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The role of autonomic nervous system activity in peripartum depression

Final dissertation

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List of abbreviations

Ach: Acetylcholine

ANS: Autonomous nervous system

AV: Atrioventricular

BBI: Beat-to-beat interval

BMI: Body mass index

BP: Blood pressure

BRs: Baroreflexes

CAN: Central Autonomic Network

CBT: Cognitive-behaviour therapy

COVID-19: Coronavirus disease 2019

CNS: Central nervous system

CRH: Corticotropin-releasing hormone

DSMV-TR: Diagnostic and Statistical Manual of Mental Disorders (5^{th} edition – text revision)

ECG: Electrocardiogram

ECT: Electroconvulsive therapy

eHealth: Electronic health

EPDS: Edinburgh Postnatal Depression Scale

HF: High frequency

HPA: Hypothalamic-pituitary-adrenal

HR: Heart rate

HRV: Heart rate variability

IBI: Interbeat interval

ICC: Intraclass correlation coefficients

ICD-11: International Statistical Classification of Diseases and Related Health Problems, 11^{th} revision

IPT: Interpersonal therapy

LED: Light-emitting diode

LF: Low frequency

LoA: Limits of agreement

M: Mean

mHealth: Mobile health

NE: Norepinephrine

NST: Nucleus of the solitary tract

PCG: Phonocardiogram

PD: Photodetector

PNS: Parasympathetic nervous system

PPD: Postpartum depression

PPG: Photoplethysmography

PTSD: Post-traumatic stress disorder

RGB: Red-green-blue

rMSSD: Root mean square of successive difference between NN intervals

RRI: RR interval

RSA: Respiratory sinus arrhythmia

SA: Sinoatrial

SCID - 5: the Structured Clinical Interview for DSM-V

SD: Standard deviation

SDNN: Standard deviation of the R-R intervals

SGC: Sympathetic ganglia chain

SNS: Sympathetic nervous system

SSRI: Selective serotonin reuptake inhibitor

ULF: Ultra-low frequency

VIF: Variance inflation factor

VLF: Very low frequency

WHO: World Health Organization

1. General introduction

1.1. Postpartum depression

1.1.1. Diagnosis and prevalence

Postpartum depression (PPD) has a controversial nosology; indeed, there is little consensus in research and clinical practice about how best to categorise PPD (di Florio & Meltzer-Brody, 2015; Stewart & Vigod, 2016). In the Diagnostic and Statistical Manual of Mental Disorders (5th edition – text revision) (DSM-V-TR), PPD is classified as a major depressive episode "with peripartum onset", namely during pregnancy or within the first four weeks after childbirth (American Psychiatric Association, 2022) (*Table 1.1.*). Therefore, DSM-V-TR recognizes that the potential onset of depression during pregnancy.

Table 1.1. Diagnostic criteria of DSM-V-TR for Major Depressive Episode. Adapted from (American Psychiatric Association, 2022).

Five (or more) of the following symptoms have been present during the same 2 weeks period, for most of nearly every day, and represent a change from previous functioning:
At least one symptom is: (1) Depressed mood. (2) Markedly diminished interest or pleasure in all, or almost all, activities. Other symptoms: (3) Significant weight loss when not dieting or weight gain, or decrease or increase in appetite. (4) Insomnia or hypersomnia. (5) Psychomotor agitation or retardation. (6) Fatigue or loss of energy. (7) Feelings of worthlessness or excessive or inappropriate guilt. (8) Diminished ability to think or concentrate or indecisiveness. (9) Recurrent thoughts of death or suicidal ideation (with or without a specific plan).
The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
The symptoms are not due to the direct physiological effects of a substance (e.g. a drug of abuse, a medication) or a general medical condition (e.g. hypothyroidism), not better explained by schizoaffective disorder or other psychotic disorders, and there has never been a manic or hypomanic episode.
Specifier: With peripartum onset This specifier can be applied to the current major depressive episode or, if the major depressive episode is in partial or complete remission, the most recent episode of major depression if the onset of mood symptoms occurs during pregnancy or in the four weeks following delivery.

The second main classification system for diagnostic health information – International Statistical Classification of Diseases and Related Health Problems, 11th revision (ICD-11) – used similar criteria to those in DSM-V-TR to classify PPD (ICD-11 code: 6E20) and specified that the depressive episode must arise during pregnancy or within about six weeks after delivery (World Health Organization, 2019). However, in research and clinical practice, the potential onset of PPD is extended beyond the first six weeks, up to 12 months after childbirth (Halbreich, 2005; Putnam et al., 2015; Stewart & Vigod, 2016). The variable onset time range is because PPD that begins later than six weeks could still cause harm and require treatment (Gaynes et al., 2005; Vliegen et al., 2014). Halbreich (2005) suggests that postpartum phenomena, symptoms and complaints are associated with biological and psychosocial processes and may thus be considered to be postpartum only as long as they persist. However, the exact individualized time period differs across individuals; therefore, this will cause a different onset time for PPD (Halbreich, 2005).

The Edinburg Postpartum Depression Scale (EPDS) (Cox et al., 1987) is the most widely used self-report instrument for the screening of postpartum depressive symptoms (ACOG Committee, 2018; Knights et al., 2016). The popularity of the EPDS is explained by its good validity, sensitivity and specificity (Bergink et al., 2011; Cox et al., 1987; Levis, Negeri, et al., 2020; Sit & Wisner, 2009). Other used instruments are: Patient Health Questionnaire – 9 (Kroenke et al., 2001), Beck Depression Inventory – II (A. T. Beck et al., 1996), Center for Epidemiologic Studies Depression Scale (Radloff, 1977), Postpartum Depression Screening Scale (Beck & Gable, 2000), and Zung Self-Rating Depression Scale (Zung, 1965). However, EPDS remain a gold standard for screening depressive symptoms since it includes anxiety symptoms, which are a prominent feature of perinatal mood disorders, but excludes somatic symptoms of depression, such as changes in appetite or sleep patterns, which reflect regular peripartum adjustment and may inflate scores (ACOG Committee, 2018; Affonso et al., 2000; Putnam et al., 2015). Self-reported questionnaires are usually used in research, whereas in clinical practice, a reference standard is typically used to validate the results of screening tools (e.g., EPDS or PHQ-9) (Ukatu et al., 2018). The most common and reliable used standard to diagnose PPD is the Structured Clinical Interview for DSM-V (SCID -5).

Postpartum mental health is now firmly on the World Health Organization (WHO) agenda, with estimates suggesting that common mental disorders (i.e., anxiety and depression) have a prevalence of 13% in high-income countries and 19.8% in low- and middle-income countries (World Health Organization & Special Programme of Research, 2022). Postpartum depressive disorders are the most prevalent mental illness after childbirth; a recent systematic review and meta-analysis of depression among postpartum women reported a global prevalence of 17.2% for PPD, with Southern

Africa with the highest prevalence rate (40%) and Oceania with the lowest prevalence rate (11.1%) (Wang et al., 2021).

Like other systematic reviews and meta-analyses that investigate the prevalence of PPD in the population, the study of Wang et al. (2021) had a few methodological issues partly related to the heterogeneity of PPD (O'Hara & McCabe, 2013). The prevalence of PPD varies widely between the different studies because of the lack of uniformity in the methods of screening/diagnosis, the length of the postpartum time frame considered, and the cross-cultural and social diversity of the samples (Gavin et al., 2005; O'Hara & Swain, 1996; Shorey et al., 2018; Wang et al., 2021). The use of different assessment instruments affects the rates of PPD, with the studies using self-report tools (e.g., EPDS, PHQ-9) reporting a greater prevalence estimated than studies based on structural interviews (e.g., SCID-5) (O'Hara & Swain, 1996; Wang et al., 2021; Woody et al., 2017). This incongruence is because a self-reported instrument such as EPDS or PHQ-9 is valid for PPD screening but is insufficient for a thorough diagnosis. Moreover, the congruence of prevalence rates between the self-report tool and the structured interview is closely related to the chosen cut-off for the self-report instrument (Levis, Benedetti, et al., 2020; Lyubenova et al., 2021). However, studies that administered self-report measurements used different cut-off scores for the same instrument, making the comparison of prevalence between the different studies unreliable. A second issue is the different time points in which the PPD assessment is carried out. The most recent systematic review reported a similar prevalence of PPD through the different time periods of assessment: 1-3 months (17.7%), 3-6 months (15.3%), 6-12 months (18.2%), and greater than 12 months (17.9%) after the delivery (Wang et al., 2021). However, other systematic reviews reported nether a trend of increasing prevalence of PPD from few days to more than one year after the childbirth (Shorey et al., 2018) or a higher prevalence in the first three postpartum months with a slight decline in the following month (Alshikh Ahmad et al., 2021; Gavin et al., 2005). The difference prevalence rates at different assessment time periods is related to the heterogeneity of depression in the peripartum period, with different trajectories over the time (Kiviruusu et al., 2020; Putnam et al., 2015; Putnick et al., 2020). A last important issue in the different country and culture of the samples included in the systematic reviews. Literature reported no or little differences between prevalence rates in developed countries (Gavin et al., 2005) and a higher prevalence of PPD for women in low- and middle-income countries than women in high-income countries (Shorey et al., 2018; Z. Wang et al., 2021). Therefore, country development and income inequalities had an important effect on PPD prevalence rates.

