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Heart rate variability in preadolescents with familial risk for depression

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Abstract

Background: Depression is characterized by dysfunctions in emotional, cognitive and physiological responses. Previous research showed autonomic nervous system dysregulation – high sympathetic and/or low parasympathetic nervous system activity – in people with major depression. Specifically, reduced heart rate variability (HRV), an index of sympathetic and parasympathetic cardiac modulation reflecting emotional processing and regulation, has been found in depression. However, while evidence robustly supports reduced vagal tone in individuals with current depressive symptoms, it remains unclear whether vagal dysregulation also represents a predisposing factor that can be detected before the onset of the disorder. Therefore, the main aim of the present study was to investigate the role of cardiac vagal tone, indexed by reduced HRV, as a measure of depression vulnerability. To this end, the study focused on preadolescents with familial risk for depression because they are at higher risk of developing depressive symptoms or a full-blown depressive episode than preadolescents without a familial risk for depression.

Methods: A total of 32 healthy preadolescents took part in the study (21 F, mean age 11.9, SD ± 0.77), 16 with a family history for depression and 16 without a family history for depression. To obtain a measure of cardiac vagal tone, resting-state ECG signal was continuously recorded for 3 minutes from which HRV indexes in the time and frequency domains were derived. *T*-tests were conducted to examine the differences between the two groups in vagally-mediated HRV (SDNN, RMSSD, HF power).

Results: No significant difference emerged in vagally-mediated HRV measures between the two groups (SDNN, RMSSD, HF power; all *p*s > 0.05).

Discussion: These results suggest that reduced vagal tone may not yet be evident in early stages of vulnerability or that it may emerge later as the risk translates into clinical symptoms. Also, it is possible that disruptions in cardiac vagal function emerge later in development, perhaps in response to cumulative stress exposure, the onset of affective symptoms, or critical developmental transitions such as adolescence. Given the importance of early identification of biological risk markers, future research should adopt longitudinal designs to clarify whether alterations in cardiac vagal function develop over time in at-risk youth and contribute to the onset of depressive symptoms

CHAPTER 1: Depression: clinical features and risk factors

1.1 Clinical characteristics and epidemiology of depression

Depression is a mood disorder that causes a persistent feeling of sadness and loss of interest. Depressive disorders are one of the most disabling disorders worldwide (Institute of Health Metrics and Evaluation, Global Burden of Disease, 2024). The American Psychiatric Association's Diagnostic Statistical Manual of Mental Disorders, Fifth Edition (DSM-5, APA, 2013), classifies depressive disorders into: Major depressive disorder (MDD), Disruptive mood dysregulation disorder, Persistent depressive disorder, Premenstrual dysphoric disorder and Depressive disorder due to another medical condition. The common features of all depressive disorders are sadness, emptiness, or irritable mood, accompanied by somatic and cognitive changes that significantly affect the individual's capacity to function (Chand & Arif, 2023). According to DSM-5 these functional impairments can be activities such as taking care of oneself, the ability to work, and socialization. MDD is a common and serious mental disorder that impacts our cognition, behavior, and emotional state (American Psychiatric Association, 2024). MDD is characterized by two core symptoms, which are anhedonia and depressed mood, and at least four symptoms out of the following:

- Insomnia or hypersomnia
- Psychomotor retardation or agitation
- Fatigue or loss of energy
- Feelings of worthlessness or excessive guilt
- Difficulty thinking, concentrating, or making decisions
- Recurrent thoughts of death or suicide
- Weight loss or change in appetite

In order to formulate a diagnosis of MDD, these symptoms must be present for at least two weeks in continuity, every day for most of the day, according to DSM-5. Although most of the episodes tend to dissipate over time, approximately 50% of patients who have experienced a first – onset depressive episode recovers and never experience it again. Major depressive episodes, when untreated, may persist even for more than six months and tend to recur, specifically 35% experience a recurrent episode and 15% develop full blown MDD (Eaton et al., 2008). In a review by (Steinert et al., 2014), conducted on a community adults' sample, it was concluded that 35-60% of adults diagnosed with MDD experienced a completed stable recovery without further depressive symptoms in the three-to-49-year follow–up period, 10-17% experienced a persistent, chronic course of depression. Moreover, about 20% of all patients with major depressive episodes develop a chronic course (Gilmer et al., 2005; Spijker et al., 2002).

It is estimated that the number of people affected by depressive disorders is around 4% of the population, which equals around 324 million people on earth having depression (Institute of Health Metrics and Evaluation, Global Burden of Disease, 2024). Depressive disorders are one of the most common disorders among the general population (Figure 1.1). Women are 50% more likely to experience depression than men (World Health Organization, 2023). The prevalence of depressive disorders in the European Region increased from 4.6% in 2019 to 5.2% in 2021 (World Health Organization, 2024), probably also due to the COVID–19 pandemic. The prevalence of depressive disorders in children aged 5 – 14 years is 0.69%, and among adolescents, the prevalence is approximately 3.8% (Institute of Health Metrics and Evaluation, Global Burden of Disease, 2024). Depressive episodes are associated with substance abuse, suicidal ideation, and attempts at suicide as well as significant functional impairments (Birmaher et al., 1996). Moreover, MDD is highly comorbid with cardiovascular disorders, and depressive symptoms among adults with coronary heart disease may lead to a higher risk for mortality (Barth et al., 2004). Finally, 800.000 people die by suicide every year, and MDD is the second leading cause of death among 15 – 29-year-olds (WHO, 2017).

