UNIVERSITY OF PADOVA

Department of General Psychology

Bachelor's Degree Course in Psychological Science

Final dissertation

Heart-Brain Disruptions in Depression: Exploring the Bidirectional Relationship

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Overview:

Abstract

This thesis reviews the interaction between depression and cardiovascular disease (CVD), positing that the relationship is bidirectional. Depression has been recognized as a significant global health issue that predisposes people to CVD. In turn, the presence of CVD can trigger or worsen depression, creating a vicious cycle of deterioration in mental and physical health. Different mechanisms have been identified that could explain this bidirectional relationship, among which dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, autonomic nervous system imbalances, alterations in the level of brain-derived neurotrophic factor (BDNF), inflammatory pathways and lifestyle behavior. By integrating data from various studies, this thesis highlights the complex interactions between mental health and heart disease.

Chapter 1

Depression

a. Depression

Depressive disorders are one of the most common causes leading to disabilities worldwide (Santomauro et al., 2021). The World Health Organization (2017) classified depression as the leading cause of global disability, with more than 264 million people affected around the world. The Diagnostic and Statistical Manual of Mental Disorders—Fifth Edition (American Psychiatric Association, 2013) defined Major Depressive Disorder (MDD) by the presence of at least one major depressive episode that lasted at least two weeks without manic or hypomanic episodes. It should be noted that at least one symptom has to be depressed mood or anhedonia (that is, loss of pleasure or interest in activities) and should last nearly most of the day nearly every day (Criterion A). Other five or more symptoms include change in appetite and/or weight, sleep (insomnia or hypersomnia), decreased energy level, unexplainable feeling of guilt, difficulty thinking and concentrating, presence of suicidal thoughts, attempt or specific plan for a suicide. To be considered as a symptom of MDD, it should be present every day for at least 14 consecutive days; however, suicidal thoughts must be recurrent. MDD may antecede the Persistent Depressive Disorder or occur simultaneously with it. The Persistent Depressive Disorder, previously known as chronic major depressive disorder and dysthymic disorder, is specified by the presence of a depressed mood lasting nearly every day for two years, and it has to include at least two of the following symptoms: change in appetite, amount of sleep, low energy and self esteem, poor concentration and feeling of

hopelessness. The World Health Organization's International Classification for Diseases and Related Disorders (ICD-11) elucidated the single episode depressive disorder by featuring one depressive episode which is characterized by at least two weeks lasting depressed mood or decreased interest in activities. It has to coincide with other cognitive, behavioral, or neurovegetative symptoms. Compared to DSM 5, ICD-11 distinguishes mild, moderate, severe and unspecified severity forms of depression with or without psychotic symptoms.

Depression is a mood disorder that is present in all groups regardless of age, sex, and social status (Anzolin et al., 2022), and is considered a risk factor for cardiovascular disease (Ford et al., 1998). However, patients who have a cardiovascular disorder are also more likely to experience depression (Zeng et al., 2024). Depression and CVD are bidirectional related conditions and often co-exist (Raič, 2017; see Figure 1).

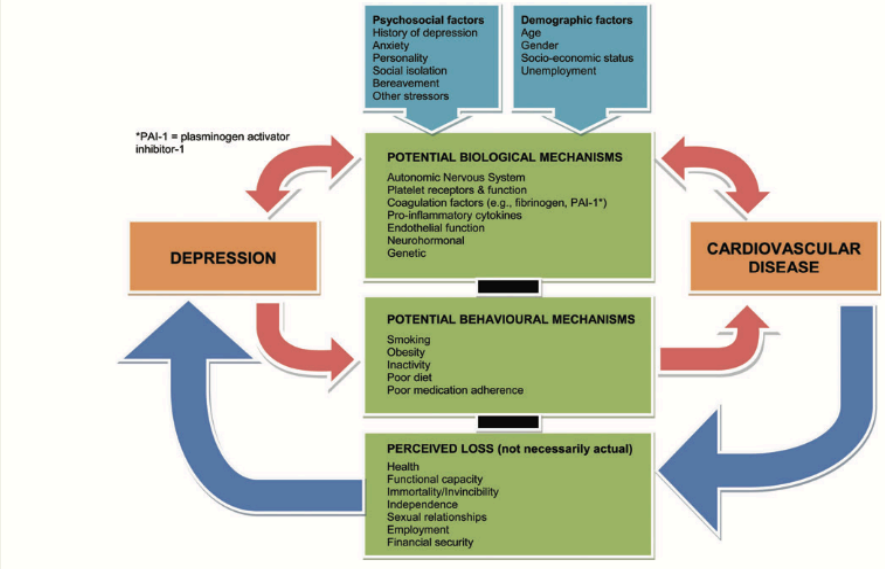

Figure 1 Potential factors that could explain the relationship between cardiovascular disease and depression.

