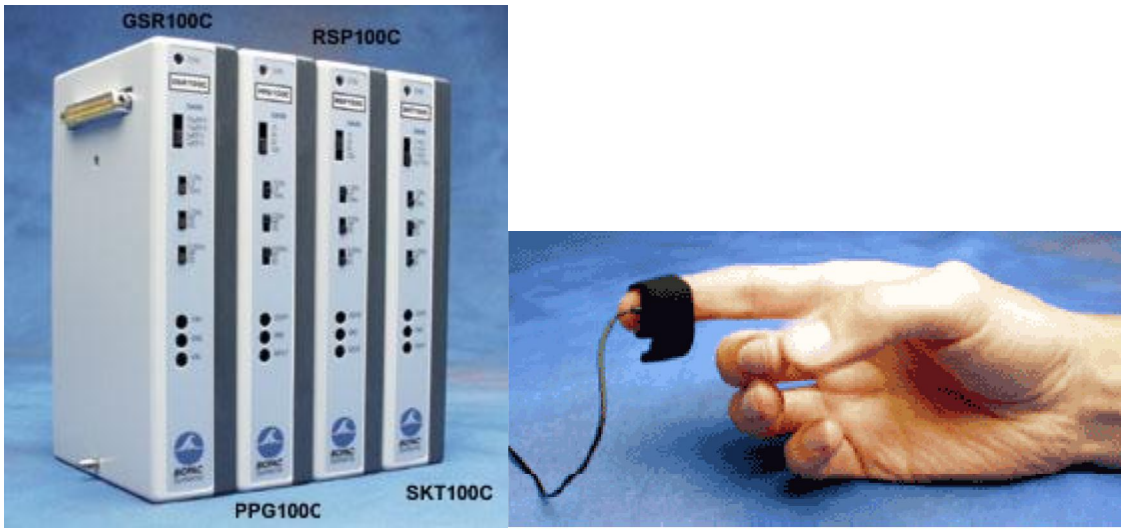


Figure 3.6a) Photoplethysmogram amplifier PPG100C [82] and b) photoplethysmogram transducer TSD 200 [85]

3.3.3 Skin Temperature (ST)

Temperature of the body is regulated by the hypothalamus with neural feedback function. The hypothalamus sends more nerve impulses to the blood vessels which causes blood vessels narrowing for abandon blood flow to the skin and stimulates skeletal muscles to shivering for heat generation or sends less nerve impulses to cause dilation in blood vessel and increase blood flow and activates sweat gland for sweating. ST may slightly vary during the day and person to person [86].

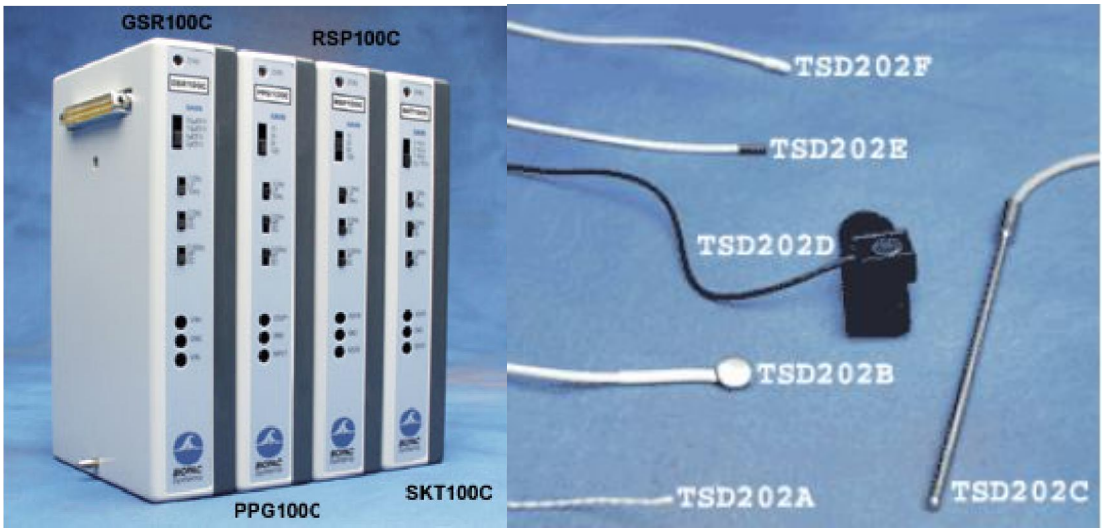


Figure 3.7a) Skin Temperature amplifier SKT100C [82] and b) skin temperature transducer TSD202B [87]

ST was recorded by BIOPAC SKT100C skin temperature amplifier (Figure 3.7(a)) [82] and TSD202B ST transducer (Figure 3.7(b)) [87]. The transducer was taped to the patient's thumb of non-dominant hand. The gain was set at 5 °F/V and the sampling rate was 200 Hz. The signal low pass filtered at 10 Hz and high pass filtered at 0.05 Hz. In Table 3.5 electrical specifications of SKT100C amplifier was given.

Table 3.5 Electrical specificications of SKT100C amplifier

Gain	5, 2, 1, 0.5 °F/V
Output Range	±10 V (analog)
Low-pass filter	1 Hz, 10 Hz,
High-pass filter	DC, 0.005 Hz, 0.5 Hz
Sensitivity	180 micro °F (100 micro °C)

3.4 Signal Processing

3.4.1 Fourier Transform

Fourier transform is a mathematical tool that is used to investigate sinusoidal components which are cosines (real part) and sines (imaginary) part of the signal to analyse system performance. Processing of these components gives information about amplitude, frequency and phases of the signal. The continuous-time (CT) Fourier series, the CT Fourier transform, the discrete-time Fourier transform (DTFT), the discrete Fourier transform (DFT), and the fast Fourier transform (FFT) are different types of Fourier transform that are used in different areas. Classic form of Fourier transform is used for CT signals and systems. The basic Fourier transform and the inverse of Fourier transform is given in Eq. (3.1) and Eq. (3.2) [88].

$$S(jw) = \int_{-\infty}^{\infty} s(t)e^{-i\omega t}dt \tag{3.1}$$

$$s(t) = \frac{1}{2\pi}\int_{-\infty}^{\infty} S(j\omega)e^{i\omega t}d\omega \tag{3.2}$$

The s(t) component represents continuos signal and multilipied by complex sinusoids. Properties of CT Fourier transform makes it useful for linear CT system analysis.

Linearity, time-differentiation, time-integration properties are helpful to solve complex integrals. The impulses and frequencies are used to specify the system and this is based on time-domain convolution property of Fourier transform. The frequency-shifting property is widely used in communication systems. The connection between CT and discrete-time (DT) is denoted by sampling and reconstruction operations. The signal *s(t)* is sampled by every *T* seconds and this denotes as $s_a(t)$ in Eq. (3.3)

$$s_a(t) = \sum_{n=-\infty}^{n=\infty} s(t)\delta(t - nT) \tag{3.3}$$

$$s_a(t) = \sum_{n=-\infty}^{n=\infty} s(nt)\delta(t - nT) \tag{3.4}$$

where $\delta(t)$ is the CT impulse function. The spectrum of sampled signal is obtained by

$$F\{s_a(t)\} = \sum_{n=-\infty}^{\infty} s_a\,(nT)\left[e^{i\omega t}\right]^{-n} \tag{3.5}$$

DTFT is obtained from Eq. (3.5) in terms of the sequence sample s[n]

$$S\left(e^{j\omega'}\right) = \sum_{n=-\infty}^{\infty} s[n]e^{-j\omega' n} \tag{3.6}$$

and its inverse is

$$s[n] = \frac{1}{2\pi}\int_{-\pi}^{\pi} S\left(e^{j\omega'}\right)e^{jn\omega'}d\omega' \tag{3.7}$$

Many properties of the DTFT are similar with CT transform except time-differentiation and time-integration properties because these are not defined for DT signals. The FFT is an algorithm to compute DTFT fastly. It reduces the complexity of DTFT computation from Order $\{N^2\}$ to Order $\{Nlog_2N\}$. The FFT is often used in spectral analyis of the signal [88].

3.4.2 Power Spectral Density (PSD)

PSD is an important method in the analysis of stationary random process that evalutes the power of the signal as a funtions of frquency. The future values of the signals cannot

be exactly determined because cannot be expressed as an analyticial funtion of time and probabilistic statments are used to find future values. Random sequences include possible realizations that each of them are related probablity of occurence. But only one realization may observed that deterministic definition of previous section is carried next section without any change. Realizations of random signals do not have finite energy but have average power and this can be used to characteried signal by PSD. PSD of a random process is the fourier transform of autocorrelation function [89].

In first definition of PSD is defined as DTFT of the covariance sequence

$$\varphi(w) = \sum_{-\alpha}^{\alpha} r(k)e^{-i\omega t} \tag{3.8}$$

The inverse transform of (3.8) gives *r(k)* that is

$$r(k) = \frac{1}{2\pi}\int_{-\infty}^{\infty} \varphi(w)e^{i\omega t}dw \tag{3.9}$$

In second definition of the PSD is

$$\lim_{N\to\infty} E\left\{\frac{1}{N}\left|\sum_{t=1}^{N} y(t)e^{-i\omega t}\right|^2\right\} \tag{3.10}$$

E represents expected value

$$= \lim_{N\to\infty}\frac{1}{N}\sum_{t=1}^{N}\sum_{s=1}^{N} E\{y(t)y*(s)\}\,e^{-i\omega(t-s)} \tag{3.11}$$

$$= \lim_{N\to\infty}\frac{1}{N}\sum_{\tau=-(N-1)}^{N-1} (N-|\tau|)r(\tau)e^{-i\omega t} \tag{3.12}$$

$$= \sum_{\tau=-\infty}^{\infty} r(\tau)e^{-i\omega t} - \lim_{N\to\infty}\frac{1}{N}\sum_{\tau=-(N-1)}^{N-1} (N-|\tau|)r(\tau)e^{-i\omega t} \tag{3.13}$$

PSD should be real number and positive number. Parametric and non parametric methods are avaiable to calculate PSD.

3.4.2.1 Non Parametric Methods

Non parametric methods begin with estimating autocorrelation sequence of a given data and then power spectrum is estimated by Fourier transform of estimated autocorrelation sequence.