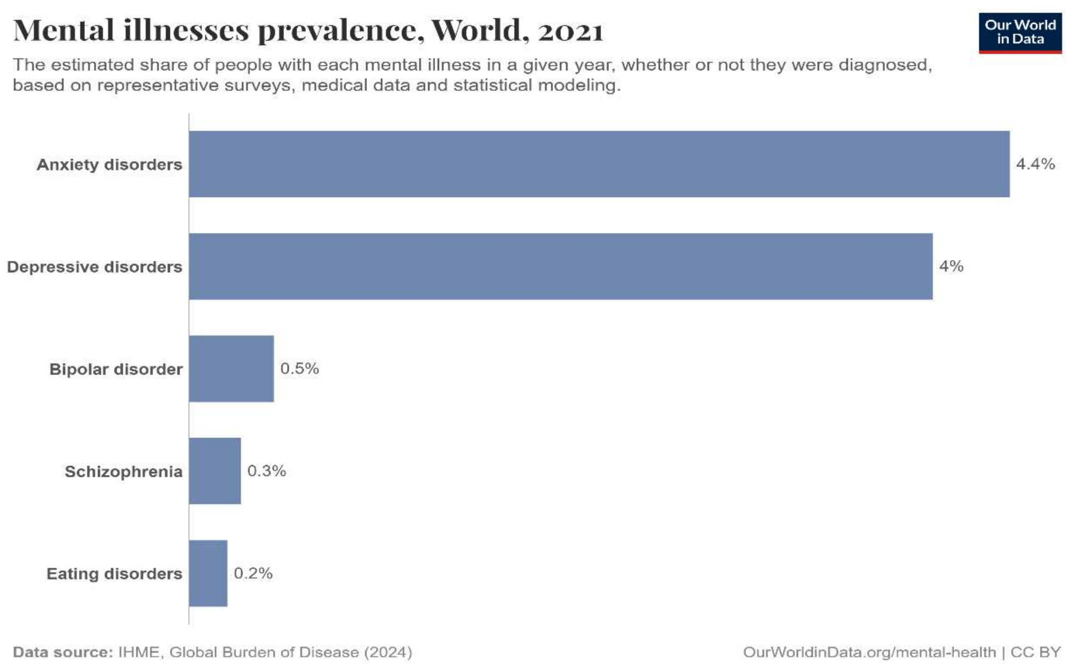

Figure 1.1 List of the most prevalent mental disorders globally (IHME, Global Burden of Disease 2024).

1.2 Risk factors of depression

Underlying mechanisms of depression as well as risk factors can be attributed to bio–psycho–social mechanisms.

Regarding biological mechanisms, the Monoamine hypothesis posits that the depletion of key monoaminergic neurotransmitters such as serotonin, dopamine, and norepinephrine might be the basis of depression (Schildkraut, 1965; Bunney & Davis 1965). This view is supported by the functioning of antidepressant drugs, which shows that decreased functioning of serotonin and norepinephrine can trigger depressive episodes, and vice versa (Delgado, 2000). The role of serotonin in depressive symptoms, confirmed in animal models, shows functioning of serotonin pathways being linked to depressed mood, cognitive dysfunction (Żmudzka et al., 2018), and altered sleep patterns (Ursin, 2002). Individuals with one or two short alleles of the serotonin transporter gene are initially at higher risk for experiencing a depressive episode (Eaton et al., 2008). The downregulation of dopaminergic systems explains one of the main symptoms of MDD, anhedonia (Belujon & Grace, 2017). Indeed, dopamine plays a critical role in the sensitivity of the reward system in the brain, which is supposed to guide motivation, pleasure, and energy to obtain rewards (Berridge & Robinson, 1998). Moreover, research using glutamatergic drugs targeting NMDA receptors shows us the role of glutamatergic neurotransmission in depression, suggesting that modulation of glutamatergic receptors may enhance excitatory activity, potentially contributing to treatment response in major depression (Serafini et al., 2013). Research on the heritability of depression indicates that genetic influence can vary based on several factors. For instance, Sullivan and colleagues (2000) estimated depression's heritability at approximately 0.37.

The interaction between genetic and environmental factors has also been a focus of research, as this interplay may contribute to the risk of developing depressive symptoms (Caspi et al., 2003). Epigenetic studies have played a key role in illustrating how environmental experiences can influence gene expression. A significant breakthrough in this area was found in research exploring how variations in the serotonin transporter gene (5-HTTLPR) interact with exposure to stress, particularly childhood maltreatment (Caspi et al., 2003). Their findings indicated that individuals carrying one or two copies of the short allele of this gene were more likely to develop severe depressive symptoms and had a higher risk of suicide following stressful life events, compared to those with two long alleles (Uher & McGuffin, 2010). After examining the core contributing elements, it is important to highlight key psychological factors that are maladaptive cognitive schemas (Keller et al., 2019; Nieto et al., 2020), difficulties in emotion regulation

(LeMoult & Gotlib, 2019), and a tendency to ruminate (Eszlari et. al., 2016; LeMoult & Joormann, 2014). Aaron T. Beck (1967) postulated the cognitive theory of depression, stating that depression is associated with the negative view of ourselves, the world around us, and the future, representing the negative triad (figure 1.2). It posits that we can acquire negative schemas due to negative experiences in childhood, social rejections, depressive behavior of a parent, or death of a parent. Therefore, cognitive schemas influence attention and memory by prioritizing information that aligns with an individual's current mood. In the context of depression, this often means a focus on negatively toned stimuli. Such interpretations are shaped by cognitive distortion such as exaggeration, minimization, black-and-white thinking, and arbitrary conclusions (Beck & Bredemeier, 2016). These maladaptive schemas and distortions in cognition, together with high neuroticism, poor social support, and stressful life events, are believed to act as early indicators of depressive symptoms but also increase the probability of recurrence of these symptoms (Burcusa & Iacono, 2007; Bishop et al., 2022).