PPD is also a growing challenge for Italy health services, with the two most recent studies reporting a prevalence of 5.8% (Ferrari et al., 2021) and 19.9% (Cena et al., 2021) within the first eight weeks or the first nine months after the childbirth, respectively. Despite the recent prevalence

data heterogeneity, Wang *et al.* (2021), considering only the 14 studies on Italian samples, reported a prevalence of 16.8% of women affected by PPD. Because of the high rate of depression in new mothers and the negative mental and physical health consequences of PPD on both the mother and newborn (O'Hara & McCabe, 2013; Shorey et al., 2018; Slomian et al., 2019; Webber & Benedict, 2019), in the recent years, there is more awareness and investigation on PPD leading also in Italy to national programmes for the prevention, diagnosis, and intervention on PPD (Palumbo et al., 2016).

1.1.2. Symptoms, course, and consequences

The symptoms of PPD do not generally appear to differ from depression at other times (O'Hara & McCabe, 2013). However, the mother may be more labile and tearful – due to the rapid changes in hormonal levels following the delivery – and must simultaneously cope with her symptoms by looking after a newborn child (Beck & Indman, 2005; Stewart & Vigod, 2019). The new mother could experience despondent mood, loss of interest or pleasure in activities, sleep disturbance (beyond that associated with the care of the baby), appetite disturbance, loss of energy, feelings of worthlessness or guilt, impaired concentration, and suicidal ideation (O'Hara & McCabe, 2013). Moreover, specific symptoms of PPD are mood lability, feeling of inadequacy as a parent, anxiety, irritability, obsessional preoccupation with the baby's health and feeding, feeling of being overwhelmed, and thoughts of harming their child (Jennings et al., 1999; Stewart & Vigod, 2016, 2019). However, not all new mothers presented the same PPD symptoms simultaneously and with the same severity. Indeed, the issues surrounding the screening and diagnosis of PPD are also caused by this heterogeneity of the symptoms reported in PPD (di Florio & Meltzer-Brody, 2015; O'Hara & McCabe, 2013).

The natural duration of PPD is variable as its onset (Putnam et al., 2015; Stewart & Vigod, 2019). As explained in *paragraph 1.1.1.*, diagnostic manuals consider plausible the onset of depression during pregnancy; therefore, many times, the diagnosticated PPD is the extension of a mood disorder started before the pregnancy (Baron et al., 2017; Kiviruusu et al., 2020; O'Hara & McCabe, 2013; Santos et al., 2017). In addition, few studies reported that one of the most important predictors of PPD is a history of mental disorders before pregnancy (e.g., mood disorders and anxiety) (Putnam et al., 2015; Stewart & Vigod, 2016, 2019). Therefore it could be possible that the vulnerability/susceptibility to mental disorders, in general, affects the course of depressive symptoms in the peripartum period (Putnam et al., 2015; Vliegen et al., 2014; Wisner et al., 2013). Literature supports these point by showing that an episode of depression identified during the postpartum period has one of three possible onset times: prior to pregnancy, during pregnancy, or during the postpartum

period (Fisher et al., 2016; Wisner et al., 2013). For instance, Yonkers *et al.* (2001) likewise found that 50% of postpartum depressed mothers reported depression onset following delivery, 25% during pregnancy and 25% before pregnancy. Moreover, a study that considered mood disorders before pregnancy showed that among 541 women with unipolar depression at pre-pregnancy, 4.6% had depressive symptoms during pregnancy and 30% after childbirth (Viguera et al., 2011). A recent systematic review reported that among women with PPD in the first month after delivery, 24% remain depressed one year after the delivery and 13% after two years; in addition, about 40% of new mothers with PPD will relapse either during a subsequent pregnancy or in a non-pregnancy period (Stewart & Vigod, 2019). These studies were crucial to understanding PPD better, but they add further variability to a mental disorder that seems to differ from a non-pregnancy depressive disorder.

Conceptual problems with the nosology of depression become apparent when one considers that depression can present different symptom clusters in different individuals (e.g., somatic or cognitive symptoms preponderance), it can manifest itself either as an excess or insufficiency of certain behaviours (e.g. hypersomnia or insomnia, weight gain or weight loss), and symptoms of major depression overlap with other disorders including dysthymia and bipolar depression (Goldberg, 2011; Musliner et al., 2016; Zimmerman et al., 2015). If depression is considered during the peripartum period, the heterogeneity of the disorder increase with several features that differentiate groups, including the timing of onset (i.e., during pregnancy *vs* postpartum), the type and severity of symptoms, and other typical psychiatric comorbidities (e.g., history of depression, other mood disorders, anxiety) (Galea & Frokjaer, 2019; Putnam et al., 2015). The difference between PPD and depressive symptoms at other times also raises the problem of whether PPD is a distinct disorder in its own right linked to childbirth or an episode of major depression that manifests in the postpartum period (di Florio & Meltzer-Brody, 2015; Galea & Frokjaer, 2019; O'Hara & McCabe, 2013; Putnam et al., 2015). Many researchers have examined this question in an attempt to clarify whether or not PPD is, in fact, a separate diagnostic entity. For instance, Whiffen et al. (1992) reviewed 24 studies examining the prevalence, symptomatology, course, duration, relapse and aetiology of PPD and concluded that PPD did not differ qualitatively from non-postpartum depression (Whiffen, 1992). Indeed, the fact that the only difference between postpartum and non-postpartum depression was the severity of the disorder may not be helpful to the concept of a separate diagnosis (Whiffen, 1992; Whiffen & Gotlib, 1993). However, Cooper and Murray (1995) supported the idea of PPD as a specific entity by comparing women for whom PPD was their first experience of depression (i.e., *de novo* group) with those for whom PPD was a recurrence of a previous affective disorder (i.e., recurring group). The study showed that the recurring group had a greater risk for subsequent non-postpartum depressive episodes from 2 to 5 years after childbirth, whereas the *de novo* group had a

greater risk for PPD, supporting the argument for a diagnostic distinction for PPD (Cooper & Murray, 1995; Murray et al., 1995). Studies investigating the distinctiveness of PPD from non-postpartum depression show mixed findings, as reported by different reviews (Batt et al., 2020; di Florio & Meltzer-Brody, 2015; O'Hara & McCabe, 2013). Currently, there is insufficient evidence to classify PPD as a separate disorder (Batt et al., 2020). Nevertheless, the distinction between depression occurring in the peripartum period and depression occurring at other times is important for both research and clinical practice (di Florio & Meltzer-Brody, 2015; O'Hara & McCabe, 2013). Moreover, it should differentiate between episodes occurring during pregnancy and after childbirth, as the pathogenetic factors involved are likely to differ and may require specialized treatment (di Florio & Meltzer-Brody, 2015; Putnam et al., 2015).

Despite difficulties in classifying PPD, the consequences of this disorder are acknowledged and affect both the mother and the infant. For example, a recent systemic review concludes that PPD diminishes women's mental health and quality of life, affecting their perception of parenting and creating a hostile and non-stimulant environment, which leads to detrimental effects on behaviour, cognition, and mental/physical health of the child (Slomian et al., 2019). For instance, women with PPD had lower psychological well-being and mood scores (Dietz et al., 2009; Lilja et al., 2012), which can increase the likelihood of these women engaging in risky health behaviours, such as the use of addictive substances or suicidal ideation (Chapman & Wu, 2013; Stewart & Vigod, 2019). Moreover, PPD was associated with more difficulties in marital relationships (Slomian et al., 2019), often resulting in paternal postnatal depressive symptoms (Barooj-Kiakalaee et al., 2022; J. H. Goodman, 2004; Rao et al., 2020). In addition, PPD has been shown to affect numerous maternal caretaking behaviours, leading to reduced length and quality of breastfeeding (Dennis & McQueen, 2007; Dias & Figueiredo, 2015) and poor interest in the health, basic needs and safety of the infant (O'Hara & McCabe, 2013; Zajicek-Farber, 2009). This parenting style is often the result of a mother-child interaction characterized by hostility, unresponsiveness, less sensitivity, and impaired attachment to the infant (Brummelte & Galea, 2016; Dietz et al., 2009). The psychological sufferance of the mother and the maladaptive parenting could influence, in the long term, the optimal behavioural, emotional, cognitive, and physical development of the child. For instance, PPD was associated with higher levels of child internalizing and externalizing psychopathology (S. H. Goodman et al., 2011), higher levels of fear and anxiety (Slomian et al., 2019), poorer language and IQ development (Grace et al., 2003; Stewart & Vigod, 2019), and higher incidence of gastrointestinal symptoms and poorer child cardiovascular functioning (Brummelte & Galea, 2016; O'Hara & McCabe, 2013). Thus, PPD does not only affect the mother's well-being but has many direct and

indirect adverse effects on the child's development. Therefore, detecting and treating postpartum depression as early as possible seems crucial to avoid harmful consequences.