3.4.2.1.1 Periodogram

The periodogram is the one of the ways to estimate power spectral density. It is found by estimating autocorrelation. Autocorrelation is determined with Eq.(3.14) [90]

$$r_x(k) = \lim_{N\to\infty}\left\{\frac{1}{2N+1}\sum_{n=-N}^{N} x_{n+k}{x_k}^*\right\} \tag{3.14}$$

Autocorrelation can be estimated, if x_n is only avaliable for finite interval *[0, N-1]*. Eq (3.14) is modified as

$$\widehat{r_x}(k) = \frac{1}{N}\sum_{n=0}^{N-1-k} x_{n+k}{x_k}^* \qquad k = 0, 1, \dots, N-1 \tag{3.15}$$

The periodogram is estimated by taking DTFT of the autocorrelation

$$\widehat{P_{per}}\left(e^{jw}\right) = \sum_{k=-N+1}^{N-1} \widehat{r_k}\,(k)e^{-jk\omega} \tag{3.16}$$

To express the periodogram by itself, let x_{N-n} be the finite lenght N signal such as

$$x_{N,n} = \begin{cases} x_n & 0 \le n < N \\ 0 & else \end{cases} \tag{3.17}$$

$x_{(N,n)}$ is the product of x_n and rectangular window:

$$x_{N,n} = W_n^R x_n \tag{3.18}$$

After that the autocorrelation is defined as

$$\widehat{r_x}(k) = \frac{1}{N}\sum_{-\infty}^{\infty} x_{N,n+k}\, x_{N,n}^* = \frac{1}{N} x_{N,k} * x_{N,-k}^* \tag{3.19}$$

The periodogram is found by taking the Fourier transform of autocorrelation and the convolution theorem:

$$\widehat{P_{per}}\left(e^{jw}\right) = \frac{1}{N}X_N\left(e^{j\omega}\right)X_N^*\left(e^{j\omega}\right) = \frac{1}{N}\left|X_N\left(e^{j\omega}\right)\right|^2 \tag{3.20}$$

3.4.2.1.1.1 Welch Method

Welch method is used to estimate power spectrum [91]. In Welch method, the data segments are allowed to ovelap and to compute the periodogram each data segment is windowed. Data segment are given mathematically [89];

$$y_j(t) = y((j-1)K + t) \qquad t = 1, \ldots, M \qquad y = 1, \ldots, S \tag{3.21}$$

where $(j-1)K$ is the starting point of jth data segment. The windowed periodogram according

to $y_j(t)$ is computed as

$$\acute{\phi}_J(w) = \frac{1}{MP}\sum_{t=1}^{M}\left|v(t)y_j(t)e^{-i\omega t}\right|^2 \tag{3.22}$$

where P represents the power of the temporal window $\{v(t)\}$:

$$P = \frac{1}{M}\sum_{t=1}^{M}|v(t)|^2 \tag{3.23}$$

The Welch periodogram is found by averaging these modified periodogram [89]:

$$\acute{\varphi}_W(w) = \frac{1}{S}\sum_{j=1}^{S}\acute{\phi}_J(w) \tag{3.24}$$

Welch method uses fewer methods than other methods. It calculated short sequences of signal rather than whole signal and it is advantegous when study with machine that has limited core storage [91].

3.5 Statistical Analysis

Indepent Sample Student's t-test and Paired Sample t-test was performed for statistical anlysis of the recorded signals.

3.5.1 The Student's t-test

The probability distribution is the statistical interference that specify the probability to all possible values of discrete random variable with their possible probabilities. The t-distribution (Figure 3.8) [92] is the one of the probability distribution that is used to

estimate mean of population that fits the normal distribution and standart deviation is not known.

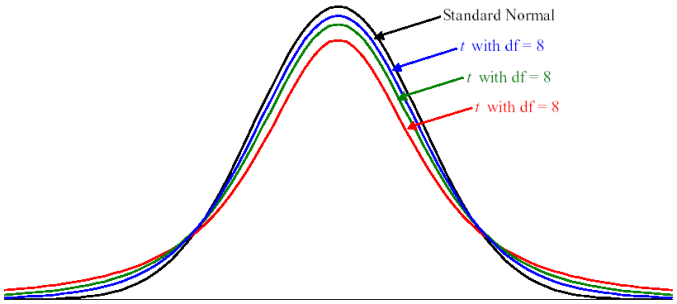


Figure 3.8 t-distrubition [92]

z value for confidence interval is calculated for normal distribution by

$$z = \frac{\bar{x} - \mu}{\sigma/\sqrt{n}} \tag{3.25}$$

where the $\bar{x}$ is the sample mean, μ is the mean of the population, n sample size, σ is standart deviation of the population. In t-distrubition σ is not known and estimated by

$$s^2 = \frac{1}{N-1}\sum_{i=1}^{N}(x_i - x)^2 \tag{3.26}$$

and called sample standart deviation. The s is applied to equation (3.25) and t value calculated by

$$t = \frac{\bar{x} - \mu}{s/\sqrt{n}} \tag{3.27}$$

The Student's t-test uses t-distribution and is commonly used hypothesis testing method that is based on difference between means of two population. One nominal group and one measurement variable need to perform this test and nominal group have to be only two choice [93].

3.5.1.1 The Indepent Sample Student's t-test

The independent sample student's t-test is used when compared two group collected independently from themselves and connected to each other via nominal group. In this test it is assumed that distribution of the populations normal and variances of two

population are equal to each other. To calculate the test first pooled standart deviation has to be calculated by

$$s_p{}^2 = \frac{(n_1 - 1){s_1}^2 + (n_2 - 1){s_2}^2}{n_1 + n_2 - 2} \tag{3.27}$$

where $n_1 + n_2 - 2$ is the degree of freedom. The equation for calculation t value become [94]

$$t = \frac{\overline{x_1} - \overline{x_2}}{\sqrt{\frac{s_p{}^2}{n_1} + \frac{s_p{}^2}{n_2}}} \tag{3.28}$$

3.5.1.2 Paired Sample Student's t-test

The paired sample t-test is used for samples that are in same group and measurements are taken twice or their units are matched with each other. Paired sample t-test compares paired values of two group, considers the variation within each group and produce a *t* value (Eq. 3.29)

$$t = \frac{\frac{\sum d}{N}}{\sqrt{\frac{\sum d^2 - \frac{(\sum d)^2}{N}}{N(N-1)}}} \tag{3.29}$$

In formula, d is the difference between matched samples and *N* is number of samples [94].

CHAPTER 4

RESULTS

In this chapter, results of analyzing skin temperature, skin conductance and blood volume pulse signals that were collected from both patient and control group is explained. For signal processing, algorithms in MATLAB® (v. 7.8.0 R2009a) software was used for signal processing and statistical analysis is done by the SPSS® (v. 21) software. The differences between patients and controls were detailed briefly. Figure 4.1 shows BIOPAC® Software Interface during record SC, PPG and ST signals from patients.

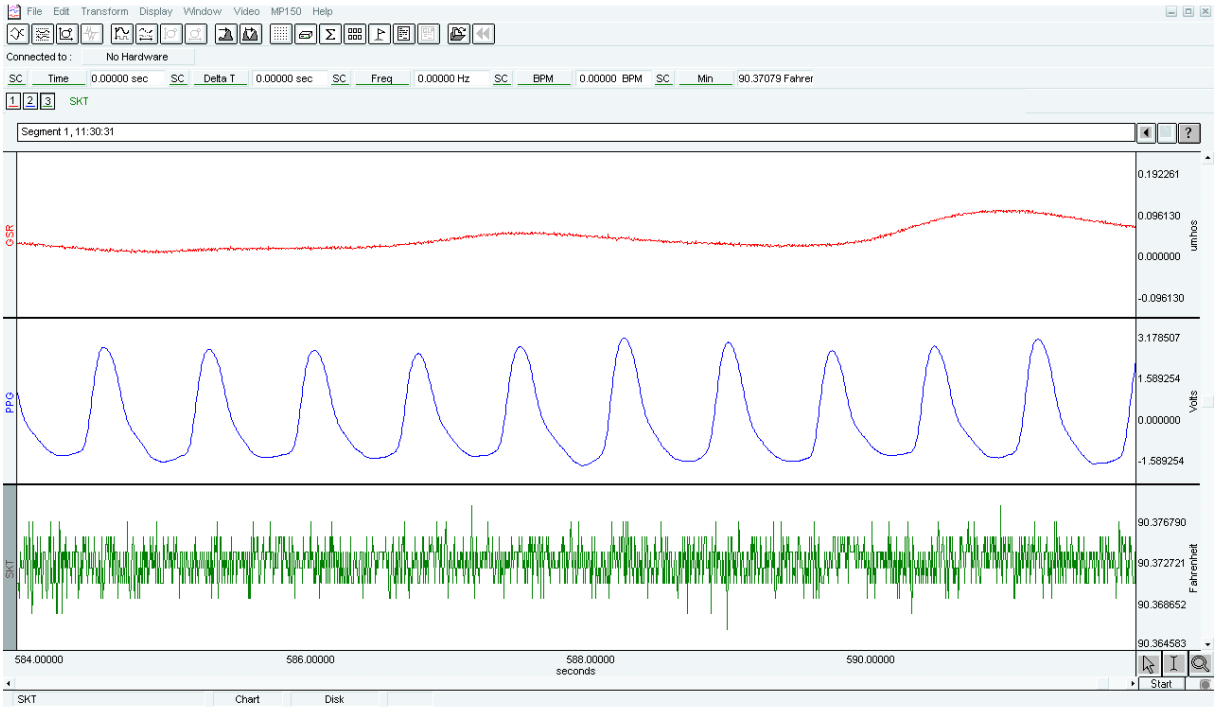


Figure 4.1 A BIOPAC Software Interface screenshot while recording data

4.1 Skin Temperature

Skin temperature (ST) analysis was applied for both patient and control group for all periods of the record. Descriptive statistical information about mean and standard deviation is given in Table 4.1. Figure 4.2 is the graph of change in ST signal during all procedure and figure 4.3 shows the change in ST both the patient and control group at all periods.

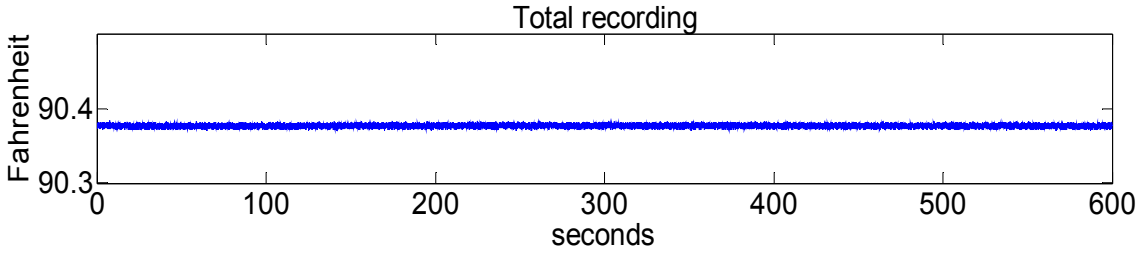


Figure 4.2 Changes in skin temperature signal during total recording in the patient group

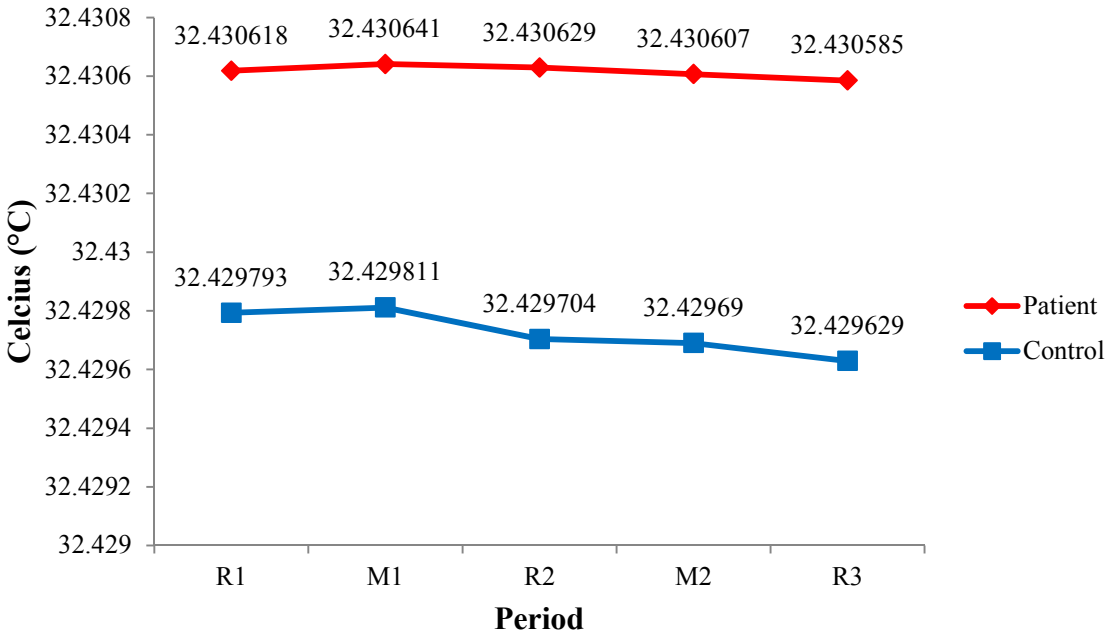


Figure 4.3 Change in skin temperature at different periods. R1 is first resting period, M1 is active auditory stimuli period, R2 is second resting period, M2 sedative auditory stimuli and R3 is third resting period