Figure 1. Potential risk factors that could explain the relationship between cardiovascular diseases and depression (Hare et al., 2013).

b. Alterations in brain in depressed patients

Research on neurobiological alterations in depressed patients outlines several areas of the brain with structural and functional abnormalities. Changes in frontal cortex volume are considered the most common abnormalities in depressed patients. The most significant functional and structural abnormalities occur in part of the anterior cingulate cortex (ACC; specifically Brodmann area 24), orbitofrontal cortex (OFC), the middle prefrontal cortex, the dorsolateral prefrontal cortex (dlPFC), and other areas of the prefrontal cortex (Zhang et al., 2016; see Figure 2).

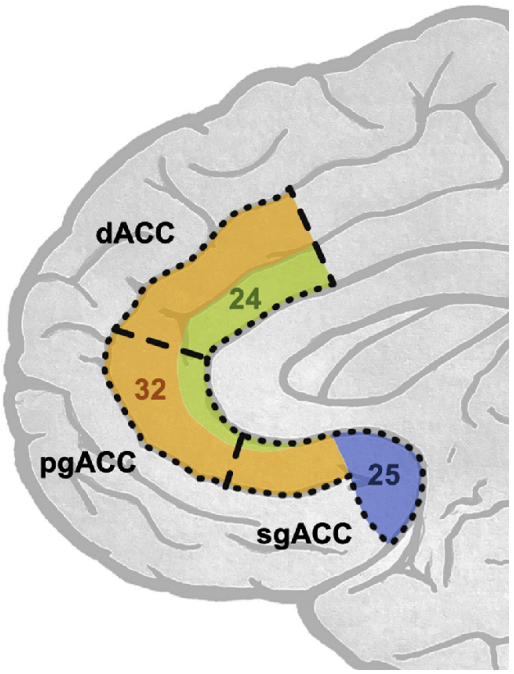

Figure 2. The anterior cingulate cortex (ACC) consists of subgenual (sgACC), perigenual (pgACC) and dorsal (dACC) parts (Laith et al., 2021).

ACC plays an important role in the regulation of mood and cognitive processes (Zhang et al., 2016). Schlund et al. (2012) noted that depressed patients showed reduced activation in the ACC. Biased processing of negative stimuli and an imbalanced intrinsic functional network within the brain could be the result of subgenual disruption of ACC (dACC) (Lai, 2021). Furthermore, hypoactivation in the ventral and dorsal striatum and increased activation of the medial prefrontal cortex (mPFC) and dlPFC could be associated with anhedonia (Pizzagalli and Roberts, 2021). However, reduced brain activity in bilateral OFC can be associated with reduced suppression of negative stimuli in depression (Zhang et al., 2016). Furthermore, emotional bias, apathy, and loss of motivation could be explained by loss of volume of gray matter in the left middle frontal gyrus (Peng et al., 2016).

Furthermore, disturbances in the ventral striatum, which is a part of the basal ganglia, may result in impulsive behavior and suicidal tendencies (Dombrovski et al., 2011). And another study shows that MDD patients who committed suicide, in fact, have a decreased volume of gray matter in the ventral striatum (Jacobs et al., 2016).

c. Cardiovascular diseases increase the risk for depression

Cardiovascular diseases are a group of disorders of the heart and blood vessels and include coronary heart disease, cerebrovascular disease, rheumatic heart disease, and other conditions (WHO, 2024). Coronary heart disease is a condition in which the arteries cannot supply oxygenated blood to the heart (Vos et al., 2016). Cerebrovascular disease is diagnosed when blood flow to the brain or its meninges is affected (Australian Institute of Health and Welfare,