1.1.3. Risk factors and pathogenesis

Several studies focused on the psychological, social, and biological predictors of PPD to identify women at more risk of developing this mood disorder. Among the potential psychosocial predictors of PPD, stress levels are one of the most documented factors in literature (Hutchens & Kearney, 2020; Yim et al., 2015). A recent systematic review reported that peripartum chronic stressors (e.g., general perceived stress, financial stress, work-related stress) are a more consistent predictor of PPD than episodic stressors (e.g., catastrophic events, stressful life events) (Yim et al., 2015). Moreover, literature has consistently shown that experiencing depressive or anxiety symptoms during pregnancy or a history of psychiatric disorders before the pregnancy could be a significant factor that predicts PPD (Guintivano et al., 2018; Hutchens & Kearney, 2020; O'Hara & McCabe, 2013; Payne & Maguire, 2019). Therefore, it seems that a psychological predisposition to mental disorders could increase the likelihood of developing PPD. The link between mental vulnerability and the development of postpartum mood disorders could be related to neuroticism, namely the relatively stable tendency over time to experience negative affect in response to a stressful situation (Ormel et al., 2013). Recent literature supported this idea showing that neuroticism is the most important personality trait associated with PPD and could affect how women cope with pregnancy stressors (Puyané et al., 2022). This finding supported the cognitive-behavioural model of PPD in which psychological vulnerabilities (e.g., neuroticism) prior to and during pregnancy would predict increases in depressive symptoms following a stressful life event such as childbirth (O'Hara et al., 1982, 1991).

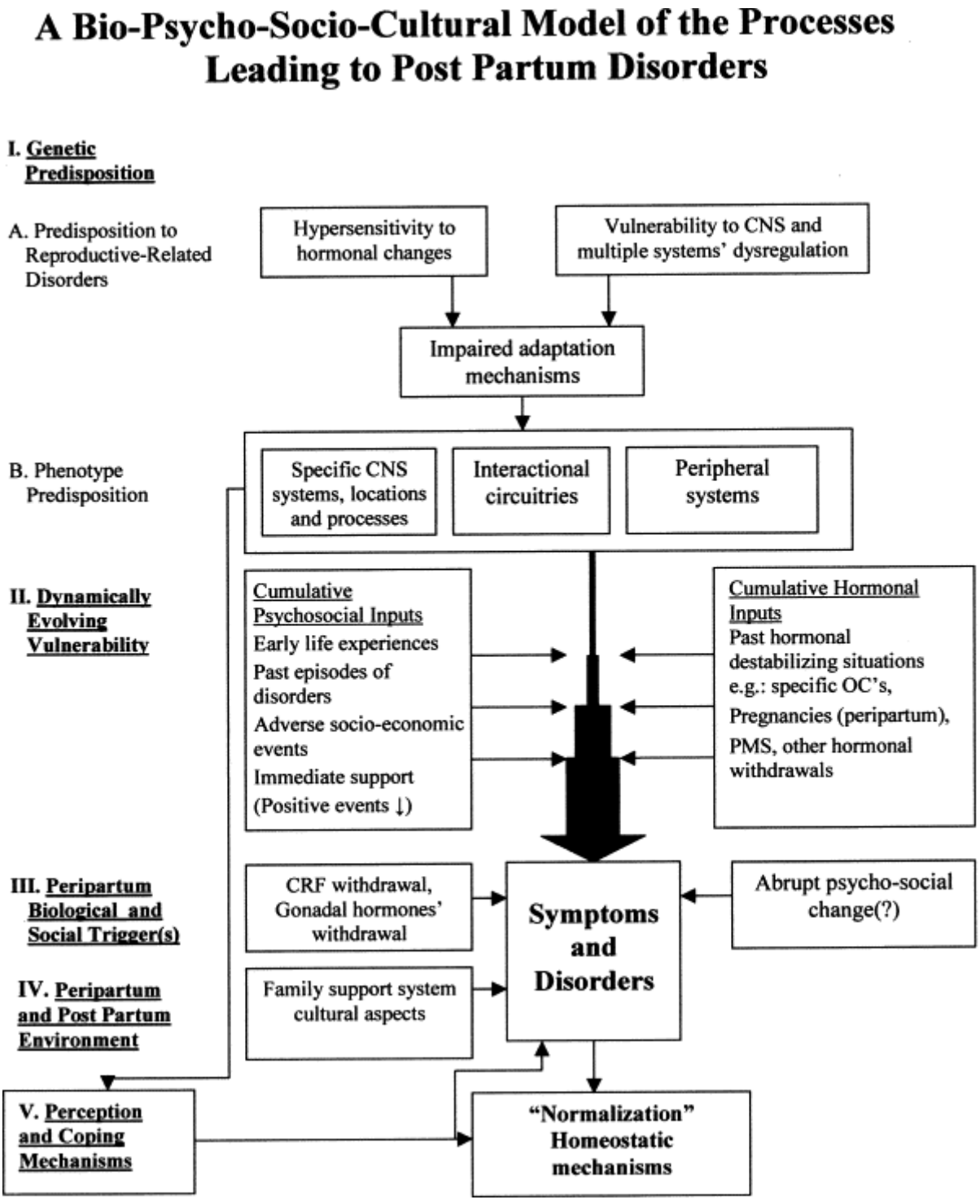
Another crucial risk factor of PPD is the quality of interpersonal relationships (Hutchens & Kearney, 2020; Yim et al., 2015). According to Yim et al. (2015), women who perceived higher levels of social support and were satisfied with support from their partner or family during pregnancy had a lower risk of developing PPD. Recent literature supported the finding of the review mentioned above, showing a significant buffering effect of social support against the probability of developing PPD (Cho et al., 2022; Pao et al., 2019). The findings are in line with Psychosocial Stress Theory (Pearlin, 1989) and, in particular, with the idea that the potentially harmful effect of a stressor – in this case, pregnancy – on health outcomes and psychological well-being could be mitigated by coping strategies and social support resources (Abdollahi et al., 2016; Zheng et al., 2022). On the other side, abusive and unsupportive relationships and lack of perceived social support are significant predictors of the

onset and severity of PPD (Hutchens & Kearney, 2020). Interestingly, Norhayati et al. (2015) found that poor marital relationship is an important predictor of PPD in both developed and developing countries.

Among biological processes, the dysregulation of several reproductive (e.g., estrogen and progesterone) and stress hormones (e.g., corticotropin-releasing hormone) seems to play a crucial role in the aetiology of PPD (O'Hara & McCabe, 2013; Payne & Maguire, 2019; Stewart & Vigod, 2019; Yim et al., 2015). The hormonal withdrawal theory posits that the steeper increase of estradiol, progesterone and cortisol during pregnancy and the drastic decrease of these hormones immediately after childbirth caused dysregulation of body homeostasis processes of the body that could lead to PPD (Bloch et al., 2000; Glynn et al., 2013; Serati et al., 2016; Yim et al., 2015). It should be noted that although all women experience a dramatic decrease in hormone levels after delivery, only a small subset of women develop PPD (O'Hara & McCabe, 2013). Bloch et al. (2000) showed that depression symptoms were significantly higher during the hormonal withdrawal phase in women with a prior history of PPD, while the group with no history of mood disorders showed minimal change in mood scores. Moreover, recent systematic reviews reported mixed findings when the hormonal withdrawal was analysed as predictor of PPD (Payne & Maguire, 2019; Stewart & Vigod, 2019; Yim et al., 2015). Another point to consider is that hormonal changes affect the activity of few brain areas (e.g., hypothalamus, prefrontal cortex, amygdala) and modulate neurotransmitter systems (e.g., serotonin system, dopamine system) which alteration is strictly related with depressive symptom (Payne & Maguire, 2019). Therefore, it could be hypothesized that the hormonal withdraw could affect only a subgroup of vulnerable women and that a potential mechanism that led to PPD was the interaction between central nervous and hormonal systems (O'Hara & McCabe, 2013; Payne & Maguire, 2019). However, the psychobiological and neurophysiological pathways that are involved in PPD are unclear and more studies are needed on these topics (Payne & Maguire, 2019; Stewart & Vigod, 2019).

As we have seen, the pathogenesis of PPD is as varied and multifactorial as the diagnosis and is thought to originate from the interaction between biological, psychological, and social factors (Stewart & Vigod, 2019; Yim et al., 2015). A schematic and integrative model of all potential factors that could lead to postpartum mental disorders, such as PPD, is shown in *Figure 1.1*. (Halbreich, 2005).

Figure 1.1. A bio-psychosocial-cultural model of processes leading to postpartum disorders. *Notes:* CNS: central nervous system, OC: oral contraceptives, PMS: premenstrual syndrome, CRF: corticotrophin releasing factor. Reprinted from Journal of Affective Disorders, Volume 88 (1), Halbreich, "Postpartum disorders: Multiple interacting underlying mechanisms and risk factors", page 3, 2005, with permission from Elsevier.