Table 4.1 Descriptive statistics about skin temperature in the patient and control group

	Patient Group		Control Group	
Period	Mean (°C)	Standard Deviation	Mean (°C)	Standard Deviation
R1	32.430618	0.0019	32.429793	0.0012
M1	32.430641	0.0020	32.429811	0.0010
R2	32.430629	0.0019	32.429704	0.0012
M2	32.430607	0.0019	32.429690	0.0013
R3	32.430585	0.0019	32.429629	0.0014

The patient and control group were compared each other with SPSS® statistical package, paired sample Student's t-test. The level of confidence interval was chosen 95% thus the significant difference between groups was accepted when p value smaller than 0.05. The results showed that there is significant difference between first (M1) and second music (M2) periods ($p=0.014$), second resting (R2) and M2 periods ($p=0.028$), R2 and third resting (R3) periods ($p=0.009$) and M1 and R3 periods ($p=0.013$) in patient group. In control group, the difference between M1 and R2 ($p=0.035$) and M1 and R3 ($p=0.035$) periods were significant. The highest ST was recorded in M2 period and the lowest ST was observed at R3 period in both patient and control group. Patient group's mean ST was higher than control group in all periods. The comparison between patient and control group was performed by SPSS statistical package, independent sample Student's t test and results are given in Table 4.2. The difference between patient and control group are significant in all periods ($p<0.005$).

Table 4.2 Comparison of skin temperature between the patient and control group

Periods	R1	M1	R2	M2	R3
Mean Diff.	0.0014	0.0015	0.0016	0.0016	0.0017
Std. Err. Diff.	0.0005	0.0005	0.0006	0.0006	0.0006
p value	0.019	0.018	0.011	0.012	0.010

4.2 Galvanic Skin Response

Figure 4.4 shows change in galvanic skin response (skin conductance – SC) during the signals recording. Table 4.3 lists the mean and standard deviation of SC analysis results of patient and control group in all periods. Histogram presentation of SC values is in Figure 4.5.

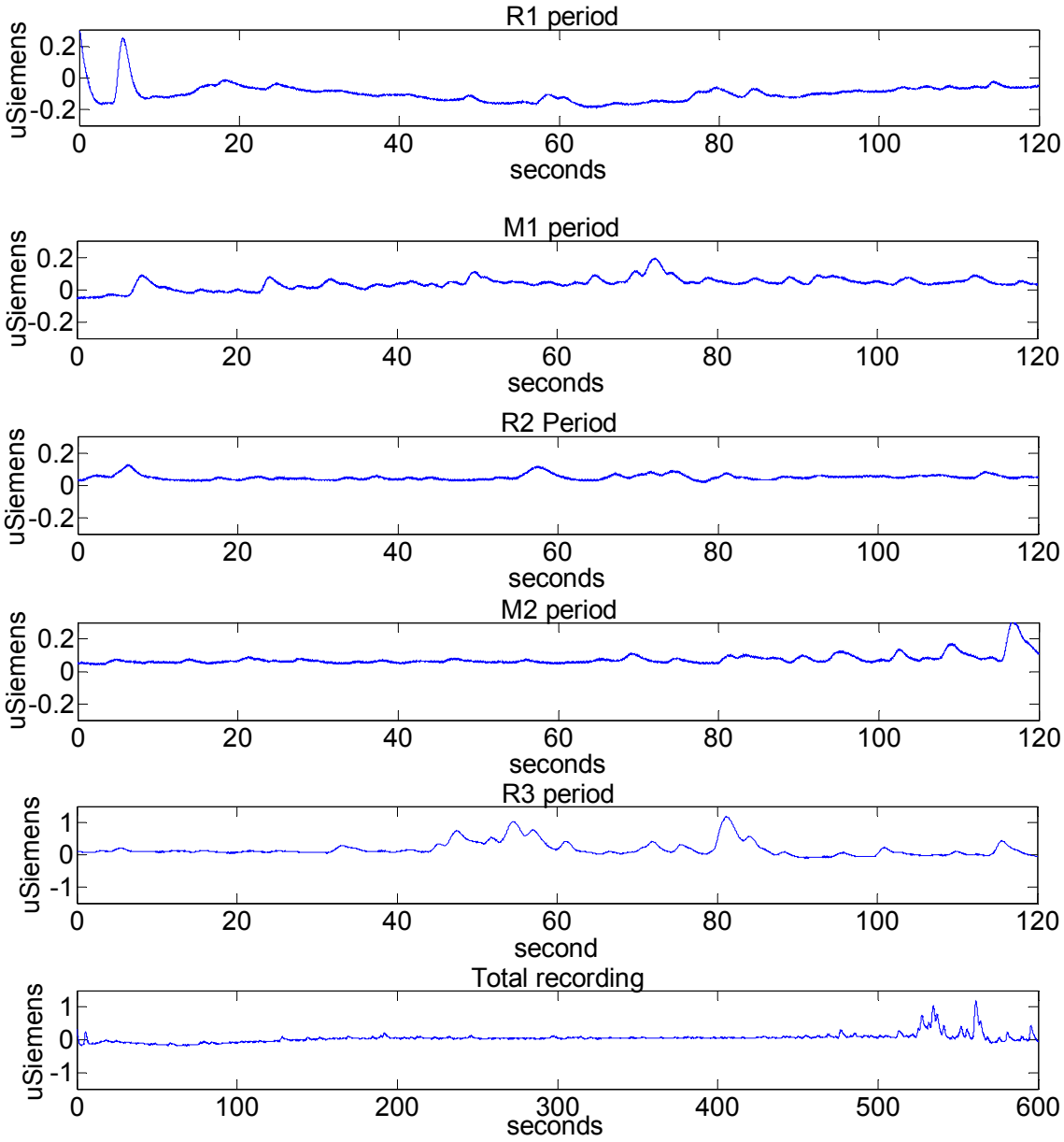


Figure 4.4 Change in skin conductance signal during the procedure in the patient

Paired sample Student's t-test were performed to analyze the difference between periods. Confidence level was chosen as 95% and significant difference was accepted when p value is less than 0.05.There are significant change between R1 and R2 (p=0.00), M1 (p=0.00), M2 (p=0.00) and R3 (p=0.00) periods in patient group. And also

M1-R3 (p=0.00), R2-M2 (p=0.027), R2-R3 (0.00) and M2-R3 (p=0.00) periods are also significantly different between each other. In control group, the significant difference is observed in R1-M1 (p=0.0), R1-R2 (p=0.0), R1-M2 (p=0.0), R1-R3 (p=0.002), M1-R3 (p=0.0), R2-M2 (p=0.018), R2-R3 (p=0.0) and M2-R3 (p=0.0) periods (Table 4.4). Highest SC value of patient group is recorded in R3 period but it is recorded in M2 period in control group. The increment of SC is observed in M1 after R1 period and M2 after R2 period in both groups. Independent sample Student's t-test was used to compare between patient and control group. The results of this comparison are written in Table 4.5. In M2 and R3 periods the significant difference is observed.

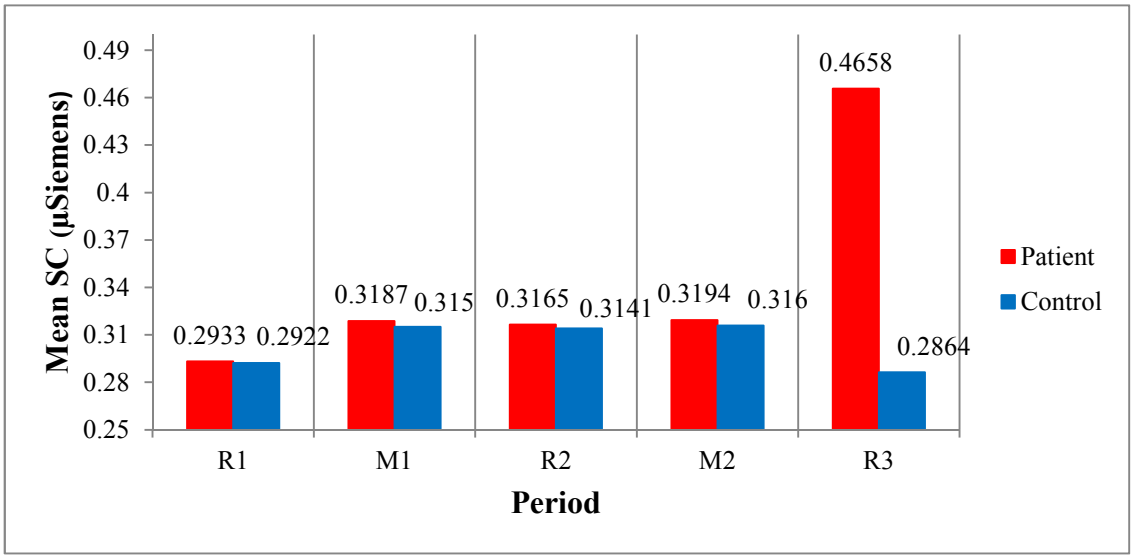


Figure 4.5 Skin conductance of the patient and control groups in periods

Table 4.3 Statistics about skin conductance in the patient and control group

	Patient Group		Control Group	
Period	Mean (µSiemens)	Standard Deviation	Mean (µSiemens)	Standard Deviation
R1	0.2933	0.0156	0.2922	0.0050
M1	0.3187	0.0068	0.3150	0.0042
R2	0.3165	0.0042	0.3141	0.0023
M2	0.3194	0.0050	0.3160	0.0024
R3	0.4658	0.0049	0.2864	0.0020

Table 4.4 Comparison of skin conductance between periods in the patient and control group

	Patient Group		Control Group	
Periods	Mean ± (SD) (μSiemens)	p Value	Mean ± (SD) (μSiemens)	p Value
R1-M1	0.0254 ± (0.016)	0.00	0.0227 ± (0.008)	0.00
R1-R2	0.0232 ± (0.018)	0.00	0.0218 ± (0.006)	0.00
R1-M2	0.0261 ± (0.018)	0.00	0.0236 ± (0.006)	0.00
R1-R3	0.1725 ± (0.012)	0.00	0.0058 ± (0.006)	0.00
M1-R3	0.1471 ± (0.007)	0.00	0.0285 ± (0.005)	0.00
R2-M2	0.0028 ± (0.004)	0.027	0.0017 ± (0.002)	0.018
R2-R3	0.1493 ± (0.007)	0.00	0.0277 ± (0.004)	0.00
M2-R3	0.1464 ± (0.008)	0.00	0.0295 ± (0.003)	0.00

Table 4.5 Comparison of skin conductance between the patient and control group

Periods	R1	M1	R2	M2	R3
Mean Diff.	0.0010	0.0037	0.0023	0.0035	0.1794
Std. Err. Diff.	0.0042	0.0020	0.0012	0.0014	0.0013
p value	0.814	0.086	0.068	0.023	0.000

4.3 Blood Volume Pulse

The heart rates of the both group are detected from recorded PPG signals by MATLAB software algorithm. In Table 4.6 maximum and minimum heart rates are given. The highest maximum heart rate is detected during R1 period in patient and R3 period in control group. In patient group, heart rate is decreased from R1 period to R3 period and then increased in R3 period but in control group, heart rate is increased during R1 period to R3 period, decreased in M2 period and reached the maximum value in R3 period. Comparison between periods in both heart beats of the patient and control group is given in Table 4.7. There was no significant difference observed in the patient group but in the control group between R1-R2 and M1-R2 periods p value was lowered than 0.05.