2015). They are one of the significant public health problems worldwide, taking the lives of an estimated 17.9 million people each year (WHO, n.d.). The comorbidity of depression and cardiovascular diseases have been shown in several studies, both cross-sectional and prospective (Grippo and Johnson, 2002). For example, every fifth patient with coronary artery disease or heart failure faces clinical depression, which is at least three times more prevalent than in the general population (Cohen et al., 2015). Cardiovascular patients are more likely to develop depression than the general population with a prevalence of 20 to 45 percent (Raič, 2017). However, depressive symptoms can often be ignored in cardiac patients, especially after myocardial infarction (Raič, 2017) and congestive heart failure, as depression and cardiovascular disorders have some common symptoms, such as fatigue, insomnia, reduced concentration, and lack of energy (Musliu et al., 2013). Mortality rates in patients with congestive heart failure increase if untreated depression is present (Jiang et al., 2002).

d. Depression increase the risk for cardiovascular diseases

Patients with depression have a shorter life expectancy of 10 to 17.5 years compared to the general population. In addition to suicide, the high prevalence of cardiac disorders could be another major reason for premature death in patients diagnosed with depression (Correl et al., 2017). Depression is believed to have a direct influence on the pathophysiology of different organ systems, including blood pressure, heart rate, vasomotor tone, vascular resistance, blood viscosity, and plasma volume (Lang & Borgwardt, 2013). Possible processes leading to the incidence of coronary diseases include

hypothalamic-pituitary-adrenal (HPA) gland failure, inflammation, lifestyle changes such as smoking and sedentary life (Tofler et al., 2017). All these processes can be associated with the manifestation of myocardial infarction, coronary heart disease, cardiac arrhythmias, congestive heart failure, and isolated systolic hypertension that increases morbidity and mortality in patients (Lang et al., 2013). Patients with depressive disorder were also found to be twice as likely to develop cardiac disease (Buljan, 2016). Depression is also considered a risk factor for the atherosclerosis process (shown in Figure 3) where cholesterol, fat, and other substances form plaque in the inner layers of the arteries (Rafieian-Kopaei et al., 2014).

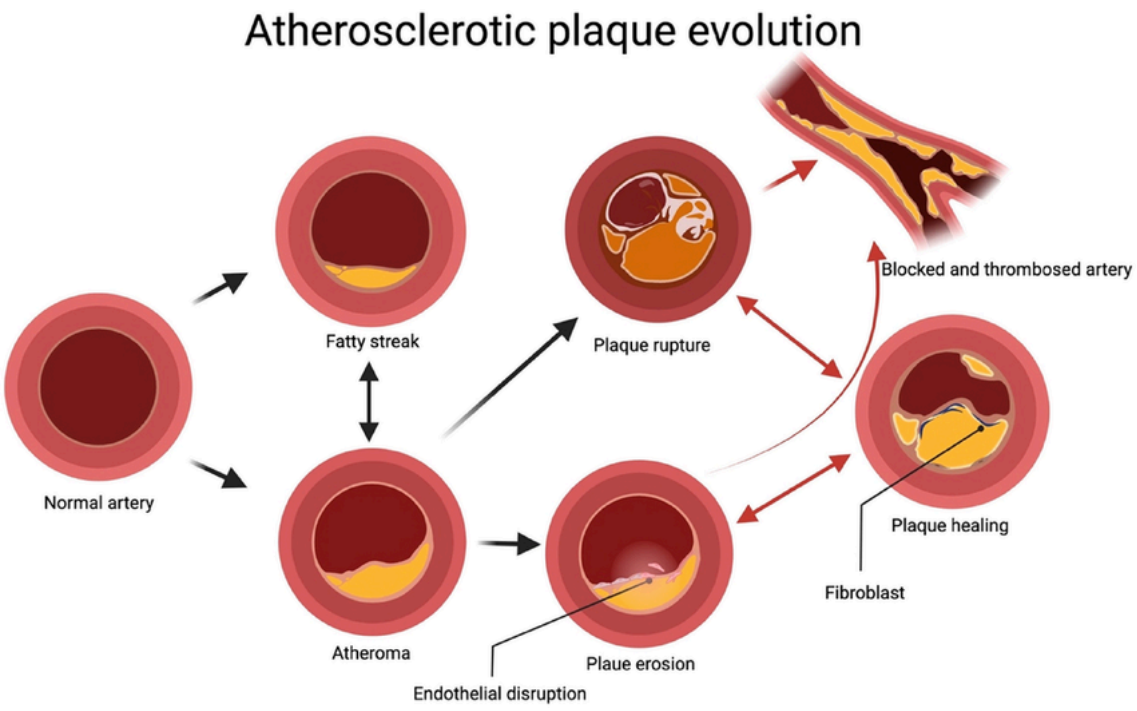

Figure 3. Atherosclerosis (Noothi et al., 2023).