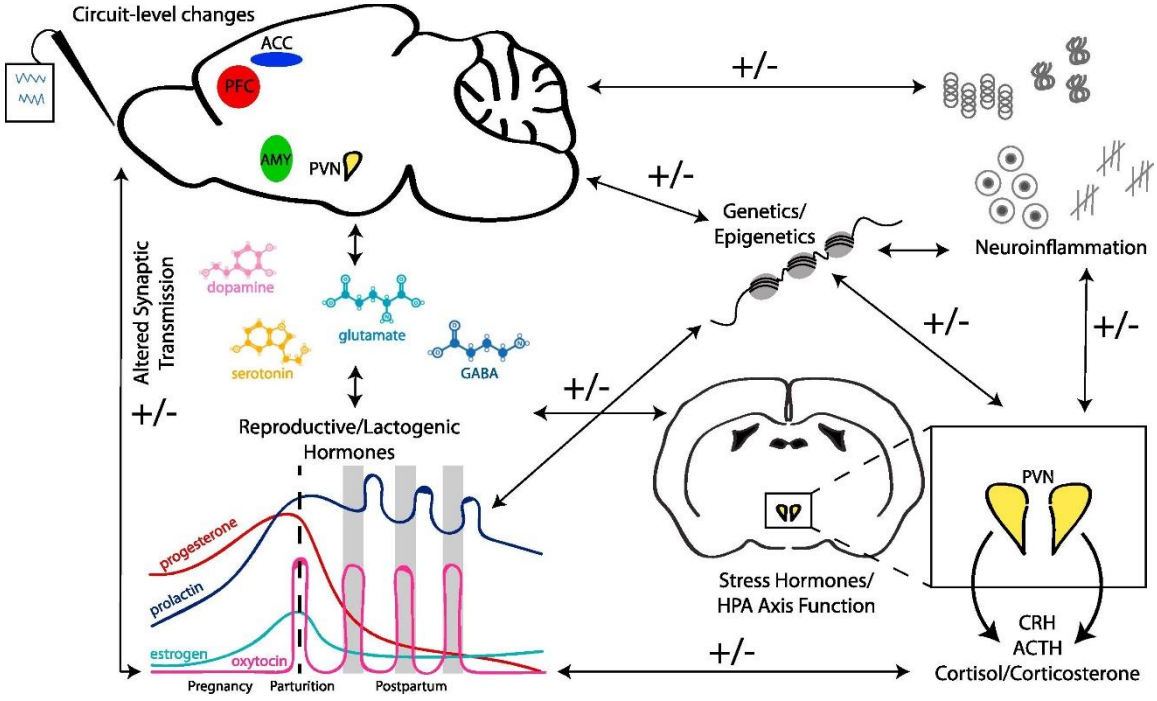


Halbreich hypothesised that postpartum mental disorders have a common denominator: they occur during periods of hormonal change, implying common vulnerability and similarity of triggers (Halbreich, 2005). The main idea of the model was that the hypersensitivity to hormonal changes and dysregulation of body homeostasis – controlled by the central nervous system (CNS) and peripheral systems – were constantly shaped by hormonal (e.g., withdrawal of hormonal secretion) and psychosocial (e.g., partner/family support, cognitive perceptions, coping mechanisms) input during the peripartum period, and the dysregulation of these systems could lead to postpartum mental

symptom and disorders. Subsequent reviews highlighted the crucial role of the change of biological factors during the peripartum period in the pathophysiology mechanism contributing to PPD (Payne & Maguire, 2019; Stewart & Vigod, 2019; Yim et al., 2015). Stress, history of mood disorders, and previous adverse life events seem to be an important risk factors for PPD, probably for the effect of these psycho-social conditions on the hypothalamic-pituitary-adrenal (HPA) axis and the secretion of stress hormones. Few studies reported that accelerated corticotropin-releasing hormone (CRH) trajectories and higher levels of CRH in mid-to-late pregnancy might be predictive of PPD symptoms during the first few postpartum months (Bloch et al., 2003; Glynn & Sandman, 2014; Hahn-Holbrook et al., 2013; Yim et al., 2009). Importantly, stress and emotional disorders are also associated with epigenetics factors, which refer to changes in gene expression – due to environmental influences – carried out by mechanisms that are not DNA encoded but rather from DNA methylation and histone modification (Toyokawa et al., 2012; Yim et al., 2015). In particular, there is an interrelationship between epigenetics and neuroendocrine changes associated with PPD, where variations in DNA methylation of the oxytocin receptor gene are negatively correlated with levels of few reproductive hormones, such as serum estradiol and the ratio of allopregnanolone to the progesterone that, in turn, could also influence HPA axis function (Bell et al., 2015; M. Kimmel et al., 2016; Payne & Maguire, 2019). The importance of changes in the levels of reproductive hormones after the delivery in the onset of PPD is highlight by different reviews (Schiller et al., 2015; Serati et al., 2016). Their suggestion was that reproductive hormones may exert influence especially in a subgroup of a "hormone sensitive" PPD phenotype, as estrogen (e.g., estradiol and progesterone) is closely tied to the HPA-axis and inflammation. Indeed, although all women experience a dramatic decrease in hormone levels after delivery, only a small subset of women develop PPD (Bloch et al., 2003). Therefore, the hormone withdrawal theories of PPD suggest that withdrawal of estrogens and progesterone are proximate causes of depression in some vulnerable women (Payne & Maguire, 2019; Yim et al., 2015). Epigenetic changes in women who later develop PPD have also been associated with neuroinflammatory changes, affecting the expression of genes related to estradiol regulation and maternal behaviours (Garfinkel et al., 2016; Guintivano et al., 2014). However, studies examining the inflammatory process in the context of PPD reported conflict results; therefore, further studies on this pathway are needed (Payne & Maguire, 2019; Stewart & Vigod, 2019; Yim et al., 2015). However, it has been proposed that disruption in peripartum neuroinflammatory activity may contribute to postpartum depression. HPA axis is one of the potential causes of neuroinflammatory changes during pregnancy (Anderson & Maes, 2013). Thus, disruption in HPA axis functioning and altered stress hormone levels can impact immune function. Conversely, immune challenges can also activate the HPA axis, leading to altered levels of stress hormones. Thus, disruptions in the crosstalk

between stress hormones and neuroinflammation may contribute to postpartum depression (Payne & Maguire, 2019). Furthermore, the neuroendocrine changes in the peripartum period (e.g., change in allopregnanolone levels) could have an important role in triggering PPD through the modification of glutamatergic, GABAergic, and monoaminergic signaling (MacKenzie & Maguire, 2014; Schiller et al., 2015). Thus, it is possible that stress, neuroinflammation, and altered synaptic transmission could lead to brain circuit dysfunction in brain regions of the maternal care network (i.e., amygdala, cingulate cortex, prefrontal cortex, striatum, and insula), leading to postpartum depression (P. Kim et al., 2016). In summary, there is a complex interplay between stress, HPA axis dysfunction, the change in reproductive hormones levels, neuroinflammation, and altered synaptic transmission in network communication in brain regions associated with emotional regulation, reward/motivation, and executive function (*Figure 1.2.*) (Payne & Maguire, 2019).

Figure 1.2. Complex interplay between the potential pathological mechanisms contributing to postpartum depression. This figure highlights the diverse potential pathological mechanisms associated with postpartum depression, including disruptions in reproductive/lactogenic hormones, stress and HPA axis dysfunction, neuroinflammation, epigenetics, altered synaptic transmission, and circuit-level changes in network communication in brain regions associated with mood and/or the "maternal care network". This complex interplay between the genetic, environmental, and synaptic/network function highlights the potential diversity in the underlying neurobiology of postpartum depression. *Notes:* CNS: central nervous system, OC: oral contraceptives, PMS: premenstrual syndrome, CRF: corticotrophin releasing factor. Reprinted from Frontiers in Neuroendocrinology, Volume 52, Payne & Maguire, "Pathophysiological mechanisms implicated in postpartum depression", page 176, 2019, with permission from Elsevier.



These bidirectional influences highlight the diversity of the underling neurobiology of PPD, explaining in part the great heterogeneity of PPD.

1.1.4. Prevention and treatment

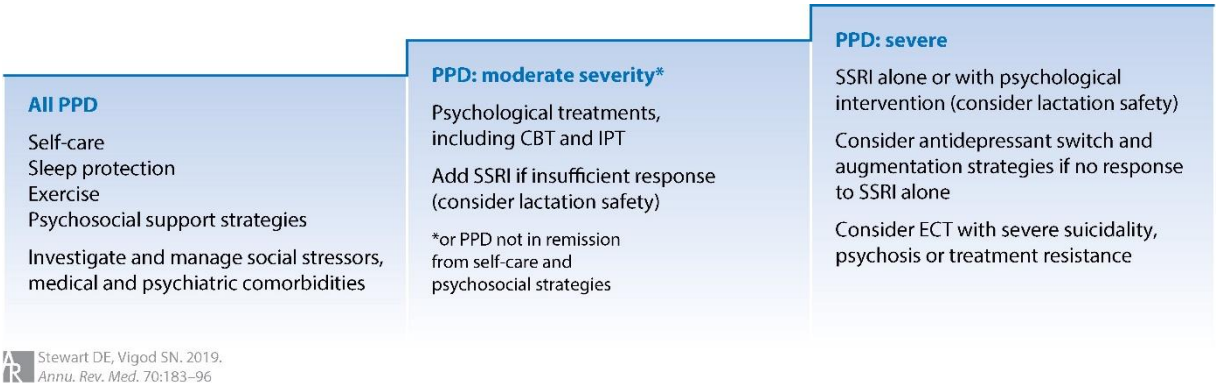
One of the main problems with preventing and treating PPD is the poor identification of depression cases in the prepartum period (Hadfield & Wittkowski, 2017). During pregnancy and in the neonatal period, women often interacted with obstetric teams and paediatric primary care, which are determinants in detecting depressive symptoms (ACOG Committee, 2018; Dennis & Chung-Lee, 2006). Given the heterogeneity of PPD, the different times of onset, and the various pathways that could let to this mood disorder, the early identification of women at risk of PPD is a very challenging aspect (Putnam et al., 2015; Santos et al., 2017). As we see in *paragraph 1.1.1*., simple and reliable diagnostic instruments have been developed in order to identify depressive symptoms in peripartum. For instance, the administration of the Edinburgh Postnatal Depression Scale (EPDS) is recommended by the American College of Obstetricians and Gynaecologists and the American Academy of Paediatrics to identify possible postpartum depression (ACOG Committee, 2018; Earls et al., 2019). However, few studies indicated the underdiagnosis of PPD (Currie & Rademacher, 2004; Halbreich, 2005; Stowe et al., 2005). The main reasons for this phenomenon are related to maternal attitudes toward PPD screening and the insufficient knowledge and training of maternity care services to diagnose and treat peripartum depressive symptoms (Currie & Rademacher, 2004; Hadfield & Wittkowski, 2017). For instance, qualitative and quantitative studies revealed that one of the most critical barriers affecting mothers' decisions to ask for help was concerns for community mental health stigma (Dennis & Chung-Lee, 2006; Hadfield & Wittkowski, 2017). New mothers did not talk about their mental health problems for the fear child being taken away, saw themselves as a "failure" for experiencing PPD symptoms, and thought that the professionals expected that they cope on their own with their mood disorders. Moreover, many health professionals thought that it was not their responsibility to recognize PPD symptoms, had insufficient knowledge about postpartum mental disorders, and tended to normalize depressive symptoms after childbirth (Currie & Rademacher, 2004; Dennis & Chung-Lee, 2006).