Table 4.6 Maximum and minimum peaks of PPG signals of the patient and control group

		Patient Group		Control Group	
Heart Rate		Mean	Standard Deviation	Mean	Standard Deviation
R1	Max.	175	38	174.67	18.5
	Min.	174.3	37.7	174	18.5
M1	Max.	172.3	31.2	176.5	24.6
	Min.	171.5	31.1	175.4	24.3
R2	Max.	169.5	22.6	186.4	31.9
	Min.	168.8	22.5	185.9	31.8
M2	Max.	166.2	20.1	184.8	31.8
	Min.	165.6	20.1	184.2	31.9
R3	Max.	169	23	190.7	45.1
	Min.	168.3	22.7	189.9	45.1

Table 4.7 Comparison of heartbeat between periods in the patient and control group (mean ± standard deviation)

Heart Beat		Patient Group		Control Group
Periods	Mean ±SD	p value	Mean ±SD	p value
R1-M1	2.8 ± 12.066	0.384	1.733 ± 12,702	0.605
R1-R2	5.533 ± 21.600	0.338	11.933 ± 20,499	0.041
R1-M2	8.733 ± 21.486	0.138	10.267 ± 23,386	0.111
R1-R3	6.0 ± 21.935	0.307	15.933 ± 37,134	0.119
M1-R2	2.733 ± 17.637	0.558	10.2 ± 15,612	0.024
M1-M2	5.933 ± 14.753	0.142	8.533 ± 16,932	0.071
M1-R3	3.2 ± 13.655	0.379	14.2 ± 32,107	0.109
R2-M2	3.2 ± 8.654	0.174	1.667 ± 11,286	0.576
R2-R3	0.467 ± 9.775	0.856	4.0 ± 20,125	0.454
M2-R3	2.733 ± 7.056	0.156	5.667 ± 22,296	0.342

Power spectral density analysis was performed with Welch's periodogram algorithm. Mean and standard deviation of power spectrum components which are power, maximum amplitude and frequency are illustrated in Figure 4.6 and given in Table 4.8 for patient and control group. Power spectrum of both groups is given in figure 4.7. The histogram of means of both groups is shown in Figure 4.8.

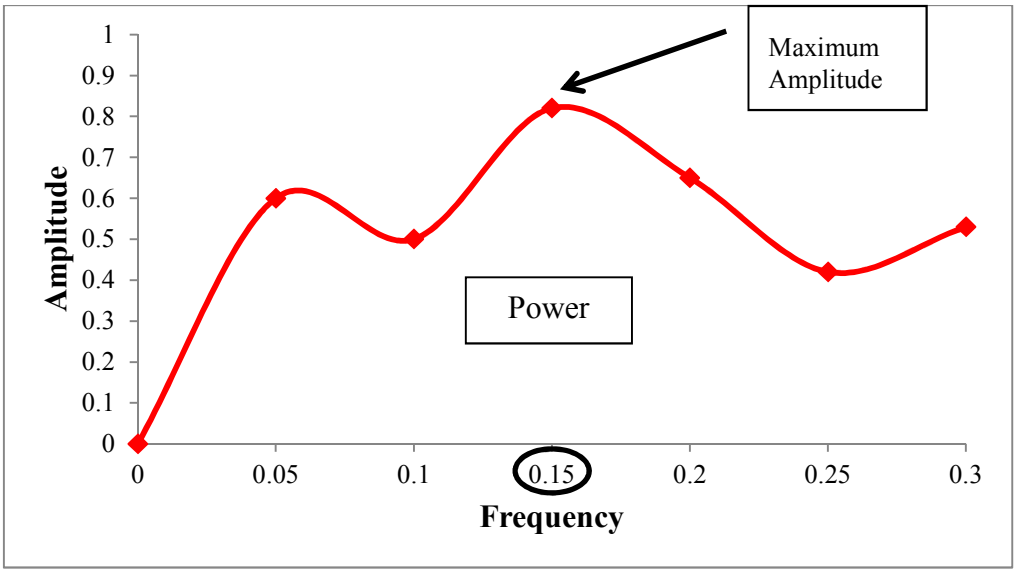


Figure 4.6 Components of heart rate variability. Power is the area under the curve, maximum amplitude is the highest peak in the graph and frequency is the where maximum amplitude is observed

Table 4.8 Mean and standard deviation (mean ± SD) of HRV components between the patient and control group. R1, R2 and R3 is referred to first, second and third resting periods, M1 is active auditory stimuli and M2 is sedative auditory stimuli.

	Patient group			Control group		
Period	Power (Watt)	Maximum Amplitude (Volt)	Frequency (Hz)	Power (Watt)	Maximum Amplitude (Volt)	Frequency (Hz)
R1	0.4794 ± (0.0011)	0.8811± (0.1536)	0.2213 ± (0.0414)	0.4783 ± (0.0008)	0.5056 ± (0.1481)	0.5163 ± (0.0262)
M1	0.6036 ± (0.0007)	0.7907 ± (0.1559)	0.1251 ± (0.0473)	0.4787 ± (0.0020)	0.4938 ± (0.1189)	0.3643 ± (0.0360)
R2	0.6038 ± (0.0008)	0.8248 ± (0.1676)	0.2195 ± (0.0424)	0.4783 ± (0.0007)	0.5057 ± (0.1435)	0.3642 ± (0.0378)
M2	0.6036 ± (0.0007)	0.7843 ± (0.1474)	0.5209 ± (0.0196)	0.4782 ± (0.0006)	0.4714 ± (0.1586)	0.3607 ± (0.0356)
R3	0.6037 ± (0.0007)	0.8197 ± (0.1373)	0.0477 ± (0.0226)	0.6029 ± (0.0005)	0.4839 ± (0.1650)	0.3620 ± (0.0350)

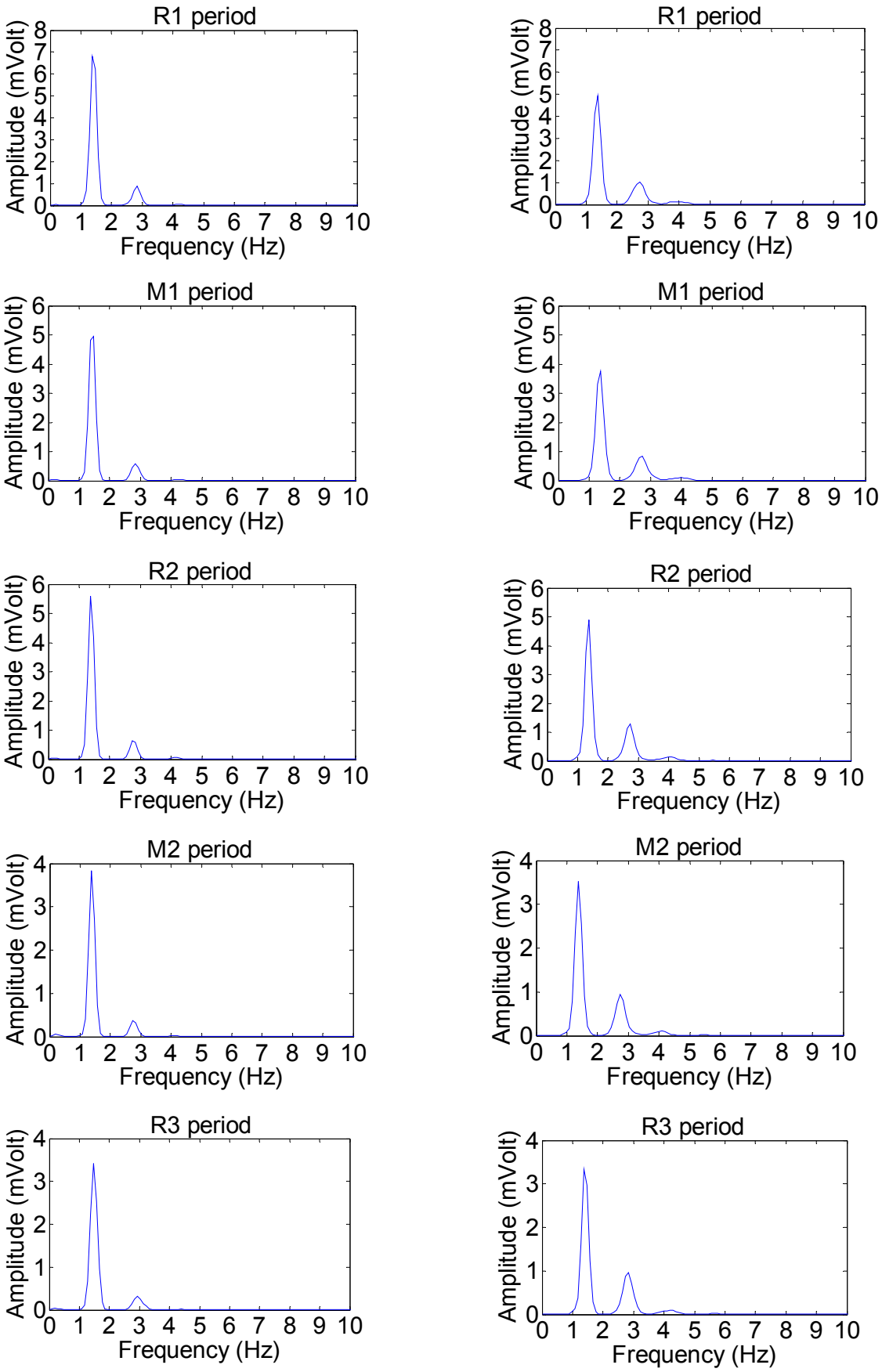
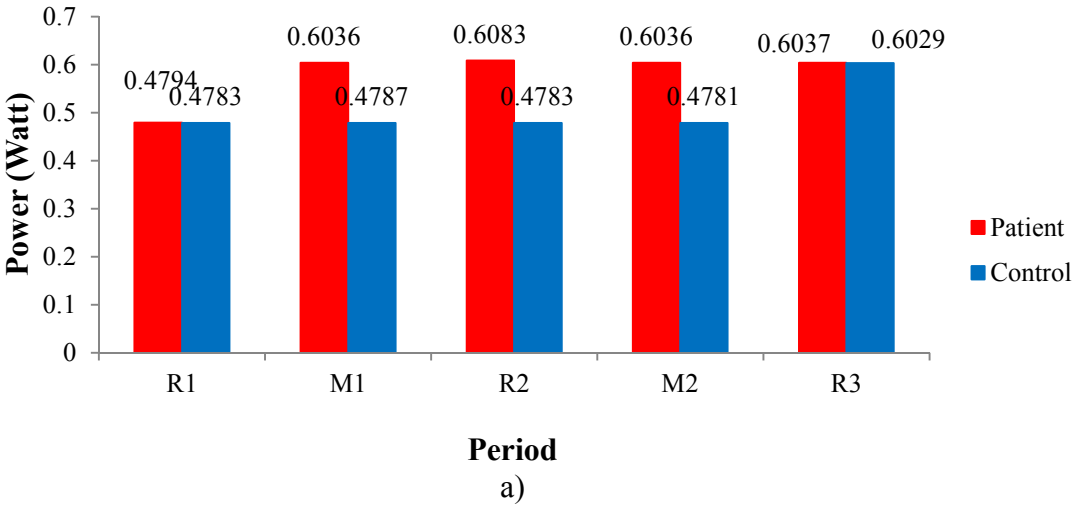
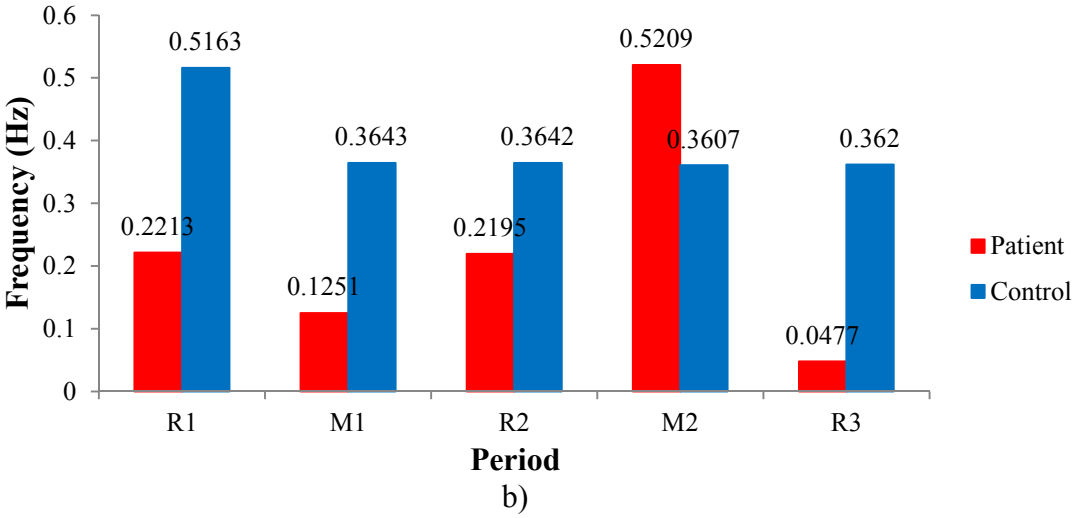