In addition, depression predicts the incidence of coronary artery disease in patients with no previous history of depression (Grippo & Johnson, 2002). For example, one study found that the first depressive episode was observed in many patients before the development of cardiovascular diseases (Freedland, 1992). Depression is considered a sufficient risk factor, which means that it is a condition that guarantees the occurrence of a disorder for the manifestation of cardiovascular disorders (Bujian, 2016). For example, in the study conducted by Jokinen and Nordstrom (2008), 30% of hospitalized patients with mood disorder died of cardiovascular disease. These results confirm the hypothesis that depression is an important risk factor for cardiovascular death.

Chapter 2

Mechanisms underlying the relationship between depression and cardiovascular diseases

a. Hypothalamic-pituitary-adrenal axis

The hypothalamic-pituitary-adrenal axis (HPA) is considered to be one of the main actuators of response to stressful stimuli by releasing glucocorticoid hormones to allow the individual to respond to environmental or internal requests (Pereira et al., 2012). The stress response process is initiated after the individual faces a threat or a negative stimulus, at that point in the hypothalamus the production of corticotropin-releasing hormone (CRH). CRH then stimulates the release of another hormone, adrenocorticotropic hormone (ACTH), in the pituitary gland (Misiak et al., 2020). Consequently, ACTH binds to receptors in the adrenal cortex (that is, the outer region and the largest part of the adrenal gland) determining the release of glucocorticoids, among which the most common is cortisol. Cortisol modulates the stress response through a negative feedback (see Figure 4) by sending a feedback to the hypothalamus and the pituitary gland to decrease the production of CRH and ACTH (Misiak et al., 2020).

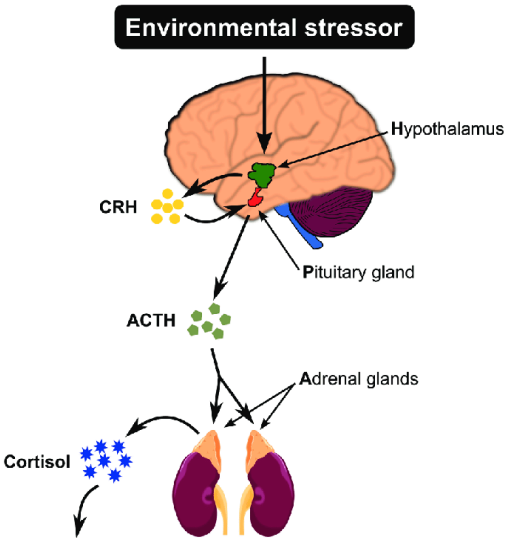

Figure 4. The hypothalamic-pituitary-adrenal (HPA) axis (Plusquellec, 2023).

Every dangerous or threatening situation, such as a car accident, animal attack, or myocardial infarction, stimulates HPA activation (Feng et al., 2016). Furthermore, chronic stress is associated with hyperactivation of the HPA axis and excessive release of glucocorticoids. Hyperactivation on the HPA axis is believed to be an important mechanism involved in the development of depression, as it is associated with elevated circulating cortisol levels (Mlyniec, 2015). Indeed, research shows elevated levels of ACTH and cortisol in people diagnosed with MDD (Choi et al., 2018). Hyperactivation of the HPA axis is also associated with many cardiovascular disease risk factors such as visceral obesity, hypercholesterolemia and hypertriglyceridemia (elevated levels of cholesterol and fats in the blood), increased blood pressure, elevated heart rate, and diabetes (Rosmond and Björntorp, 2000). Consistent with this hypothesis, Joseph and Golden (2017) showed that the HPA axis is associated with stress, depression, and diabetes, which is strongly associated with CVDs.

However, more longitudinal evidence is required to understand how the HPA axis links depression and CVD.

b. Autonomic Nervous System and Heart Rate Variability

Another important mechanism that links depression and CVDs is an alteration in the functioning of the autonomic nervous system (ANS), which controls the activity of all visceral organs (see Figure 5). Alteration of the ANS in the heart is reflected in reduced heart rate variability (HRV). HRV reflects the interaction between the sympathetic nervous system and parasympathetic branches of the autonomic nervous system (ANS). On the one hand, the sympathetic branch of the ANS is responsible for increased activity of physiological systems in response to stressful events, also called the fight or flight response, which determine increased heart rate, cardiac output, blood pressure, muscle tension. Activation of the parasympathetic branch of ANS, on the other hand, reduces these activities, leading to the so-called rest and digest response characterized by a lower heart rate and blood pressure (Kidwell & Ellenbroek, 2018).