The PPD diagnosis is obviously possible only after the delivery; however, focusing on preventing PPD could be an optimal option to avoid the development of mood disorders after childbirth. Moreover, women are motivated to self-care during pregnancy and frequently contact health care providers (Werner et al., 2015). Psychosocial and psychological interventions during pregnancy and early postpartum significantly reduce the number of women who develop PPD (Dennis & Dowswell, 2013; Stewart & Vigod, 2016). A recent systematic review comparing the efficacy of

various interventions to prevent PPD corroborates these results showing that counselling intervention – in particular cognitive-behaviour therapy (CBT) and interpersonal therapy (IPT) – could be effective in preventing PPD, especially in women at high-risk of postpartum mood disorders (O'Connor et al., 2019). The efficacy of these treatments is strictly related to the well-known psychosocial risk factors during pregnancy of PPD (e.g., chronic and life stressors, lack of social support, prior history of psychopathology) (O'Hara & McCabe, 2013; Stewart & Vigod, 2019). Indeed, the psychological and psychosocial interventions tend to focus on these different psychosocial risk factors providing the tools to deal positively during pregnancy and avoid the trigger of the different potential biopsychosocial pathways that can lead to PPD. On the other side, biological prevention treatments during pregnancy (e.g., psychotropic medications, hormone treatments, omega-3 fatty acids treatment) showed mixed success, partly due to the uncleanliness of biological and physiological risk factors of PPD (O'Connor et al., 2019). Moreover, recent systematic reviews indicated that the clinical effectiveness of alternative preventive methods during pregnancy – such as exercise-based or biofeedback interventions – need to be better explored and established (Carter et al., 2019; Herbell & Zauszniewski, 2019; Zhou et al., 2022).

Unfortunately, prevention of PPD is not a common practice nowadays (O'Connor et al., 2019), and often women arrive at health care centres or hospitals with mild or high levels of depressive symptoms. Overall, the treatment of PPD consists of psychosocial treatments and pharmacotherapy. *Figure 1.3.* reported a summary of suggested treatments according to the severity of the woman's depressive symptoms(Stewart & Vigod, 2019).

Figure 1.3. Stepped care management of PPD. The safety of mother and infant should be continually reassessed at each level of care such that emergency services can be initiated if required. Notes: CBT: cognitive-behaviour therapy; ECT: electroconvulsive therapy; IPT: interpersonal therapy; SSRI: selective serotonin reuptake inhibitor. Used with permission of Annual Review of Medicine, from "Postpartum depression: pathophysiology, treatment, and emerging therapeutics", Stewart & Vigod, Volume 70, page 190, 2019; permission conveyed through Copyright Clearance Center, Inc.



Postpartum women tend to prefer psychological over medication treatments, particularly if they are breastfeeding (Stewart & Vigod, 2016; Weissman et al., 2004; Werner et al., 2015), and two systematic reviews report the safety of few SSRIs (i.e., sertraline and paroxetine), but fewer safety data for the other SSRIs (Becker et al., 2016; Thomson & Sharma, 2017). Fortunately, there are numerous empirically supported psychological treatments for PPD, and the most common are CBT and IPT. These treatments could be administered in individual or group formats, in-person (i.e., in the clinic or at home) or remotely (e.g., by telephone, internet or using smartphones), and are short-term (e.g., an average length of around 10 to 12 sessions) and more acceptable than medication treatments by women (O'Hara & McCabe, 2013; Stewart & Vigod, 2016, 2019). CBT and IPT efficacy profiles are similar to usual care or control interventions. Gains are demonstrated post-treatment immediately and in longer-term follow-up (six months after treatment) (Stewart & Vigod, 2019). However, when PPD is not sufficiently responsive to psychological treatment or women have severe PPD symptoms, antidepressants are the first line of treatment (Kim et al., 2014). Unlike psychological treatments, medication management requires less intense contact with mental health professionals, less time and is also likely to be less expensive than psychological treatments. However, beyond the problem of the safety of the use of medications during breastfeeding, antidepressant medication has a side effects on patients, and it could be possible that the medicines were not taken in the way and with the dosage prescribed (Stewart & Vigod, 2019). Literature on the efficacy of medication treatments are scarce and reported mixed findings; more studies are needed to understand the effect of antidepressant on improving PPD (O'Connor et al., 2019; Thomson et al., 2012). Electroconvulsive therapy (ECT) could be a treatment of choice in severe PPD, especially in intractable suicidality or psychotic symptoms. Gressier et al. (2015) reviewed eight studies and eight case reports that indicated the benefits of using ECT in mood postpartum disorders, especially depression. It was well tolerated and gave a fast response. However, the requirement of a general anaesthetic and the potential side effects on memory make ECT an option for most women only if psychological or medication treatment did not have effects on PPD symptoms.

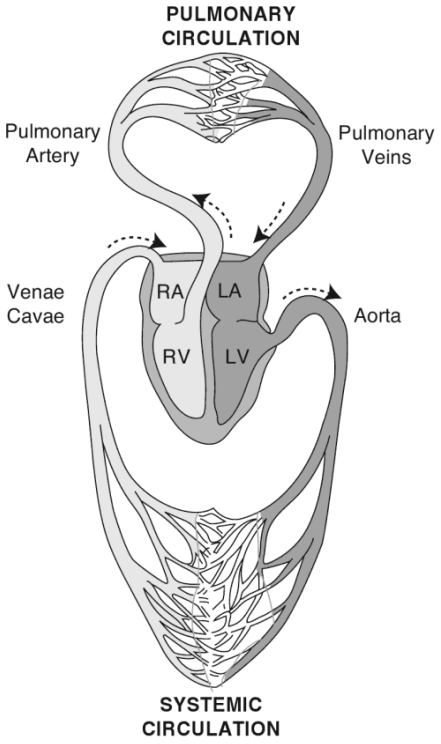
1.2. Heart rate variability

1.2.1. Physiology of cardiovascular autonomic regulation

The heart is the main component of the cardiovascular system and is the pump that moves blood through blood vessels, providing the needed oxygen and nutrients to the body (Sarlo & Pennisi, 1998; Weinhaus, 2015). The internal anatomy of the heart reveals four chambers composed of cardiac muscle (i.e., myocardium). The two upper chambers (i.e., atria) function mainly as collecting

chambers; the two lower chambers (i.e., ventricles) are much stronger and function to pump blood (Sarlo & Pennisi, 1998; Shaffer et al., 2014; Weinhaus, 2015). The role of the right atrium and ventricle is to collect deoxygenated blood from the body and pump it to the lungs (i.e., pulmonary circulation). The role of the left atrium and ventricle is to collect oxygenated blood from the lungs and pump it throughout the body (i.e., systemic circulation) (Gordan et al., 2015; Weinhaus, 2015). *Figure 1.4.* showed a schematic representation of the two different circulation systems.