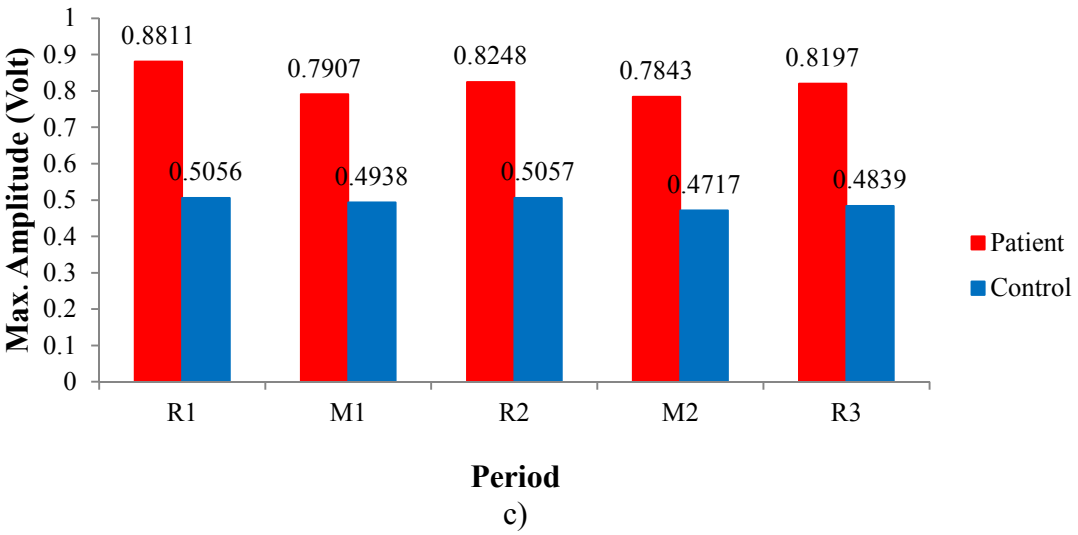
Figure 4.7 Power spectrum of the patient and control group at different periods. Left column shows the patient group and right column shows the control group.



a)



b)



c)

Figure 4.8 Power (a), frequency (b) and maximum amplitude (c) of the patient and control group

Paired sample Student's t-test was performed for comparison of the periods between them. The confidence level was set at 95% and difference is counted significant when p value is smaller than 0.05. There are significant difference in power between R1-M1, R1-R2, R1-M2 and R1-R3 periods (p=0.00). For maximum amplitude the difference is observed in R1-M1, R1-M2 and R2-M2 periods and for frequency the significant difference is found in between all periods ($p \leq 0.01$) except R1-R2 periods in patient group. In table 4.9 mean and standard deviation of all combination of periods are given briefly. In control group, significant difference is found in between R1-R3, M1-R3, R2-R3 and M2-R3 periods in power component of HRV (p=0.00). There is no significant difference in maximum amplitude between periods except R2-M2 period that p value is 0.044 in that period. In frequency component, significant difference is observed between R1-M1, R1-R2, R1-M2, and R1-R3 (p=0.00). Other comparison results are given in Table 4.10.

In patient group the power is increased from R1 period to M2 period, then it is decreased slightly in M2 period and it is increased less in the end of R3 period. Maximum amplitude is decreased during M1 period, then increased in R2 period and reached the lowest value at M2 period. Frequency is decreased in M1 period and then increased in R2 period. It reaches highest value in M2 period and lowest value in R3 period. In the control group, power has lowest value in R1 period, then it increases and same in other periods. Maximum amplitude has highest value in R1 period. It decreases in M1 period, increases in R2 period and then reaches the lowest value in M2 period. Frequency is higher in R1 period in contrast to other periods. It decreases in M1 and R2 periods and has lowest value in M2 period. It increases slightly in the last period.

Results of independent sample Student's t-test show the comparison between patient and control group at same periods. In R1 period the p value of power is 0.004, p value of maximum amplitude is 0.00 and frequency p value is 0.00. For all other periods except R3, p values of power are found 0.00. In R3 period it is found 0.001. Maximum amplitude and frequency comparison is also shows the significant difference for all periods (p=0.00).

Table 4.9 Comparison of components of HRV; power, maximum amplitude and frequency between periods in the patient group. $p \leq 0.05$ is accepted for significant difference. Resting periods were named as R1, R2 and R3 sequentially and auditory stimulus are abbreviated as M1 and M2 and SD is abbreviation of standard deviation.

	Power (Watt)		Maximum Amplitude (Volt)		Frequency (Hz)	
	Mean ± SD	p value	Mean ± SD	p value	Mean ± SD	p value
R1-M1	0.1241559 ± 0.0006	0.000	0.0904456 ± 0.0676	0.000	0.0962256 ± 0.0867	0.001
R1-R2	0.1243468 ± 0.0008	0.000	0.0563485 ± 0.1030	0.053	0.0017845 ± 0.0069	0.334
R1-M2	0.1241595 ± 0.0010	0.000	0.0967696 ± 0.1320	0.013	0.2995841 ± 0.0591	0.000
R1-R3	0.1242706 ± 0.0009	0.000	0.0613816 ± 0.1179	0.063	0.1735859 ± 0.0634	0.000
M1-R2	0.0001909 ± 0.0004	0.120	0.0340971 ± 0.0703	0.081	0.0944411 ± 0.0874	0.001
M1-M2	0.0000036 ± 0.0004	0.978	0.0063240 ± 0.0844	0.776	0.3958097 ± 0.0319	0.000
M1-R3	0.0001147 ± 0.0005	0.385	0.0290640 ± 0.0977	0.269	0.0773603 ± 0.0275	0.000
R2-M2	0.0001873 ± 0.0004	0.107	0.0404212 ± 0.0655	0.031	0.3013686 ± 0.0604	0.000
R2-R3	0.0000762 ± 0.0007	0.674	0.0050331 ± 0.1108	0.863	0.1718014 ± 0.0642	0.000
M2-R3	0.0001111 ± 0.0006	0.465	0.0353880 ± 0.1002	0.193	0.4731700 ± 0.0089	0.000

Table 4.10 Comparison of components of HRV; power, maximum amplitude and frequency between periods in the control group

	Power (Watt)		Maximum Amplitude (Volt)		Frequency (Hz)	
	Mean ± SD	p value	Mean ± SD	p value	Mean ± SD	p value
R1-M1	0.0004532 ± 0.0020	0.393	0.0117310 ± 0.105	0.672	0.1519999 ± 0.013	0.000
R1-R2	0.0000020 ± 0.0003	0.981	-0.0001327 ± 0.129	0.997	0.1521300 ± 0.014	0.000
R1-M2	0.0000874 ± 0.0005	0.530	0.0342066 ± 0.158	0.416	0.1556362 ± 0.013	0.000
R1-R3	0.1245863 ± 0.0006	0.000	0.0216978 ± 0.170	0.628	0.1543635 ± 0.014	0.000
M1-R2	0.0004512 ± 0.0020	0.401	-0.0118637 ± 0.062	0.473	0.0001301 ± 0.012	0.967
M1-M2	0.0005406 ± 0.0020	0.329	0.0224756 ± 0.086	0.333	0.0036363 ± 0.007	0.084
M1-R3	0.1241331 ± 0.0020	0.000	0.0099668 ± 0.101	0.708	0.0023636 ± 0.013	0.496
R2-M2	0.0000894 ± 0.0003	0.269	0.0343394 ± 0.060	0.044	0.0035062 ± 0.010	0.216
R2-R3	0.1245843 ± 0.0004	0.000	0.0218305 ± 0.071	0.258	0.0022335 ± 0.009	0.381
M2-R3	0.1246737 ± 0.0002	0.000	0.0125089 ± 0.049	0.341	0.0012727 ± 0.008	0.551

CHAPTER 5

DISCUSSION AND CONCLUSION

Mood disorders are common mental disorders and major depressive disorder (MDD) is the one of the most known mood disorder in nowadays. MMD affects individuals' life quality negatively and besides it also influences patient's relatives and family. This change in life quality like insomnia or sleep a lot, weight gain or loss, disturbance in concentration or else causes decrease in work performance and this costs more than treatment of MDD [95]. Delay in diagnosis of MDD or ignorance of signs and symptoms of illness are important reasons of high prevalence of MDD. In 2030 unipolar major depression will be third leading causes of burden of disease [96].

MDD is diagnosed with mental status examination (MSE) that is based on doctor's observations about patient and psychiatric tests which are used for scoring depression. Psychiatric tests are effectuated by criteria that are based on American Psychiatric Association's Diagnostic and Statistical Manual for Mental Disorders (DSM-IV-TR) and World Health Organization's International Statistical Classification of Diseases and Related Health Problems (ICD-10). But still there are no laboratory tests for diagnose MDD. Different biological pathways of MDD result different antidepressant production so that medicine treatment needs trial periods to measure effects of medicine in patients and this cause latency in recovery especially in treatment-resistive depression.