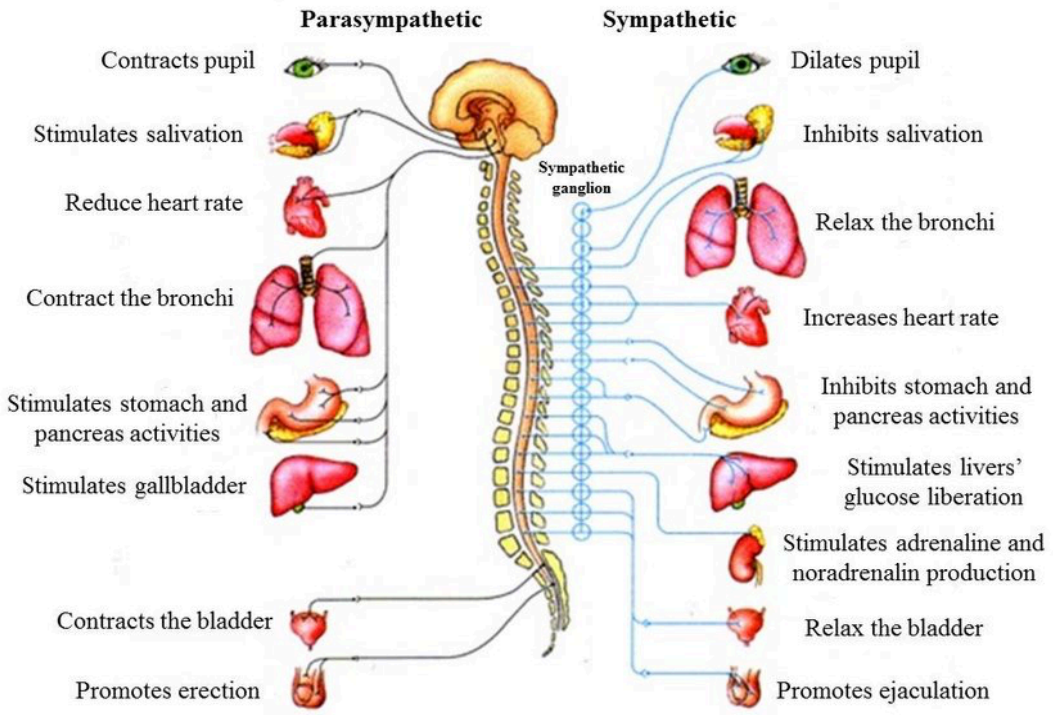

Figure 5. Functions of sympathetic and parasympathetic nerves (Kanthack, 2018).

High resting parasympathetic activity helps to preserve cardiac activity, while high sympathetic activity increases the risks of arrhythmias and sudden cardiac death (Kemp et al., 2010). A possible explanation for the high mortality in patients with CVD could be a chronic heart disturbance of heart (e.g., ANS imbalance characterized by excessive sympathetic activation and low parasympathetic activation, reflected by low HRV) due to long-term dysregulation of the ANS.

On the one hand, Chalmers et al. (2016) found that depression and other mental disorders are associated with a reduced HRV. According to a meta-analysis, patients with more severe depression have lower HRV than less depressed patients, as there seems to be a dose response relationship between HRV and the severity of depression (Kemp et al., 2010).

On the other hand, decreased HRV, which is associated with dysregulation of ANS, increases vulnerability to stress (Vaschillo, 2008). Reduced parasympathetic (vagal) control on the heart, in turn, increases the likelihood of ischemia and malignant arrhythmias. This interaction can be seen as an infinite circle where depression impairs autonomic control of the heart and the resulting impairment of cardiovascular health increases vulnerability to stress (Siepmann et al., 2022).