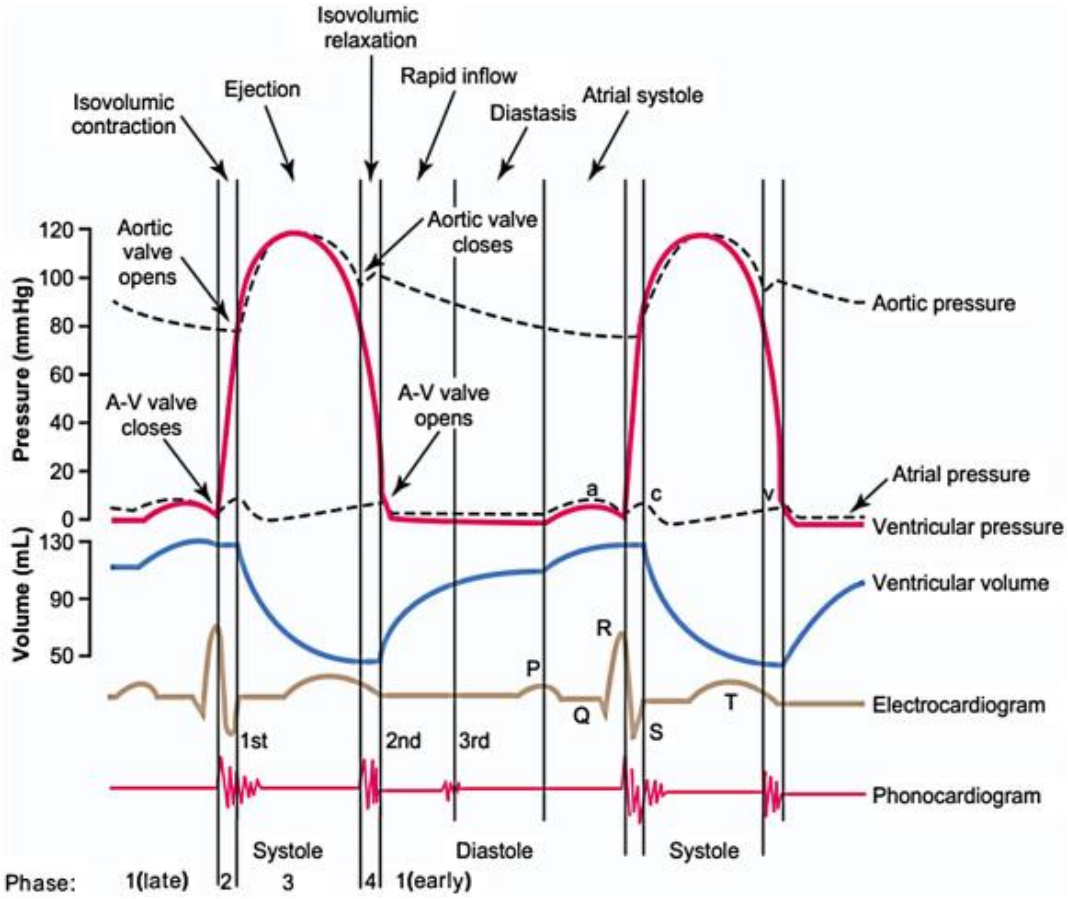
Figure 1.4. Circulation of the blood. Light grey part: deoxygenated blood; dark grey part: oxygenated blood. RA: right atrium; RV: right ventricle; LA: left atrium; LV: left ventricle. The figure is adapted and modified from (Starling, 1926).



Cardiac cycle events can be divided into diastole and systole. Diastole represents ventricular relaxation/filling, and systole represents ventricular contraction/ejection (Shaffer et al., 2014; Weinhaus, 2015). Systole and diastole occur in both the right and left heart, though with very different pressures. Diastole begins with the closing of the aortic valve (or pulmonic) and ends with the closing of the mitral valve (or tricuspid). This period encompasses ventricular relaxation and filling. Diastole is when the blood vessels return blood to the heart to prepare for the next ventricular contraction. Systole begins when the mitral valve (or tricuspid) closes and concludes with the aortic valve (or pulmonic) closure. This stage of the cardiac cycle represents ventricular contraction, forcing blood into the arteries. When a ventricle contracts, the pressure within the ventricles will become greater

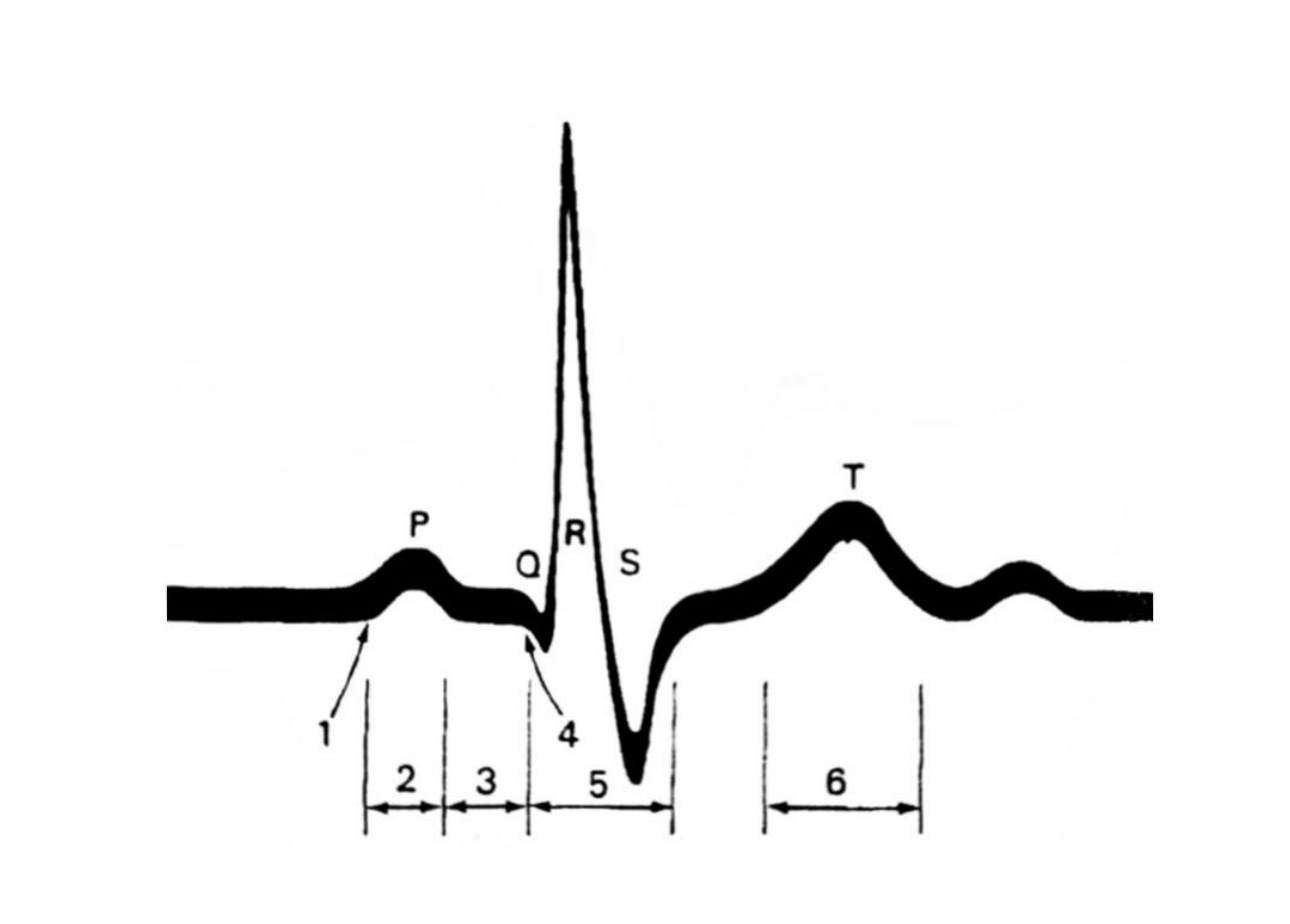
than adjacent blood vessels, and the valves will allow the blood out (Sarlo & Pennisi, 1998; Shaffer et al., 2014) (*Figure 1.5.*).

Figure 1.5. Typical cardiac cycle events for left ventricular function include changes in aortic pressure, atrial pressure, ventricular pressure, ventricular volume, electrocardiogram (ECG) and Phonocardiogram (PCG). Reprinted from Ostadfar, Biofluid Mechanics, Academic Press, 2016, with permission from Elsevier.



The mechanical processes of the cardiac cycle are related and caused by different electrical events (Ostadfar, 2016). The electrocardiogram (ECG) is the biological signal representing the cardiac electrical activity we can detect from the body surface. The ECG consisted of waves with different amplitudes and frequencies related to particular electrical cardiac events (*Figure 1.6.*). Briefly, the P wave represent the atrium depolarization and anticipate the mechanic contraction of atriums and the flow of blood in the ventricles. The QRS complex is characterized by the depolarization of ventricles that led to the mechanic contraction of ventricles and to the ejection of blood int the systemic and pulmonary circulation. Lastly, the T wave indicate the repolarization of ventricles, namely the ventricular relaxation. The relaxation of atriums follow the P wave, but in the ECG the electrical wave for this mechanical event is hide by the QRS complex (Sarlo & Pennisi, 1998; Shaffer et al., 2014).

Figure 1.6. ECG signal with a focus on heart electrical activity. Notes: P: P wave, QRS: QRS complex; T: T wave; 1: depolarization of sinoatrial (SA) node; 2: atrial depolarization; 3: depolarization of atrioventricular (AV) node; 4: atrial repolarization; 5: ventricular depolarization; 6: ventricular repolarization. The figure is adapted and modified from (Stern et al., 2000).