In this thesis, skin temperature (ST), skin conductance (SC) and blood volume pulse (BVP) signals were collected simultaneously from both 39 depression patients but some of these patients were elected because they already diagnosed with cardiovascular or coronary artery disease and started to use medications like anticoagulant or heart rate suppressor that affects autonomous cardiac function. Patients who use medication

constantly for another illness except CAD was also eliminated due to effects or side effects medications that may affect autonomous nerve system activation. Two different kind of music were used as auditory stimuli to decrease and increase the heartbeat. First music (M1) was loud symphony that was used to increase the heartbeat and second music (M2) was calm, instrumental classical Turkish music which aimed to decrease heartbeat in both group. The record began with resting state (R1), after M1 period again resting state started (R2) and finally after M2 period last resting state (R3) began. During the recording subjects sat up chair and did not move.

ST was slightly higher in M1 period than R1 period in patients and then it decreased. This change occurred same way in control group. Patient group started with high ST value in records and continued in that way and at all periods had higher ST values than control group. In control group, there was significant decrement in R2 period but this change did not occur in patients group. The higher ST value in patient group may be result of increased sympathetic activity but they did not show significant difference between resting and auditory stimulation periods. This showed us there was no change in room temperature during recording signals.

SC value was lowest in R1 period and reached highest value at R3 period in patients group. Due to calm auditory stimulation and resting state, expected results was decrement in R3 period but in patients' group results was significantly opposite of them. In control group, SC in R3 period was lower than R1 period which was expected beginning of the study. The unusual difference in patient group can be explained by decreased sensitivity in stimulations due to central nervous system dysfunction. Auditory stimulus which was used in M2 period to calm the subjects may be effected some subjects and they became melancholy. This affection was higher in depressed patients and resulted as R3 period. The change in SC value did not effected by room temperature because the ST was not change enormously during the record. It showed us all changes were response to auditory stimuli periods and resting states. In previous studies, MDD patients were showed decreased sensitivity in different kind of stimuli and increased skin response [97-99].

Effects of MDD in cardiovascular (CV) functions in human body were studied during last decade. Several mechanisms also explained to prove relationship between CVD and MDD. Autonomous nerve system (ANS) is always subject of interest of researchers due to its role in heartbeat regulation. Heart rate variability (HRV) is good evidence for

cardiac autonomic regulation and mostly investigated on ECG signal. PPG is the non-invasive and easy-to-use technique that can work as ECG and HRV may be performed on PPG signal.

Heart rate (HR) of patients was lesser than control group at all periods. During M1, HR of control group was increased compared to R1. However, in patients group HR was decreased at M2 period. This difference was expected between two groups in response to active music. During R3, HR of patients continued to decrease while patients' values increased. When calm auditory stimulus was started, HR of both groups was decreased significantly and finally in R3 period both groups had increased HR. At the end of the recording, patients had lower HR from their starting HR while controls were opposite of this. Patients showed increased parasympathetic activation and/or vagal function due to auditory stimulation while control group had higher parasympathetic activity. Another reason of this result could be duration between two auditory stimuli. R2 period was not enough to calm down of the heart.

Power component of HRV was calculated for both group and patients were higher values than control group. R1 period the value of power was almost similar to control group. In M1 period there was no change in controls but patients' power value was significantly higher than controls and R1 period. Control group reached highest value during R3 period but still it was lesser than power value of patients. Significant difference in M1, R2 and M2 periods between patients and control could be sign of bradycardia in patients group [100] or dysfunction of vagus nerve [101]. In maximum amplitude (MA) component of patient group was also higher values at all periods than control group and highest value was detected in R1 period and lowest value was in M2 period. Significant change was occurred between R1-M1, R1-M2 and R2-M2 periods in patient group. In control group these period were different, R2-M2, M2-R3 and R2-R3 periods that significant difference was observed. R2-M2 period was common in both group. Amplitude of HRV gives information about ANS balance that higher amplitude shows higher autonomic balance. High MA was expected in control group but it resulted opposite of this hypothesis. Frequency value of patients reached highest number at M2 period while control group had lowest value in M1 period and patient group had abnormal decrement in R3 period but there was no such difference in control group.

In conclusion, the significant difference was expected between periods in the control group and no such difference between periods in the patient group. These results may be related with severity of depression and moderate depression was not enough to show difference in between periods. The smoking ratios may also influence the results. The control group consisted of janitors who are working in physically exhausting job and this reason may affect the heart beat regulation in that group [102].

REFERENCES

[1] World Health Organization, (2009). “Global Health Risks: Mortality and burden of disease attributable to selected major risks” WHO Library Cataloguing-in-Publication Data.

[2] Guinjoan S.M., Bernabó J. L., Cardinali D. P., (1995). “Cardiovascular tests of autonomic function and sympathetic skin responses in patients with major depression”, J Neurol Neurosurg Psychiatry, 59:299-302.

[3] Koschke M., Boettger M. K., Schulz S., Berger S., Terhaar J., Voss a., Yeragani V. K., Bär K. J., (2009). “Autonomy of Autonomic Dysfunction in Major Depression”, Psychosomatic Medicine, 71(8): 852-860

[4] Nugent A. C.,Bain E. E., Thayer J. F., Sollers III J. J.,Drevets W. C., (2011). “Heart rate variability during motor and cognitive tasks in females with major depressive disorder.”, Psychiatry Research: Neuroimaging, 191:1–8

[5] Udupa K., Sathyaprabha T.N., Thirthalli J., Kishore K.R., Lavekar G.S., Raju T.R., Gangadhar B.N., (2007). “Alteration of cardiac autonomic functions in patients with major depression: A study using heart rate variability measures”, Journal of Affective Disorders, 100:137–141.

[6] Kim B.S., Bae J.N., Cho M.J., (2010). “Depressive symptoms in elderly adults with hypotension: different associations with positive and negative affect.”, J Affect Disord., 127(1-3):359-64.

[7] Boettgera M.K., Greiner W., Rachow T., Brühl C., Bär K.-J. (2010). “Sympathetic skin response following painful electrical stimulation is increased in major depression.”, PAIN®, 149:130–134

[8] American Psychiatric Association (APA) (2000). Diagnostic and Statistical Manual of Mental Disorders, 4th edition Text Revision, Washington DC, USA.

[9] Goodwin F.K, Jamison K.R. (1990). Manic-Depressive Illness, Oxford University Press, Oxford, England.

[10] Sadock B.J., Sadock V. A. (eds) (2000). Kaplan & Sadock’s Comprehensive Textbook of Psychiatry, 7th edition, Lippincott Williams &Wilkins, Philedelphia, USA.

[11] Maj M., Sartorius N. (2002). WPA Series Evidence and Experience in Psychiatry: Volume 1 – Depressive Disorders, Wiley, England.

[12] Neuroscience Education Institute. (2009). Understanding and Managing the Pieces of Major Depressive Disorder, NEI Press, California, USA.

[13] Parker G., (2002). Dealing with depression: a commonsense guide to mood disorders, 1st ed.,Allen & Unwin, Australia.

[14] Griez E. J. L., Faravelli C., Nutt D. J., Zohar J. (2005). Mood disorders: clinical management and research issues, John Wiley & Sons, England.

[15] Steptoe A., (2007). Depression and Physical Illness, Cambridge University Press, New York, USA.

[16] Trzepacz, PT; Baker RW (1993). The Psychiatric Mental Status Examination, Oxford University Press, Oxford, England.

[17] World Health Organization (WHO) (1992). The ICD-10 Classification of Mental and Behavioral Disorders.

[18] Power M., (2004). "Mood Disorders a Handbook of Science and Practice", University of Edinburgh and Royal Edinburgh Hospital, Wiley, England.

[19] Stein D. J., Kupfer D. J., Schatzberg A. F., (2006). The American Psychiatric Publishing textbook of mood disorders, 1st ed., American Psychiatric Publishing, Arlington.

[20] Ustün T.B., Ayuso-Mateos J.L., Chatterji S., Mathers C., Murray CJ., (2004). "Global burden of depressive disorders in the year 2000" Br J Psychiatry, 184:386-92.

[21] Kessler R. C., Berglund P., Demler O., Jin R., Koretz D., Merikangas K.R., et al.,(2003) "The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R)", JAMA, 289:3095–105

[22] World Health Organization (WHO), 2012a. Facts and figures. Prevalence of mental disorders. www.euro.who.int/en/what-we-do/health-topics/noncommunicable-diseases/mentalhealth/facts-and-figures

[23] Vikram P., Simon G., Chowdhary N., Kaaya S., Araya R., (2009). "Packages of care for depression in low- and middle-income countries", PLOS Med, 6(10):1-7.

[24] Craighead W. E., Sheets E. S., Brosse, A. L., Ilardi, S. S. (2007). "Psychosocial treatments for major depressive disorder", In P. E. Nathan, & J. M. Gorman (Eds.), A guide to treatments that work (3 ed), Oxford University Press, New York.

[25] Cyranowski J.M., Frank E., Young E., Shear M.K., (2000). "Adolescent onset of the gender difference in lifetime rates of major depression: a theoretical model", Arch Gen Psychiatry, 57:21–27

[26] Murphy G.E., (1998). "Why women are less likely than men to commit suicide",Comprehensive Psychiatry, 39: 165-175.

[27] WHO (2012). http://www.who.int/mediacentre/factsheets/fs369/en/, [access time: 02.08.2013]

[28] Cahill L., Prins B., Weber M., McGaugh J.L.,(1994). "Beta-adrenergic activation and memory for emotional events", Nature, 371:702–704.

[29] Anderson I.M., Parry-Billings M., Newsholme E.A., Poortmans J.R., Cowen P.J. (1990a). "Decreased plasma tryptophan concentration in major depression: relationship to melancholia and weight loss", Journal of Affective Disorders, 20: 185-191.

[30] Modell S., Yassouridis A., Huber J., Holsboer F., (1997). "Corticosteroid receptor function is decreased in depressed patients", Neuroendocrinology, 65: 216-222

[31] Asberg M, Traskman L, Thoren P., (1976). "5-HIAA in the cerebrospinal fluid: a biochemical suicide predictor?", Arch Gen Psychiatry, 33:1193–1197.

[32] Anand A., Charney D.S., (2000). "Norepinephrine dysfunction in depression", Journal of Clinical Psychiatry, 61:16-24

[33] Horton R.W., (1992). "The neurochemistry of depression: evidence derived from studies of postmortem brain tissue", Molecular Aspects of Medicine, 13: 191-203.

[34] Checkley S.A., (1992). Neuroendocrinology. Handbook of Affective Disorders,2nd editition, Churchill Livingstone, Edinburgh.

[35] Dinan T.G. (2001). The hypothalamic-pituitary-adrenal axis in antidepressant action. In Leonard B.E. (ed) Antidepressants. Basel: Birkhauser

[36] Naranjo CA, Tremblay LK, Busto UE (2001). "The role of the brain reward system in depression", Prog Neuropsychopharmacol Biol Psychiatry, 25:781–823.

[37] McLean A., Rubinsztein J.S., Robbins T.W., Sahakian B.J., (2004). "The effects of tyrosine depletion in normal healthy volunteers: implications for unipolar depression", Psychopharmacology, 171:286–297.

[38] Griez E. J. L., Faravelli C., Nutt D. J., Zohar J. (2005). Mood disorders: clinical management and research issues, John Wiley & Sons, England.