c. Role of brain-derived neurotrophic factor

Brain-derived neurotrophic factor (BDNF) plays a crucial role in neuronal survival and growth, acts as a neurotransmitter modulator, and participates in neuronal plasticity, which is essential for learning and memory (Bathina & Das, 2015). According to the neurotrophic hypothesis (Duman & Li, 2012), one of the most important factors in depressive symptoms is the reduced level of BDNF. A reduced level of BDNF could affect neuroplasticity and neurogenesis and promote cell atrophy, which as a result could lead to depression (Kuhlmann et al., 2017). Furthermore, BDNF also participates in angiogenesis, the formation of new blood vessels, and promotes the survival of vascular smooth cells, cardiomyocytes, endothelial cells, and atherosclerotic vessels. In general, high levels of BDNF play a protective role against CVD, while low levels are considered risk factors (Kuhlmann et al., 2017). Not only has BDNF been linked with a higher CVD risk, but a recent meta-analysis revealed that stroke patients who had a low level of BDNF were more likely to develop depression (Fioranelli et al., 2023). Under normal conditions, the brain attempts to increase BDNF levels to protect neurons from breakdown and promote neurogenesis. However,

sometimes this adaptive mechanism does not occur, leading to a subsequent decrease in BDNF levels (Clarkson et al., 2011). As a potential consequence, the neurogenesis process slows down and neuronal loss is observed, which, in turn, can lead to the development of depression (Dou et al., 2022).

d. Immune system and inflammation

Depression involves inflammatory pathways, which are well-recognized risk factors for the development of CVD, coronary artery disease, heart failure, and atherosclerosis (Huffman et al., 2013). Inflammatory cytokines are proteins secreted by immune cells that promote inflammation in tissues (Takeuchi & Akira, 2010). They have been documented to be associated with atherosclerotic plaque formation, progression, and rapture (Dantzer & Capuron, 2017; see Figure 4). Depression has been associated with elevated levels of cytokines, both in medically healthy patients and in patients with a history of cardiac disease. Similarly to how depression influences inflammation, CVDs can also elevate systemic inflammatory markers that can impact the central nervous system, potentially triggering or exacerbating depressive symptoms.

There are two potential mechanisms that can explain the relationship between inflammation, depression, and CVDs. First, elevated levels of enzymes that break down tryptophan, precursor of serotonin (see Figure 6), are associated with elevated levels of inflammatory cytokines in patients with CVD (Wirleitner, 2005). This could result in reduced levels of serotonin and subsequent depression.

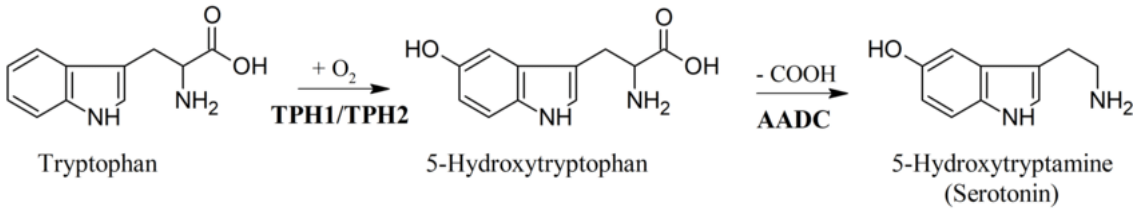

Figure 6. Process of serotonin synthesis (Maffei, 2021).

The second mechanism might involve the neural-immune interaction. In depressed patients, reduced serotonin levels can be associated with elevated levels of cytokines that could lead to cardiovascular outcomes (Huffman et al., 2013).

e. Lifestyle

Depressed patients are less likely to engage in a healthy lifestyle, including a healthy diet and regular exercise (Ziegelstein et al., 2000). Furthermore, depressed patients have higher risk behaviors, such as smoking and alcohol consumption, leading to cardiovascular problems. Pennix (2016) claims that depressed people not only smoke more often but are also less likely to quit smoking than non-depressed people. It is well known that smoking, both active and passive, increases the risks of coronary plaque rupture, acute coronary syndrome and sudden cardiac death (Kondo et al., 2019).

Chapter 3

Conclusion

This thesis provides a comprehensive overview of the bidirectional relationship between depression and cardiovascular disease. It describes several abnormalities in the brain areas in depressed patients, including alterations in ACC, OFC, mPFC, and dlPFC. Most importantly, it outlines the physiological and psychological mechanisms that can alter the prognosis and treatment strategies for both conditions. These mechanisms include hyperactivation of the HPA axis, reduced HRV, reduced level of brain-derived neurotrophic factor, elevated levels of cytokines, and unhealthy lifestyle behaviors. A better understanding of the mechanisms underlying the bidirectional relationship between depression and cardiovascular disease could help to identify early the person at higher risk. Furthermore, this could help to develop new preventive strategies and multidisciplinary interventions targeting behavioral, affective and physiological factors associated with higher risk.

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