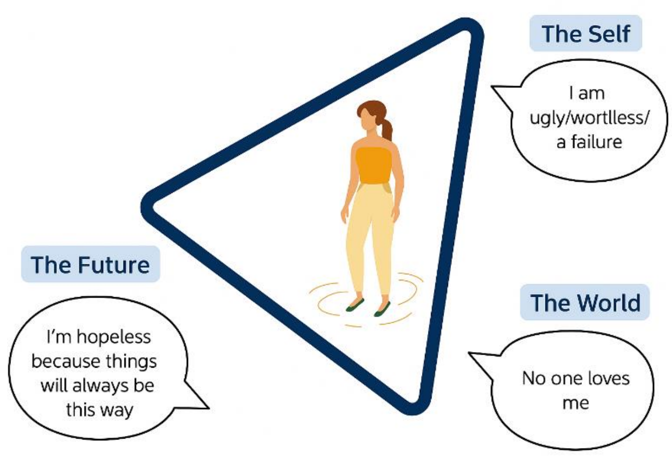

Figure 1.2: Representation of the negative triad and examples of attitudes towards the self, the world and the future. Taken from Massive Online Open Course with Simone Messerotti Benvenuti & Valentina Cardi, Clinical and Emergency Psychology, Federica Web Learning (2021).

Regarding psychological factors, emotion regulation strategies are typically developed early in life and are often shaped by parental behavior. Problems with emotion regulation are linked to an increased risk of experiencing depressive symptoms during adolescence (Silk et al., 2003). Rumination is another key psychological factor linked to subclinical levels of depression. Roberts and colleagues (1998) found that individuals who engage in rumination tend to experience more intense and longer-lasting negative emotional states. The study also suggests that rumination may be a cognitive expression of neuroticism, reflecting difficulties in emotional regulation. This difficulty in emotion regulation is associated with both the persistence and severity of depressive symptoms (Lemoult & Joormann, 2014) and with the likelihood of developing depressive episodes in young adulthood (Gibb et al., 2012; Woody et al., 2016). Rumination is considered a significant risk factor for the emergence of depressive symptoms (Moretta & Messerotti Benvenuti, 2022).

Lastly, regarding socio-environmental factors, adverse childhood experiences, unhealthy lifestyle practices (physical inactivity, smoking, alcohol abuse), psychosocial stressors (job insecurity, poor social support) may increase the risk for depression (Almeida et al., 2011). For younger individuals risk factors for depression are recent negative events, low income and smoking (Schaakxs et al., 2017) Negative parent–child quality relationship is associated with higher level of depression and can lead to higher vulnerability for depression in adolescence (Li et al., 2025). However, the perceived lower quality of relationship with parents in adolescence is also associated with the increased risk for depression (Branje et al., 2010). Specifically, exposure and experience of paternal physical abuse or sexual abuse, but also maternal overcontrol, are indicators of a highly chronic course of MDD (Klein et al., 2009). These individuals are also more resistant to pharmacological treatment. Overall, emotional abuse and neglect are associated with adulthood depression (Mandelli et al., 2015).

Depressive symptoms are linked to other contextual factors, such as socio-economic status (Lund et al., 2010), but also individual factors such as level of education, employment, marital status and gender (Rai et al., 2013). A contextual risk factor can be considered also the accessibility of health services, as Evans-Lacko and colleagues (2018) reported that individuals with low to middle socio-economic status are less likely to go through treatment for specific mental disorders as well as the highest rate of treatment is associated with the highest education.

1.2.1. The role of family history for depression

Family history is a recognized risk factor for depression, potentially increasing susceptibility to the disorder through genetic predisposition or the inheritance of gene-related alterations (Dean, 2024). Individuals who have at least one family member with MDD history are twice as prone to develop MDD (Gronemann et al., 2025). A more recent study involving Danish twins found that genetic contributions to depression could range between 15% and 34% (Wium-Andersen et al., 2020). Notably, this study found no significant differences in heritability between males and females. A longitudinal study conducted by Yan and colleagues (2021) confirmed the correlation between maternal depressive symptoms and the regulation of sadness and anger in girls and preschool children. The results show insights of girls, whose mothers present elevated levels of depressive symptoms, turn frustration into sadness faster than girls whose mothers have low levels of depressive symptoms and have impaired emotion regulation. On the other hand, being exposed to at least one childhood adverse event has a 1.5-fold increased risk of developing MDD. We can conclude that both family history of MDD and each childhood adverse experience, separately or combined, were associated with greater risks of MDD (Gronemann et al., 2025). The research demonstrated that having a close family member with mood disorders, such as depression or bipolar disorder, increases the risk of depression turning chronic. In a cross-sectional study, depressed parents were found to have four different parenting styles. A parenting style, out of the four, found to increase a child's risk for depression 5.29 times was indifference parenting, characterized by low care and full autonomy, meaning they show very little emotional warmth and support to the child and do not encourage independence (Wang et al., 2021).

CHAPTER 2: Heart Rate Variability

2.1 Heart rate variability (HRV): an index of sympato-vagal balance

Heart rate variability (HRV) refers to the fluctuations in time between consecutive heartbeats, which helps the body adapt efficiently to changing environmental demands (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). HRV represents the variation in interbeat intervals (IBI) over a given time period. The IBI corresponds to the distance between R-R peaks, which on average is eight hundred milliseconds (Shaffer et al., 2014).