[39] Frodl T., Meisenzahl E.M., Zetzsche T., Born C., Groll C., Jager M., Leinsinger G., Bottlender R., Hahn K., Möller H.-J., (2002). "Hippocampal changes in patients with a first episode of major depression", American Journal of Psychiatry, 159: 1112-1118.

[40] Drevets W.C., Ongur D., Price J.L. (1998) "Neuroimaging abnormalities in the subgenual prefrontal cortex: implications for the pathophysiology of familial mood disorders", Molecular Psychiatry, 3: 220-226.

[41] Öngür D., Drevets W.C., Price J.L., (1998). "Glial reduction in the subgenual prefrontal cortex in mood disorders", Proceeding of the National Academy of Science of the USA, 95:13290–13295.

[42] Goodwin G.M. (1996). "Functional imaging, affective disorder and dementia", British Medical Bulletin, 51: 495-512.

[43] Empana J.P., Sykes D.H., Luc G., Juhan-Vague I., Arveiler D., Ferrieres J.,et al., (2005) "Contributions of depressive mood and circulating inflammatory markers to coronary heart disease in healthy European men: The Prospective Epidemiological Study of Myocardial Infarction (PRIME)", Circulation, 111:2299 –2305.

[44] Anderson I.M., (2001). "Meta-analytical studies on new antidepressants", British Medical Bulletin, 57:161–178.

[45] Barbui C., Hotopf M., Freemantle N., Boynton J., Churchill R., Eccles M.P. et al. (2000). "Selective serotonin reuptake inhibitors versus tricyclic and heterocyclic antidepressants: Comparison of drug adherence", Cochrane Database Systematic Review, 4:CD002791.

[46] Smith, D., Dempster, C., Glanville, J., Freemantle, N. & Anderson, I. (2002). "Efficacy and tolerability of venlafaxine compared with selective serotonin reuptake

inhibitors and other antidepressants: A meta-analysis", British Journal of Psychiatry, 180: 396–404.

[47] American Psychiatric Association, (2006). APA Practice Guidelines for the Treatment of Psychiatric Disorders: Comprehensive Guidelines and Guideline Watches 1.

[48] Driessen E., Hollon S.D., (2010). "Cognitive Behavioral Therapy for Mood Disorders: Efficacy, Moderators and Mediators". Psychiatric Clinics of North America 33 (3): 537–55.

[49] Gershon A.A., Dannon P.N., Grunhaus L., (2003). "Transcranial Magnetic Stimulation in the Treatment of Depression", Am J Psychiatry, 160:835-845.

[50] Nahas Z., Marangell L.B., Husain M.M., Rush A.J., Sackeim H.A., Lisanby S.H., Martinez J.M., George M.S.,(2005). " Two-year outcome of vagus nerve stimulation (VNS) for treatment of major depressive episodes", The Journal of Clinical Psychiatry, 66(9):1097-1104.

[51] Matthews K, Eljamel M.S., (2003). "Vagus nerve stimulation and refractory depression: please can you switch me on doctor ?" BrJ Psychiatry, 183: 181-183.

[52] World Health Organization, Cardiovascular diseases (CVDs), http://www.who.int/mediacentre/factsheets/fs317/en/# [access time: 06.02.2012]

[53] Blazer D.G., Kessler R.C., Mcgonagle K.A., Swart M. S., (1994). "The prevalence and distribution of major depression in a national community sample", Am J Psychiatry, 151:979-986.

[54] Mulle J. G., Viola Vaccarino V., (2013). "Cardiovascular Disease, Psychosocial Factors, and Genetics: The Case of Depression", Progress in Cardiovascular Diseases, 55:557–562

[55] Penninx B.W., Beekman A.T., Honig A., Deeg D.J., Schoevers R.A., van Eijk J.T., van Tilburg W., (2001) "Depression and cardiac mortality: results from a community-based longitudinal study". Arch Gen Psychiatry. 58:221-227.

[56] Pitt B., Deldin P.J., (2013). "Depression and cardiovascular disease: have a happy day just smile!", European Heart Journal., 31(9):1036-1037.

[57] Howren MB, Lamkin DM, Suls J. (2009). "Associations of depression with C-reactive protein, IL-1 and IL-6: a meta-analysis", Psychosom Med. 71:171–86.

[58] Chauvet-Gélinier J-C., Trojak B., Vergès-Patois B., Cottin Y., Bonin B. (2013). "Review on depression and coronary heart disease"Archives of Cardiovascular Disease 106:103-110

[59] Kilbourne A.M., Rofey D.L., McCarthy J.F., Post E.P., Welsh D., Blow F.C., (2007). "Nutrition and exercise behavior among patients with bipolar disorder" Bipolar Disorder, 9:443—52

[60] Gottlieb S.S., Khatta M., Friedmann E., Einbinder L., Katzen S., Baker B., Marshall J., Minshall S., Robinson S., Fisher M.L., Potenza M., Sigler B., Baldwin C., Thomas S.A. (2004). "The Influence of Age, Gender, and Race on the Prevalence of Depression in Heart Failure Patients", FAAN Journal of the American College of Cardiology, 43(9).1542-1549.

[61] Shimbo D., Child J., Davidson K., Geer E., Osende J.I., Reddy S., Dronge A., Fuster V., Badimon J.J., (2002). "Exaggerated serotonin-mediated platelet reactivity as a possible link in depression and acute coronary syndromes", Am J Cardiol. 89:331e333

[62] von Kanel R., Mills P.J., Fainman C., Dimsdale J. E., (2001). "Effects of psychological stress and psychiatric disorders on blood coagulation and fibrinolysis: a biobehavioral pathway to coronary artery disease?" Psychosom Med., 63:531-544.

[63] Grippo A.J, Johnson A.K. (2009). "Stress, depression, and cardiovascular dysregulation: a review of neurobiological mechanisms and the integration of research from preclinical disease models." Stress, 12:1–21.

[64] Rajagopalan S, Brook R, Rubenfire M, Pitt E., Young E., Pitt B., (2001). "Abnormal brachial artery flow-mediated vasodilation in young adults with majör depression", Am J Cardiol., 88:196-198.

[65] Nemeroff C.B., Goldschmidt-Clermont P.J., (2012). "Heartache and heartbreak – the link between depression and cardiovascular disease.", Nat Rev Cardiol., 9:526–39.

[66] Gnanasekaran G. (2011). "Epidemiology of Depression in Heart Failure", MPH Heart Failure Clinics 7(1):1–10

[67] Allen J. (2007). "Photoplethysmography and its application in clinical physiological measurement.", Physiol. Meas.28:R1–R39.

[68] Matthews S.C., Nelesen R.A., Dimsdale J.E., (2005). "Depressive symptoms are associated with increased systemic vascular resistance to stress", Psychosomatic Medicine, 67(4):509–513.

[69] Agelink M.W., Boz C., Ullrich H., Andrich J., (2002). "Relationship between major depression and heart rate variability. Clinical consequences and implications for antidepressive treatment", Psychiatry Research, 113 (1–2):139–149.

[70] Davydov D.M., Shapiro D., Cook I.A., Goldstein I., (2007). "Baroreflex mechanisms in major depression", Progress in Neuropsychopharmacology & Biological Psychiatry, 31(1): 164–177.

[71] Tonhajzerova I., Ondrejka I., Javorka K., Turianikova Z., Farsky I., Javorka M., (2010). "Cardiac autonomic regulation is impaired in girls with major depression", Progress in Neuro-Psychopharmacology & Biological Psychiatry, 34: 613–618

[72] Frasure-Smith N., Lespérance F., Irwin M.R., Talajic M., Pollock B.G., (2009)."The relationships among heart rate variability, inflammatory markers and depression in coronary heart disease patients", Brain, Behavior, and Immunity, 23: 1140–1147

[73]

[74] Schwier C., Kliem A., Boettger M.K., Bär K.J., (2011) "Increased Cold-Pain Thresholds in Major Depression", The Journal of Pain, 11(3):287-290

[75] Boettger S., Hoyer D., Falkenhahn K., Kaatz M., Yeragani V.K., Bär K.J., (2008). "Nonlinear broad band dynamics are less complex in major depression", Bipolar Disorder 10:276–84

[76] Wikipedia, The Free Encyclopedia, Symphony No. 10 (Shostakovich), http://en.wikipedia.org/wiki/Symphony_No._10_(Shostakovich), Access time: 02.08.2013

[77] Cervellin G. and Lippi G. (2011). “From music-beat to heart-beat: A journey in the complex interactions between music, brain and heart”, European Journal of Internal Medicine, 22:371–374.

[78] Iwanaga M., Kobayashi A. and Kawasaki C. (2005). “Heart rate variability with repetitive exposure to music”, Biological Psychology, 70:61–66.

[79] BIOPAC Systems Canada Inc., Research, http://www.biopac.ca/research.aspx , Access time: 02.08.2013

[80] Cliffs Notes, Nervous System, http://www.cliffsnotes.com/sciences/psychology/psychology/psychology-biological-bases-of-behavior/nervous-system Access time: 02.08.2013

[81] Fox S. I. (2009). Fundamentals of Human Physiology, McGraw Hill, New York.

[82] BIOPAC Systems Inc., Product Sheet, Transducer Module GSR100C, http://www.biopac.com/Product_Spec_PDF/GSR100C.pdf Access time: 02.08.2013

[83] BIOPAC Systems Inc., Product Sheet, TSD203-Electrodermal response transducer http://www.biopac.com/Product_Spec_PDF/TSD203.pdf Access time: 02.08.2013

[84] BIOCOM Technologies, Heart Rate Variability Analysis Scientific Background, http://www.biocomtech.com/hrvscientific Access time: 02.08.2013

[85] BIOPAC Systems Inc., Product Sheet, Pulse Photopletysmogram Transducers http://www.biopac.com/Product_Spec_PDF/Pulse%20Transducer.pdf Acces time: 02.08.2013

[86] Berne M. R., Levy M. N., Koeppen B.M., Stanton A. B., (2006). Physiology, 4th edition, Mosby, Philadelphia

[87] BIOPAC Systems Inc., Product Sheet, TSD202 Series Tempeature Transducers, http://www.biopac.com/Product_Spec_PDF/TSD202%20Series.pdf Acces time: 02.08.2013

[88] Madisetti V. K. (2010). The digital signal processing handbook, 2nd edition, CRC Press, USA.

[89] Stoica P. and Moses R. (2005). Spectral Analysis of the Signal, Pearson Prentice Hall, New Jersey, USA.

[90] Lecture 08: Spectrum estimation – nonparametric methods, http://www.ee.lamar.edu/gleb/adsp/Lecture%2008%20-%20Nonparametric%20SE.pdf Access time: 02.08.2013

[91] Welch P. (1967). “The us eof fast fourier transform for the estimation of power spectra: A method based on time averaging over short, modified periodograms.” , IEEE Trans. Audio Electroacoust., AE15:70-73.

[92] Confidence interval and the Student's t-test by Joy Ying Zhang, http://projectile.sv.cmu.edu/research/public/talks/t-test.htm Access time: 02.08.2013

[93] Dişçi R. (2008). Temel ve Klinik Biyoistatistik, 1st Edition, İstanbul.

[94] Daniel W. W. (2005). Biostatistics: A foundation for Analysis in the Health Science, 8th edition , Wiley, USA.

[95] Kleine-Budde K., Müller R., Kawohl W., Bramesfeld A., Moock J., Rössler W., (2013). "The cost of depression – A cost analysis from a large database.", Journal of Affective Disorders 147:137–143.