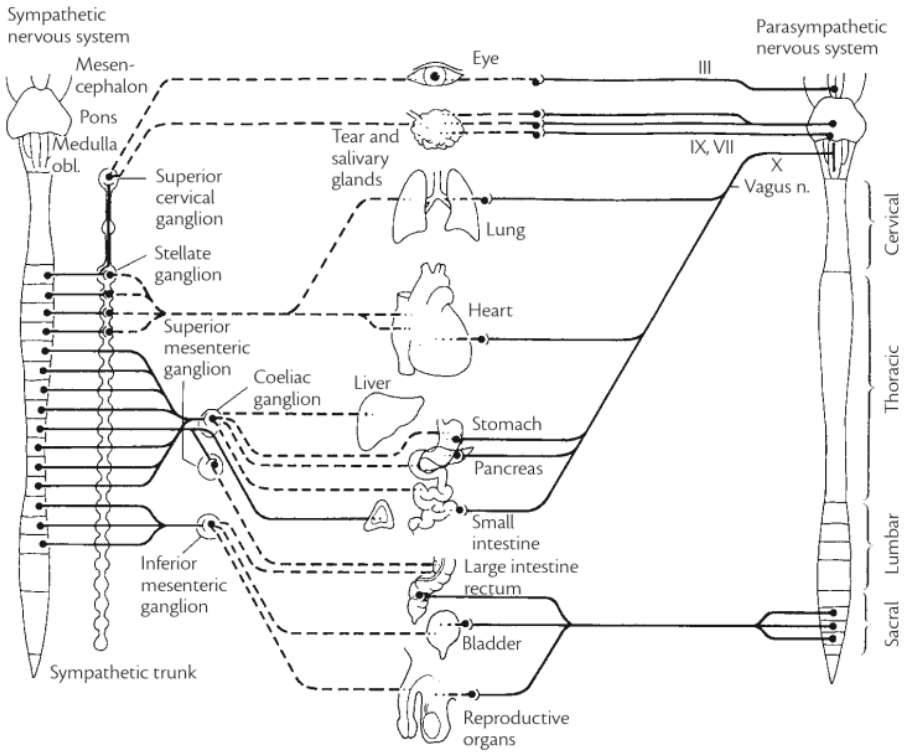


The heart has an intrinsic conduction system that consists of autorhythmic cells. As a result, it can spontaneously depolarise to initiate heartbeats from its rhythmic pacing discharge and coordinate heart electrical activity. The sinoatrial (SA) node, located in the right atrium, is the first pacemaker that starts the electrical impulse resulting in the depolarisation and contraction of the atrium (Gordan et al., 2015; Shaffer et al., 2014). This electrical impulse is distributed throughout the heart through the internodal pathway, atrioventricular (AV) node, AV bundle, branches of the bundle of His, and Purkinje fibres (Sarlo & Pennisi, 1998). Without the extrinsic (hormonal and neural) influences, the SA node creates about 100 beats per minute; however, to meet the body's oxygen requirement under variable conditions, cardiac output (and thus heartbeat) must vary. The autonomic nervous system (ANS) could help respond to the organism's changing requirements.

The ANS is an important part of the control of different physiological systems (e.g., heart rate, blood pressure, respiration, gastrointestinal motility, etc.) (*Figure 1.6.*) (Jänig & McLachlan, 2013;

Levy & Martin, 1984). The ANS is predominantly an efferent system transmitting impulses from the central nervous system (CNS) to regulate visceral functions of the body (Singh et al., 2018). The CNS comprises the brain, brainstem, and associated nuclei and bundles of visceral fibres in the spinal cord (Weinhaus, 2015). The CNS receives, integrates, and distributes commands through efferent (i.e., motor) nerves based on the feedback from afferent (i.e., sensory) impulses. Efferent nerves that service autonomic control are organised in a sequential neuron pathway for transmission of information: a preganglionic neuron, which starts in the CNS and exists along a cranial or spinal nerve, and a postganglionic neuron which exists entirely outside the CNS (Jänig, 2016; Jänig & McLachlan, 2013; Shaffer et al., 2014).

Figure 1.7. Schematic representation of the efferent ANS. The figure highlight the craniosacral parasympathetic and thoracolumbar sympathetic outflow to various target organs. Figure from (Jänig & McLachlan, 2013).



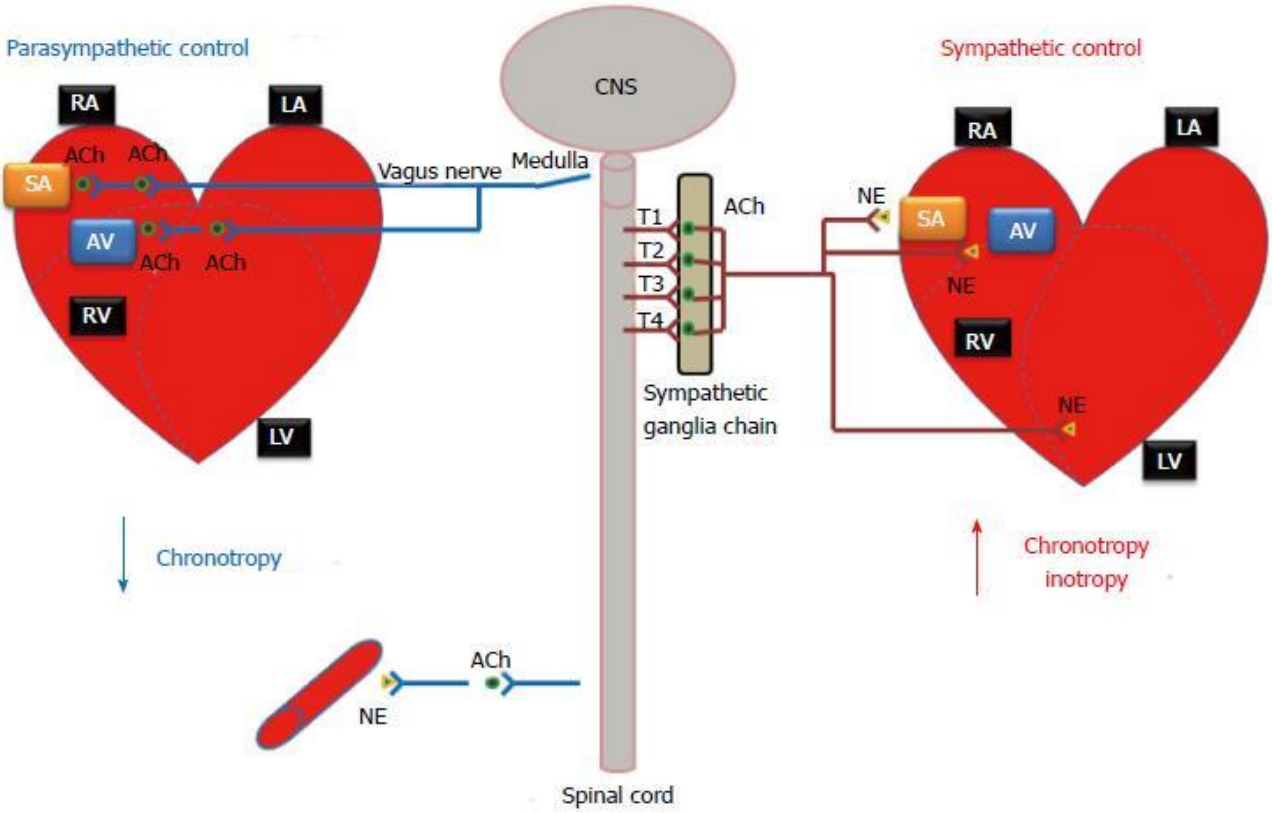
Autonomic efferent outflow to the heart originates in the medulla, a structure found within the brainstem and centre of cardiovascular regulation activity. In particular, the nucleus of the solitary tract (NST) in the medulla receives afferent input from mechanoreceptors (i.e., baroreceptors) and chemoreceptors in the carotid sinus and aortic arch regarding environmental and physiological demands (Gordan et al., 2015; Shaffer et al., 2014; Singh et al., 2018). The NTS integrates the afferent information and distributes motor information which stimulates the appropriate cardiovascular responses in the divisions of the autonomic nervous system (ANS) (e.g., increasing/decreasing heart

rate (HR), blood pressures (BP), and contractility of coronary vessels) to meet physiological demands and maintain homeostasis in the smooth muscle, cardiac muscle, and glands (Carnevali & Sgoifo, 2014). The two main divisions of the ANS include the sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS) (Jänig & McLachlan, 2013; Levy & Martin, 1984). The SNS mobilises body systems and causes the 'fight or flight response by increasing alertness and metabolic activity (e.g., increases HR, causes vasoconstriction, and increases BP), whereas the PNS conserves energy and is known for 'rest and digest' control of the body (e.g., slows HR, causes vasodilation, and decreases BP) (Jänig & McLachlan, 2013; Richter & Wright, 2013; Shaffer et al., 2014).

The heart receives extensive innervation from both the sympathetic and parasympathetic systems of the ANS (Jänig & McLachlan, 2013). The cardiac efferent sympathetic preganglionic nerves (typically all myelinated) originate from the rostral ventrolateral medulla and emerge from the upper thoracic segments of the spinal cord (T1-T4), leaving the spinal cord through the ventral anterior root of the corresponding spinal cord nerves. These nerves travel to and synapse within the sympathetic ganglia chain (SGC) that run parallel to the spinal cord on either side of the anterior face of vertebral bodies. Postganglionic efferent fibres in the paravertebral, cervical and thoracic SGC give origin to cardiac cervical nerves and cardiac, thoracic nerves (Gordan et al., 2015; Levy & Martin, 1984). These, in turn, travel to the heart and vascular tissue, where they synapse at their target sites: SA node, AV node, atria, and ventricles (Battipaglia & Lanza, 2015; Singh et al., 2018) (*Figure 1.7.*).

The cardiac efferent preganglionic parasympathetic (or vagal) neurons generate activity through nuclei located deep within the medullary reticular formation called the dorsal motor nuclei (DMN) and the nucleus ambiguous (NAmb) (Carnevali & Sgoifo, 2014; Gordan et al., 2015; Levy & Martin, 1984). The craniosacral outflow travels through the vagal nerves (10^{th} cranial nerve) that exit as a long preganglionic efferent fibre and synapses onto the postganglionic nerve fibres in the vagal nerve ganglia located in the cardiac plexus (Gordan et al., 2015; Singh et al., 2018). The vagal nerves innervate the SA and AV nodes, but few vagal efferents also sparsely innervate the atria and ventricles of the heart (Battipaglia & Lanza, 2015; Levy & Martin, 1984). (*Figure 1.4.*).