The substantial amount of research on HRV has confirmed that it is an indicator of behavioral and psychological flexibility. Indeed, HRV reflects the ability to adapt to environmental changes (Berntson et al., 2008). It is essential to consider that the heart is innervated by both the sympathetic and parasympathetic (also known as vagal) branches of the autonomic nervous system (ANS). Additionally, it is innervated by specific muscle fibers and connective tissue. In this context, HRV represents the efferent vagal activity on the heart (Shaffer et al., 2014), where higher HRV indicates greater vagal influence on the heart (McCraty & Shaffer, 2015). In these terms, we can conclude that variations in IBI may be associated with vagal ANS activity (Laborde et al., 2017; Task Force, 1996). Specifically, the parasympathetic branch (notably through the vagus nerve, which slows heart rate) and the sympathetic branch (which speeds heart rate up). In general, the heart is predominantly influenced by the vagal system, and low HRV reflects reduced vagal control (Thayer & Lane, 2000). The reduction in vagal control has been associated with reduced emotional regulation (Koch et al., 2019; Messerotti Benvenuti et al., 2015; Thayer & Lane, 2000, 2009).

2.1.2 HRV metrics and indices

The heart produces a bioelectrical signal that can be analyzed through the electrocardiogram (ECG). This results in a trace with a constant morphology, divided into specific electrical events:

- P wave, which corresponds to atrial depolarization;
- Q-R-S complex, which corresponds to ventricular depolarization and atrial repolarization;
- T wave, which corresponds to ventricular repolarization.

In psychophysiology, HRV is studied through two domains, time and frequency. Time-domain metrics such as the standard deviation of normal-to-normal (NN) intervals (SDNN) and the root mean square of successive heartbeat differences (RMSSD), with RMSSD being more sensitive to vagal (parasympathetic) influences. HRV can also be analyzed using frequency-domain methods. Regarding the frequency domains, high-frequency (HF) HRV (0.15 – 0.4 Hz) is mostly linked to parasympathetic activity via the vagus nerve, while low-frequency (LF) HRV reflects a mix of both sympathetic and parasympathetic input. Very-low-frequency (VLF) HRV may represent slower regulatory mechanisms, like those related to body temperature or hormonal cycles (Task Force, 1996; Shaffer et al., 2014; McCraty & Shaffer, 2015; Shaffer & Ginsberg, 2017).

2.2 Neural Basis of HRV

Heart rate variability is generated through complex neural communication between the heart and the brain (Tiwari et al., 2021). The connection between the heart and the central nervous system (CNS) is reflected in changes in HRV. These changes are influenced by signals from baroreceptors, which affect both the sympathetic and parasympathetic branches of the ANS, as well as by signals sent from the brain (Riganello et al., 2018). This heart-brain relationship works in both directions and is controlled by a complex communication system (Pirahanchi & Bordoni, 2023; Armstrong et. al., 2023).

The Neurovisceral Integration Model (NIM) is a crucial theoretical framework in order to understand how bain – body communication reflects on emotional and attentional regulation, behavioral adaptation and psychological well-being (Thayer & Lane, 2000). According to this model, HRV, specifically HF-HRV, is related to and is an indicator of functioning of the central autonomic network (CAN) (Thayer et al., 2012). CAN includes brain regions such as prefrontal cortex, cingulate cortex, hypothalamus, insula, amygdala, brainstem. (Figure 2.1). The model posits that higher HRV reflects more flexible and efficient prefrontal inhibitory control over subcortical systems like the amygdala, enabling better self-regulation and stress response. In contrast, lower HRV indicates reduced regulatory capacity and has been associated with emotional dysregulation and psychopathology. In a meta-analysis study by Thayer and colleagues (2012), two key subregions of the medial Prefrontal Cortex (mPFC) were found: the pregenual anterior cingulate (linked with emotion) and the subgenual cingulate (related to autonomic control). A part of the left sublenticular extended amygdala/ventral striatum was also consistently observed. The amygdala is responsible for the detection of threats and negative stimuli, suggesting that individuals with lower rHRV may have worse inhibition of threat signals (figure 2.2). Reduced HRV may reflect impaired neurovisceral integration leading to diminished top-down control over emotions, more precisely negative affect and increased vulnerability to stress, as evidenced by modulated activity in the PFC and amygdala (Steinfurth et al., 2018).