[96] Mathers C. D., Loncar D. "Projections of Global Mortality and Burden of Disease from 2002 to 2030.",

[97] Guinjoan S. M., Bemabo J.L., Cardinali D. P., (1995). "Cardiovascular tests of autonomic function and sympathetic skin responses in patients with major depression.", Journal of Neurology, Neurosurgery and Psychiatry, 58:299-302

[98] Schwier C., Kliem A., Boettger M.K., Bär K.J., (2011) "Increased Cold-Pain Thresholds in Major Depression", The Journal of Pain, 11(3):287-290

[99] Boettgera M.K., Greiner W., Rachow T., Brühl C., Bär K.-J. (2010). "Sympathetic skin response following painful electrical stimulation is increased in major depression.", PAIN®, 149:130–134

[100] McLachlan C. S., Ocsan R., Spence I., Hambly B., Matthews S., Wang L. And Jelinek H. F., (2010). "Increased total heart rate variability and enhanced cardiac vagal autonomic activity in healthy humans with sinus bradycardia.", Baylor University Medical Center Proceedings, 23(4):368–370

[101] Martens, A., Greenberg, A., & Allen, J.J.B. (2008). Self-esteem and autonomic physiology: Parallels between self-esteem and vagal tone as buffers of threat. Personality and Social Psychology Review, 12, 370-389

[102] Aboa-Éboulé C., Brisson C., Maunsell E., Mâsse B., Bourbonnais R., Vézina M., Milot A., Théroux P., Dagenais G. R., (2007). "Job Strain and Risk of Acute Recurrent Coronary Heart Disease Events", JAMA, 298(14):1652-1660

[103] Hamilton Depresyon Değerlendirme Ölçeği, http://www.turkpsikiyatri.org/arsiv/category/2-tur.html?download=5:hamilton-depresyon-olcegi Access time: 02.08.2013

[104] Beck Anksiyete Ölçeği, www.ogelk.net/formlar/diger/**beck**anktek%20sayfa.pdf Access time: 02.08.2013

[105] Hamilton Rating Scale for Depression (17-items), https://outcometracker.org/library/HAM-D.pdf Access time: 03.08.2013

[106] Counselling for the Health of it, Beck Anxiety Inventory, http://www.counselling-for-the-health-of-it.com/beck-anxiety-inventory.html Access Time: 03.08.2013

APPENDIX A

RATING SCALES

Hastanın Adı, Soyadı:	Tarih:
Hastanın Yaşı ve Cinsiyeti:	Değerlendirici:

HAMİLTON DEPRESYON DEĞERLENDİRME ÖLÇEĞİ

		Puan
1. DEPRESİF (ÇÖKKÜN) RUH HALİ	(1-5)	☐
2. ÇALIŞMA VE ETKİNLİKLER	(1-5)	☐
3. GENİTAL SEMPTOMLAR	(1-3)	☐
4. SOMATİK SEMPTOMLAR –GASTROİNTESTİNAL	(1-3)	☐
5. KİLO KAYBI		
A. ÖZGEÇMİŞİNİ DEĞERLENDİRİRKEN	(1-4)	☐
B. GERÇEK KİLO DEĞİŞİMİ	(1-4)	☐
6. UYKUSUZLUK (BAŞLARKEN)	(1-3)	☐
7. UYKUSUZLUK (ORTA)	(1-3)	☐
8. UYKUSUZLUK (GEÇ)	(1-3)	☐
9. SOMATİK BELİRTİLER (GENEL)	(1-3)	☐
10. SUÇLULUK DUYGULARI	(1-5)	☐
11. İNTİHAR	(1-5)	☐
12. PSİŞİK KAYGI	(1-5)	☐
13. SOMATİK KAYGI	(1-5)	☐
14. HİPOKONDRİ	(1-5)	☐
15. İÇGÖRÜ	(1-3)	☐
16. YAVAŞLAMA	(1-5)	☐
17. AJİTASYON	(1-5)	☐
TOPLAM		.....

Figure A.1 Hamilton Depression Rating Scale – 17 item – Turkish version [103]

Beck Anksiyete Ölçeği

Hastanın Soyadı, Adı:..... **Tarih:**.....

Aşağıda insanların kaygılı ya da endişeli oldukları zamanlarda yaşadıkları bazı belirtiler verilmiştir.
Lütfen her maddeyi dikkatle okuyunuz. Daha sonra, her maddedeki belirtinin BUGÜN DAHİL SON BİR (1) HAFTADIR sizi ne kadar rahatsız ettiğini yandakine uygun yere (x) işareti koyarak belirleyiniz.

	Hiç	Hafif düzeyde Beni pek etkilemedi	Orta düzeyde Hoş değildi ama kat lanabildim	Ciddi düzeyde Dayanmakta çok zorlandım
1. Bedeninizin herhangi bir yerinde uyuşma veya karıncalanma				
2. Sıcak/ ateş basmaları				
3. Bacaklarda halsizlik, titreme				
4. Gevşeyememe				
5. Çok kötü şeyler olacak korkusu				
6. Baş dönmesi veya sersemlik				
7. Kalp çarpıntısı				
8. Dengeyi kaybetme duygusu				
9. Dehşete kapılma				
10. Sinirlilik				
11. Boğuluyormuş gibi olma duygusu				
12. Ellerde titreme				
13. Titreklik				
14. Kontrolü kaybetme korkusu				
15. Nefes almada güçlük				
16. Ölüm korkusu				
17. Korkuya kapılma				
18. Midede hazımsızlık ya da rahatsızlık hissi				
19. Baygınlık				
20. Yüzün kızarması				
21. Terleme (sıcaklığa bağlı olmayan)				

Toplam BECK-A skoru:.....

designed by Emrah SONGUR M.D.

Figure A.2 Beck Anxiety Inventory – Turkish version [104]

Patient Name:_____ Date:_____

Hamilton Rating Scale for Depression (17-items)

Instructions: For each item select the "cue" which best characterizes the patient during the past week.

1. **Depressed Mood**
   (sadness, hopeless, helpless, worthless)
   0 Absent
   1 These feeling states indicated only on questioning
   2 These feeling states spontaneously reported verbally
   3 Communicates feeling states nonverbally, i.e., through facial expression, posture, voice and tendency to weep
   4 Patient reports VIRTUALLY ONLY these feeling states in his spontaneous verbal and nonverbal communication

2. **Feelings of Guilt**
   0 Absent
   1 Self-reproach, feels he has let people down
   2 Ideas of guilt or rumination over past errors or sinful deeds
   3 Present illness is a punishment. Delusions of guilt
   4 Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations

3. **Suicide**
   0 Absent
   1 Feels life is not worth living
   2 Wishes he were dead or any thoughts of possible death to self
   3 Suicide ideas or gesture
   4 Attempts at suicide (any serious attempt rates 4)

4. **Insomnia - Early**
   0 No difficulty falling asleep
   1 Complains of occasional difficulty falling asleep i.e., more than ½ hour
   2 Complains of nightly difficulty falling asleep

5. **Insomnia - Middle**
   0 No difficulty
   1 Patient complains of being restless and disturbed during the night
   2 Waking during the night – any getting out of bed rates 2 (except for purposes of voiding)

6. **Insomnia - Late**
   0 No difficulty
   1 Waking in early hours of the morning but goes back to sleep
   2 Unable to fall asleep again if gets out of bed

7. **Work and Activities**
   0 No difficulty
   1 Thoughts and feelings of incapacity, fatigue or weakness related to activities; work or hobbies
   2 Loss of interest in activity; hobbies or work – either directly reported by patient, or indirect in listlessness, indecision and vacillation (feels he has to push self to work or activities)
   3 Decrease in actual time spent in activities or decrease in productivity. In hospital, rate 3 if patient does not spend at least three hours a day in activities (hospital job or hobbies) exclusive of ward chores.
   4 Stopped working because of present illness. In hospital, rate 4 if patient engages in no activities except ward chores, or if patient fails to perform ward chores unassisted.

8. **Retardation**
   (slowness of thought and speech; impaired ability to concentrate; decreased motor activity)
   0 Normal speech and thought
   1 Slight retardation at interview
   2 Obvious retardation at interview
   3 Interview difficult
   4 Complete stupor

9. **Agitation**
   0 None
   1 "Playing with" hand, hair, etc.
   2 Hand-wringing, nail-biting, biting of lips

10. **Anxiety - Psychic**
    0 No difficulty
    1 Subjective tension and irritability
    2 Worrying about minor matters
    3 Apprehensive attitude apparent in face or speech
    4 Fears expressed without questioning

11. **Anxiety - Somatic**
    0 Absent
    1 Mild
    2 Moderate
    3 Severe
    4 Incapacitating
    Physiological concomitants of anxiety such as:
    Gastrointestinal - dry mouth, wind, indigestion, diarrhea, cramps, belching
    Cardiovascular – palpitations, headaches
    Respiratory - hyperventilation, sighing
    Urinary frequency
    Sweating

12. **Somatic Symptoms - Gastrointestinal**
    0 None
    1 Loss of appetite but eating without staff encouragement. Heavy feelings in abdomen.
    2 Difficulty eating without staff urging. Requests or requires laxatives or medications for bowels or medication for G.I. symptoms.

13. **Somatic Symptoms - General**
    0 None
    1 Heaviness in limbs, back or head, backaches, headache, muscle aches, loss of energy and fatigability
    2 Any clear-cut symptom rates 2

14. **Genital Symptoms**
    0 Absent
    1 Mild
    2 Severe
    0 Not ascertained
    Symptoms such as: loss of libido, menstrual disturbances

15. **Hypochondriasis**
    0 Not present
    1 Self-absorption (bodily)
    2 Preoccupation with health
    3 Frequent complaints, requests for help, etc.
    4 Hypochondriacal delusions

16. **Loss of Weight**
    A. When Rating by History:
    0 No weight loss
    1 Probable weight loss associated with present illness
    2 Definite (according to patient) weight loss

    B. On Weekly Ratings by Ward Psychiatrist, When Actual Changes are Measured:
    0 Less than 1 lb. weight loss in week
    1 Greater than 1 lb. weight loss in week
    2 Greater than 2 lb. weight loss in week

17. **Insight**
    0 Acknowledges being depressed and ill
    1 Acknowledges illness but attributes cause to bad food, climate, overwork, virus, need for rest, etc.
    2 Denies being ill at all

Total Score:_____

Figure A.3 Hamilton Depression Rating Scale – 17 item – English version [105]

Name:_____
Date ___/___/____

Below is a list of common symptoms of anxiety. Please read through each list item. Indicate how much you were bothered by each symptom listed on the left during the last week, including today, marking an X in the degree of disturbance corresponding to a column of cells on the right.

Nº	Symptoms	How much you were bothered			
		Nothing *0*	*Weak* *1*	*Moderate* *2*	*Strong* *3*
		It did not bother at all	*It bothered a little*	*It bothered me a lot but I could stand it*	*I almost could not stand it*
1	Numbness or tingling				
2	Hot sensation				
3	Wobbly				
4	Incapable of relaxing				
5	Fear of the worst happening				
6	Dizziness or lightheadedness				
7	Heart pounding or racing				
8	Restless				
9	Terrified				
10	Nervous				
11	Feeling of suffocation				
12	Hands trembling				
13	Trembling				
14	Fear of losing control				
15	Difficulty breathing				
16	Fear of dying				
17	Frightened				
18	Indigestion or discomfort in the abdomen				
19	Fainting				
20	Red Face				
21	Sweating (not due to heat)				
SCORE:					

Figure A.4 Beck Anxiety Inventory – English version [106]

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