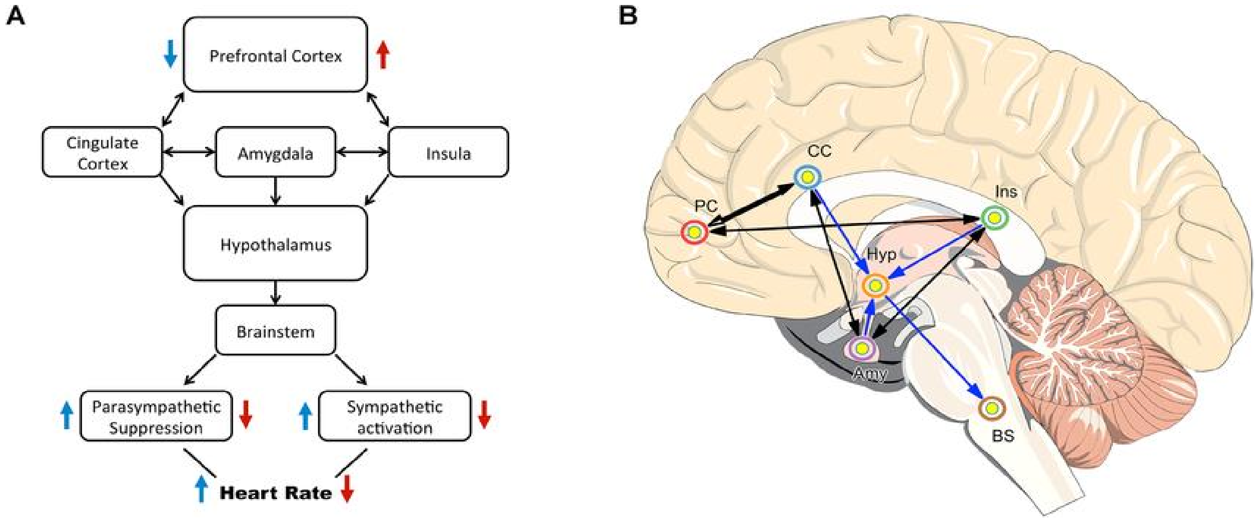

Figure 2.1 Neurovisceral integration model **(A)** Simplified depiction of the neurovisceral integration model described by Thayer and Sternberg (Thayer & Sternberg, 2006). **(B)** Brain regions relevant to the neurovisceral integration model: PC, prefrontal cortex; CC, cingulate cortex; Hyp, hypothalamus; Ins, insula; Amy, amygdala; BS, brainstem.

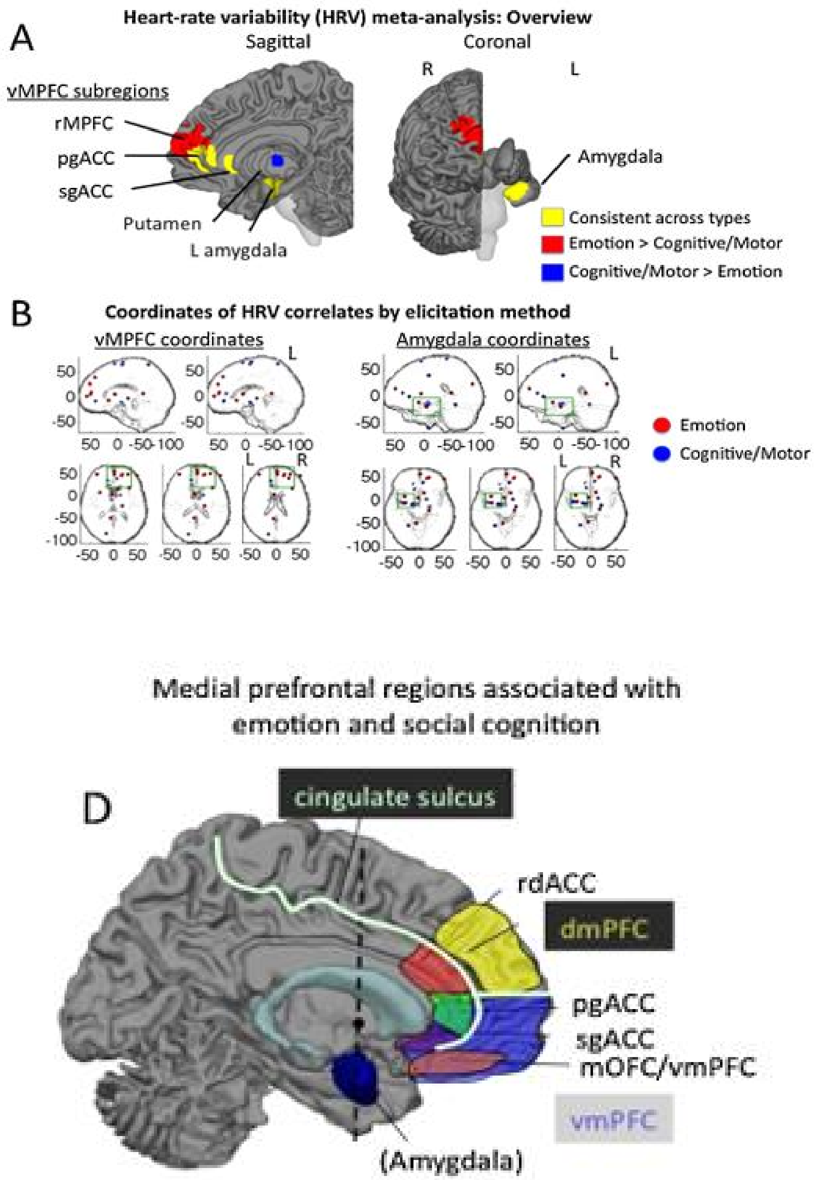

Figure 2.2. mPFC and amygdala activations during emotion regulation and cognitive/motor tasks. Areas such as amygdala and mPFC are responsible for threat detection and emotion regulation. These brain areas show activation because they are involved in autonomic, emotional and cognitive processes and are a crucial part of the CAN. From Thayer et al., 2012.

2.3 HRV in depression

Reduced HRV has been observed in individuals with depression compared to controls (Pizzi et al., 2008; Wang et al., 2013; Tonhajzerova et al., 2010). Research has consistently shown that individuals with MDD tend to display lower rHRV levels compared to non-depressed controls, and rHRV is generally found to be inversely related to depressive symptoms severity (Kemp et al., 2010). Furthermore, studies revealed that children and adolescents diagnosed with depression show lower high-frequency (HF) HRV than their non-depressed peers (Koenig et al., 2016). A decrease in rHRV has been linked to the activity of inflammatory processes (Gevirtz, 2013), which are strongly associated with both MDD (Frasure-Smith et al., 2009; Kop et al., 2010) and an elevated risk of death due to cardiovascular complications (Sabatine et al., 2007). Disruptions in ANS function, coupled with chronic immune activation, contribute to the increase in the likelihood of depressive episodes (Buchmann et al., 2022). Lastly, a lower rHRV may serve as an indicator of depression, however, patients with MDD show normalization of rHRV measures over a period of 2-week antidepressant therapy (Hartmann et al., 2019).

2.4 HRV in depression vulnerability

Several studies have suggested that rHRV may serve as a vulnerability marker for individuals at a higher depression risk, for example adults and adolescents with dysphoria (Blood et. Al., 2015; Dell'Acqua et al., 2020; Rohleder & Miller, 2008), adults with MDD in remission (Dell'Acqua et al., 2020), and adults with a familial risk for the disorder (Moretta & Messerotti, 2023). Findings indicate that this vulnerability is characterized by decreased vagal activity and increased sympathetic nervous system activation, in exploring the direction of this relationship. A study by Bassett and colleagues (2016), where rHRV was measured during the bedtime period, highlights that individuals with a history of Bipolar I disorder and recurrent MDD exhibit impaired autonomic function, specifically lower parasympathetic activation indexed by RMSSD, even during clinical remission. This finding suggests that the effects of mood disorders extend beyond acute episodes and may have lasting physiological consequences. It was also proposed that reduced HRV might not just accompany depressive symptoms but also precede their onset. In a longitudinal study conducted on a community sample, Carnevali and colleagues (2018) argued that low vagal tone could play a causative role in the development of depression. This autonomic dysfunction may generate depressive symptoms in a non-clinical setting, showing that rHRV measures in healthy individuals were able to predict the emergence of depressive symptoms in 3 years' time. More precisely, HRV assessed at an intermediate time point (time 1) was shown to be a significant mediator between rumination measured at time 0 and depressive symptoms at time 2 (figure 2.3). Understanding the role of HRV in the onset and progression of depression could support the development of targeted clinical prevention strategies.

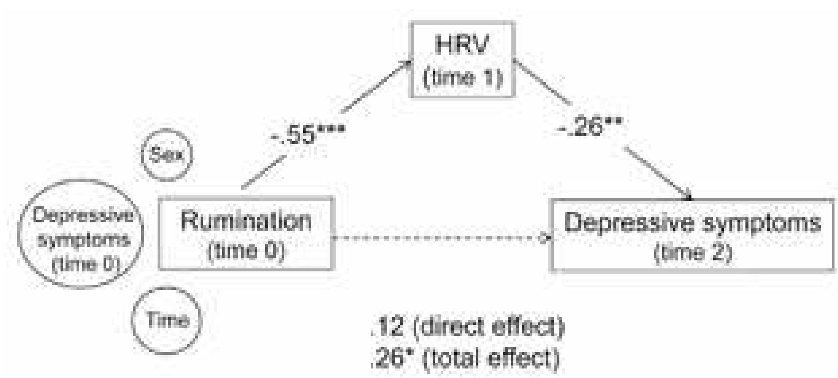

Figure 2.3: Depiction of the mediation model between rumination at time 0 and depressive symptoms at time 2 via HRV measured at time 0. From (Carnevali et al., 2018).

CHAPTER 3: The Study

3.1 Introduction and hypothesis

As described in the first Chapter, depression is a chronic and recurrent mood disorder that affects more than 300 million people globally and represents a leading cause of disability worldwide (Institute of Health Metrics and Evaluation, Global Burden of Disease, 2024). Therefore, identifying early indicators of this condition, before full-blown depression occurs, has been highlighted as a core priority (Carnevali et. al., 2018; Ernst, 2017, Koch et. al., 2019; Thayer & Lane, 2000). Vulnerability to both the onset and recurrence of depression is likely shaped by a complex interplay of biological, psychological, and environmental influences (Burcusa & Iacono, 2007). Several clinical indicators have been identified as predictors of depression, such as early age of onset, persistent subclinical symptoms, maladaptive cognitive patterns, and ineffective emotion regulation strategies (Burcusa & Iacono, 2007; Miranda & Pearson, 1988; Teasdale, 1988; ten Doesschate et al., 2010).

More recently, a multidimensional framework has been adopted to better grasp the complexity of the interacting systems within the human body. Among these, the autonomic nervous system (ANS) plays a central role in regulating various physiological functions, and its regulation has been traced to multiple brain regions (Ernst, 2017; Thayer et al., 2012). Within this framework, repeated findings reported a reduced HRV among individuals with depression, suggesting the potential role of the ANS regulation in the pathophysiological mechanisms of depression (Hartmann et al., 2019).

Despite the evidence supporting the presence of reduced HRV in MDD (Kemp et al., 2010; Koch et al., 2019; Udupa et al., 2007), studies exploring this index in at-risk populations, such as preadolescents with a familial risk for depression, are still lacking. Therefore, the aim of the present study was to assess HRV in preadolescents with a familial vulnerability to the onset of a full-blown depression to clarify whether this might represent a risk factor for the condition. To this end, two groups were enrolled in the present study: (1) preadolescents with a family history for depression, and (2) preadolescents without a family history for depression. It was hypothesized that preadolescents with a family history of depression would show reduced vagally mediated HRV parameters (time- and-frequency domain) compared to healthy controls.

3.2 Methods

3.2.1 Participants

A total of thirty-two preadolescents (21 female, mean age = 11.9 ± 0.77, range 11–14 years) took part in the study. Participants were recruited through collaboration with several lower secondary schools in the municipality of Padua. Specifically, a seminar was organized for parents, focusing on topics related to psychological well-being in preadolescence, which also included a brief presentation of the current research. Families interested in participating in the study completed an online form and were subsequently contacted by the researchers involved.

The inclusion criteria required participants to be typically developing preadolescents aged between 11 and 14 years without depressive symptoms. Preadolescents certified with disabilities (Law 104/92), learning disorders (Law 170/2010), or other special educational needs (Ministerial Directive of 27/12/2012) were excluded from the study. Additionally, preadolescents with psychiatric, neurological, or other medical conditions were also excluded. Another exclusion criterion concerned the presence (past or current) of psychiatric disorders in the parents, other than depression.

The presence of a family history of depression was assessed through the administration of the Patient Health Questionnaire-9 (PHQ-9; Spitzer et al., 1999; Italian version by Mazzotti et al., 2003) separately to both parents. Participants with at least one parent scoring 10 or higher on the PHQ-9, either currently or regarding a past depressive episode, were assigned to the experimental group with a family history of depression (n = 16, 10 female). Conversely, participants whose parents reported scores of 9 or lower on the PHQ-9, both currently and for past episodes, were included in the control group (n = 16, 11 female). Parental stress was assessed using the Parenting Stress Index-Short Form (Abidin, 1995; Italian version by Guarino et al., 2008).

The research was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by the Ethics Committee for Psychological Research, Area 17, University of Padua (protocol no. 105-b). Participants received a monetary compensation of €50.00 for taking part in the study. The demographic characteristics of the sample are reported in Table 3.1. The two participant groups did not significantly differ in terms of sex, age, or scores on the Child Depression Inventory (CDI).

Table 1.1. Descriptive statistics of participants in this study.

	With familial risk (*n* = 16)	Without familial risk (*n* = 16)
Sex (n and % of females)	10, 62.5 %	11, 68.75 %
Age	Mean = 11.9 SD = 0.85	Mean = 11.9 SD = 0.72
CDI	Mean = 10.0 SD = 5.42	Mean = 7.69 SD = 6.77

Note. CDI = Children Depression Inventory; SD = Standard Deviation.

3.2.2 Procedure

Upon arrival at the Psychophysiology Laboratory of the Department of General Psychology at the University of Padua, the parents handed the researchers involved in the study, the paper version of the informed consent form for participation in the research and the processing of personal data, which had been completed and signed.

Subsequently, the participants and their accompanying parents were shown the laboratory rooms and all the instruments relevant to the present study, in order to allow them to become familiar with the new environment. Once this phase was completed, the participants completed the computerized version of the Child Depression Inventory (CDI; Kovacs, 1985; Italian version by Camuffo et al., 1988), which aimed to investigate the possible presence of depressive symptoms in the two weeks preceding the completion of the questionnaire.

Next, the participants were taken to a room that was electrically and acoustically isolated and equipped with a good air conditioning system. They were then seated in a comfortable armchair positioned in front of a computer screen used for the administration of the experimental task. At this point, the researchers attached the electrodes for recording the electrocardiogram (ECG) and the electroencephalogram (EEG). The recording was carried out at rest for 3 minutes and during a passive emotional image viewing task. In this thesis, based on the focus and aims of the study, only the resting ECG trace was examined in order to derive resting HRV.

3.2.3 Psychological measures

During the online screening phase, both parents of the participants completed several questionnaires separately, which were sent to them via an online form (after reading, completing, and signing an initial informed consent). This form included some anamnesis questions regarding the parents and their children, aimed at exploring their lifestyle (use of alcohol or other substances) and the possible presence of current or past neurological or psychiatric disorders (for example, falling under the diagnostic categories of depressive disorders, anxiety disorders, bipolar and related disorders, schizophrenia spectrum and other psychotic disorders, and neurodevelopmental disorders).

Subsequently, the online form also included the administration of the Patient Health Questionnaire-9 (PHQ-9; Spitzer et al., 1999; Italian version by Mazzotti et al., 2003), a 9-item self-report questionnaire aimed at investigating the presence of the 9 symptoms of depression listed in the DSM-IV (APA, 1980), with the reference period being the two weeks prior to the completion of the questionnaire. An adapted version of the questionnaire was also used in order to gather information regarding the presence of any past depressive disorders. The time frame of the items was therefore adjusted so that they referred to the possible presence of a previous depressive disorder. Each item was rated on a 4-point Likert scale (0–3) intended to assess the frequency with which the symptoms occurred. The total score of the questionnaire can range from 0 to 27. In the Italian version, a cut-off score of 10 indicates the probable presence of clinically significant depression, while the severity is classified into 4 different levels based on the score: 0–4 (no depression), 5–9 (mild depression), 10–14 (moderate depression), 15–19 (moderately severe depression), and 20–27 (severe depression).

During the experimental session, the Child Depression Inventory (CDI; Kovacs, 1985; Italian version by Camuffo et al., 1988) was administered to the preadolescents. This is a self-report questionnaire used to assess the presence and severity of depressive symptoms in children, preadolescents, and adolescents. It consists of 27 items, each with three possible response options, rated on a 3-point Likert scale (0–2) in the direction of increasing severity of depressive symptoms, with a total score ranging from 0 to 54 points. In the Italian version, the following cut-off scores have been defined: 15 (mild depression), 20 (moderate depression), and 25 (severe depression).

3.2.4 ECG recording and HRV computation

The electrocardiogram (ECG) was recorded using three Ag/AgCl electrodes placed on the participant's chest in a lead II configuration. The ECG signal was continuously acquired for 3 minutes while the participants were comfortably seated at rest. For all electrodes, impedance was kept below 5 kΩ. The signal was amplified, filtered, and recorded continuously using AC amplifiers (ANT Neuro, Enschede, Netherlands). The signal sampling rate was 1000 Hz, and a band-pass filter of 0.3–100 Hz was applied during recording. The ECG signals were imported into Kubios (Tarvainen et al., 2014), where the signal was checked to verify if all the ECG peaks were detected. The time-domain measures that were extracted are the RMSSD and the SDDN, while the HF was extracted in the frequency domain. Log transformations were performed for SDNN, RMSSD and HF due to their skewed distributions.

3.3 Statistical analyses

HRV indices were log-transformed to ensure normality. Then, three separate *t*-test analysis were conducted between the two groups on each HRV measure (RMSSD, SDNN, HF) in order to test whether the two groups differed in cardiac vagal tone.

3.4 Results

The *t*-tests revealed no statistically significant differences between the two groups for any of the HRV indices (Table 3.2).

Descriptive statistics regarding HRV meassures between two groups are presented in table 3.3.

Table 3.2: *T*-test analysis between both groups in rHRV measures.

Variables	*t*-value	df	*p*-value
logSDNN	-0.60	30.0	.55

logRMSSD	-0.64	30.0	.53
LogHF	-1.55	30.0	.13

Table 3.3: Descriptive statistics of both groups in SDNN and RMSSD measures in milliseconds (ms) and HF absolute power in milliseconds squared (ms^2)

groups	SDNN (ms)	RMSSD (ms)	HF (ms^2)
With familial risk	Mean = 55.4 SD = 20.3	Mean = 55.4 SD = 25.7	Mean = 2067 SD = 2157
Without familial risk	Mean = 51.6 SD = 17.7	Mean = 54.6 SD = 23.6	Mean = 1380 SD = 1234

3.5 Discussion and conclusion

The primary aim of this study was to test whether reduced vagal tone, indexed by lower HRV, is in early indicator of depression risk in preadolescents with and without a family history for depression. This research question was grounded in a growing body of literature suggesting that alterations in autonomic nervous system (ANS) function, particularly diminished parasympathetic activity, may serve as a biological vulnerability marker for the development of depressive disorders. This is because HRV reflects a dynamic interplay between brain networks, namely the CAN which consists of brain regions including the prefrontal cortex and amygdala involved in emotion regulation, cognitive functioning, threat detection, functions that are overall associated with depressive symptoms and vulnerability (Thayer et al., 2012).

In this sample no significant differences in vagally-mediated resting state HRV indices (SDNN, RMSSD, and HF power) were observed between the at-risk and control groups.

These results suggest that reduced vagal tone may not yet be evident in early stages of vulnerability, since we know that young adults who are first degree relatives of individuals who have had or are currently experiencing depressive episodes have lower indices of rHRV meassures than controls. These indices are also similar to the rHRV measures gotten from individuals without vulnerability but experiencing depressive symptoms (Moretta & Messerotti Benvenuti, 2022).

While numerous studies have documented reduced rHRV in clinically depressed populations (Kemp et al., 2010; Koenig et al., 2016), and even in adults with subclinical symptoms or remitted depression (Dell'Acqua et al., 2020) as well as task-related cardiac deceleration being found in adults with familial risk for depression but without any symptoms (Moretta & Messerotti, 2023), the current results suggest that such autonomic dysregulation may not be present in preadolescents who are at familial risk. This raises important questions about the developmental timing of HRV alterations and the conditions under which they emerge. It is possible that disruptions in cardiac vagal function emerge later in development, perhaps in response to cumulative stress exposure, the onset of affective symptoms, or critical developmental transitions such as adolescence.

A potential explanation for the absence of HRV differences between groups is that autonomic dysfunction—particularly reduced vagal tone—may only emerge in response to psychological stress, the onset of affective symptoms, or during critical neurodevelopmental transitions such as puberty. This is consistent with the neurovisceral integration model, which suggests that latent vulnerabilities may require environmental or internal challenges to become observable (Forbes & Dahl, 2010; Thayer & Lane, 2000) Predolescence represents a time of significant hormonal, neurological, and psychosocial changes, which may interact with genetic predispositions to trigger observable physiological changes. Given that HRV is found to be a mediator between ruminative thinking and depression in a longitudinal design among younger adults (Carnevali et al., 2018), further longitudinal designs should be adopted in order to follow the mediating effect of rHRV starting from a preadolescence following participants through critical periods of development. Given the premises that reduced HRV may predict the emergence of depressive symptoms as well as the importance of early identification of depression, future research should adopt longitudinal designs to clarify whether alterations in cardiac vagal function develop over time in at-risk youth and contribute to the onset of depressive symptoms. In this framework, HRV would be sensitive to current affective states rather than predisposing risk. Since the participants in both groups were free of depressive symptoms, as confirmed by CDI scores, it is possible that HRV differences would only be visible in the presence of emotional dysregulation or emerging clinical symptoms.

This work presents several limitations. Sample size limitations, with only 16 participants in each group, could explain the insufficient statistical significance to detect small-to-moderate effects. The classification of participants into at-risk and control groups was based on the PHQ-9 scores of the parents, which, while validated, is a self-report measure and subject to potential underreporting or recall bias. A clinical diagnostic interview or access to medical records would provide more robust verification of parental depression history. Although exclusion criteria controlled for several relevant medical and psychiatric conditions, other factors potentially affecting HRV—such as physical activity levels, sleep patterns, diet, or recent stressors—were not comprehensively assessed or statistically controlled. These unmeasured variables may have influenced individual HRV levels, introducing variability unrelated to depression risk.

In conclusion, no significant group differences were found in rHRV. This does not rule out the role of this autonomic function, however, suggests further longitudinal designs with bigger samples are needed to determine whether and when early biological markers emerge in at – risk youth for developing depressive disorders.

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