Figure 1.8. ANS regulation of the heart function. CNS: Central nervous system; RA: Right atria; LA: Left atria; RV: Right ventricle; LV: Left ventricle; SA: Sino-atrial node; AV: Atrioventricular node; NE: Norepinephrine; ACh: Acetylcholine. Figure from (Gordan et al., 2015).



Sympathetic and parasympathetic nerves also possess afferent fibres to provide communication between the heart and the CNS. Sympathetic nerves have afferent fibres that transmit information from nociceptors through thoracic ganglia of the paravertebral SGC, spinal nerve, and dorsal root ganglia to the thalamus and other brain regions (Kukanova & Mravec, 2006; Palma & Benarroch, 2014; Shaffer et al., 2014). Cardiac vagal afferents transmit mechano- and chemo-sensitive neuron information from the heart – via the vagus nerve and nodose ganglia – to the NST and consequently to other brain areas (Kukanova & Mravec, 2006; Shaffer et al., 2014).

The ANS influences most heart functions by affecting the SA node, AV node, myocardium, and small and large vessel walls (Levy & Martin, 1984). In response to exercise, stress or emergency, the sympathetic nerves release the hormone norepinephrine (NE) in postganglionic neurons that – through different chemical processes – produces the following effects on the heart (Gordan et al., 2015):

(1) Positive chronotropic effect: faster depolarisation of the SA node, resulting in an increase in HR.

(2) Positive dromotropic effect: increase of the conductivity of the cardiac electrical signal throughout the heart, reducing conduction time.

(3) Positive inotropic effect: increased myocardial contractility force of both atrial and ventricular muscles.

The parasympathetic nerves affect the heart under restful conditions through the releases of the neurotransmitter acetylcholine (Ach) in the postganglionic neurons of the vagus nerve and produce the following effects on the heart (Gordan et al., 2015):

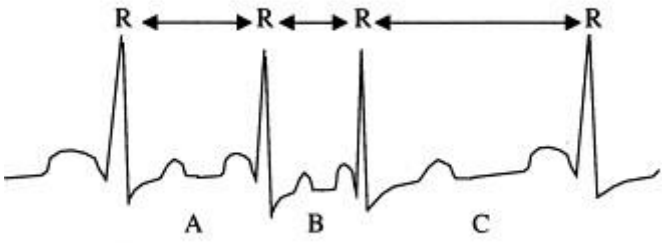
(1) Negative chronotropic effect: slower depolarisation of the SA node, resulting in a decrease in HR.
(2) Negative dromotropic effect: decrease the excitability of AV junctional tissue, slowing transmission of the electrical impulse to the ventricles.

The two branches of the ANS affect and control the cardiac activity, working together to maintain homeostasis (Shaffer et al., 2014). The dynamic balance between parasympathetic and sympathetic activity causes a continuous oscillation of the HR (Levy & Martin, 1984). The variability of HR can be used as a window into the cardiorespiratory control system and as a tool for examining the fluctuations of the sympathetic and parasympathetic branches of the ANS, but interpretation of the results depends on the conditions under which the recording was obtained and the length of the recording itself.

1.2.2. Heart rate variability: definition and background

Heart Rate Variability (HRV) represents the fluctuation in the time intervals between heartbeats (Malik et al., 1996; Shaffer et al., 2014). Like most other biological systems in the body, the heart's activity is not linear and constant. For instance, *Figure 1.8.* is reported an ECG recording in which the first RR time interval A is different from RR interval B, which in turn is different from RR interval C. Therefore, a healthy heart rate, even at rest, fluctuates in a complex way to have the flexibility to self-regulate and restore equilibrium each time it gets disrupted (Goldberger, 1991; Shaffer & Ginsberg, 2017).

Figure 1.9. An ECG signal with three RR intervals. Reprinted from Artificial Intelligence in Medicine, Volume 15 (3), Azuaje *et al*., "Predicting coronary disease risk based on short-term RR interval measurements: a neural network approach", page 281, 1999, with permission from Elsevier.



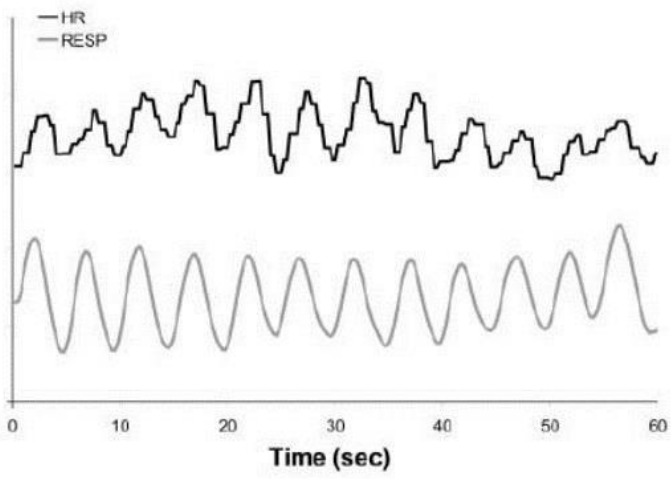
As explained in the *paragraph 1.2.1.*, HRV is produced by the interaction of multiple physiological regulatory and homeostatic systems that operate on different time scales. Circadian rhythms, core body temperature, the sleep cycle, and metabolism contribute to HRV parameters derived from 24-hour ECG. On the other side, short-term HRV measurements (i.e., HRV parameters derived from 5-15 minutes of ECG) were mainly generated from the autonomic, cardiovascular, and respiratory systems (Plaza-Florido et al., 2020; Shaffer & Ginsberg, 2017). In this thesis, we focused on short-term HRV measurements since they are the most widely used HRV parameters in psychophysiological literature and allow the researcher to obtain reliable and meaningful data under more controlled conditions compared to the HRV parameters derived from 24 hours period of ECG (Alcantara et al., 2020; Plaza-Florido et al., 2020).

Short-term HRV measurements reflect the balance between the sympathetic nervous system (SNS) and parasympathetic nervous system (PNS) branches of the heart (Levy & Martin, 1984). This complex and dynamic relationship is one source of variability in the heart rate. SNS increase the heart rate (HR), while PNS – through the vagus nerve – brings the HR down (Brodal, 2010; Khazan, 2013). However, since the heart is under tonic inhibitory control by parasympathetic influences, vagal activity in the heart predominates at rest (Shaffer et al., 2014; Shaffer & Ginsberg, 2017; Thayer et al., 2012). Moreover, the HRV implied parasympathetic dominance due to the different speeds of ANS innervations that exert their effect on the heart. In particular, sympathetic nerves' influence on the heart is too slow (> 5 seconds) to produce beat-to-beat changes than parasympathetic nerves' influence (<1 second) (Nunan et al., 2010). Thus, PNS activity (e.g., increase or decrease of vagal stimulation) mediates both a rapid and instantaneous increase and decrease of HR. Conversely, a sympathetic stimulation could increase HR in a more robust (e.g., brief stimulations can affect HR and HRV for 5-10 seconds) and long-lasting way (Shaffer et al., 2014).

The second source of variability in the heart rate is *Respiratory Sinus Arrhythmia* (RSA), which refers to the rhythmic fluctuation of the heart rate that accompanies breathing (Berntson et al., 1993). In particular, changes in HR occur in a phased relationship with inspiration and expiration

(HR increasing during inspiration and HR decreasing during expiration) (*Figure 1.9.*). This synchronous fluctuation happens because the SNS is activated with each inhalation, and the PNS is activated with each exhalation. The main component of the RSA is the activity of the vagus nerve (Ernst, 2017; Khazan, 2013). In particular, vagal efferent action on the heart was inhibited during inspiration and was reinstated during expiration through the respiratory mechanism on the brainstem. This physiological phenomenon led to the rhythmic increase or decrease in heart rate associated with respiratory cycles (Berntson et al., 1993; Porges, 1995a; F. Yasuma & Hayano, 2004).

Figure 1.10. Hypothetical visual representation of the respiratory sinus arrhythmia (RSA). In the example, the signal in the upper part of the graph is heart rate over time (HR), while the signal in the lower part of the graph is respiration rate over time (RESP). The two signals were measured simultaneously. During inspiration (ascending parts of RESP signal), the HF increase, whereas, during the expiration (descending parts of RESP signal), the HF decrease.



Another source of variability of heart rate is derived from baroreflexes (BRs) (Lehrer, 2007). BRs refer to the body's ability to regulate blood pressure (Eckberg & Sleight, 1992). Baroreceptors are stretch receptors located in the aorta and internal carotid arteries, which respond to changes in the diameter of these blood vessels, and, therefore, to changes in blood pressure. When blood pressure increases, baroreceptors send a signal to the brain to decrease HR and vascular resistance (i.e., increasing diameter of blood vessels), which subsequently result in a decrease of blood pressure. When blood pressure decreases, the baroreceptors produce the opposite effects increasing the HR and vascular tone (Shaffer & Ginsberg, 2017). Therefore, BRs were a negative feedback mechanism controlling blood pressure changes that could affect HR and HRV (Ernst, 2017). Indeed, the strength of the BRs is measured in units of change in RR intervals on the ECG (measured in milliseconds) per

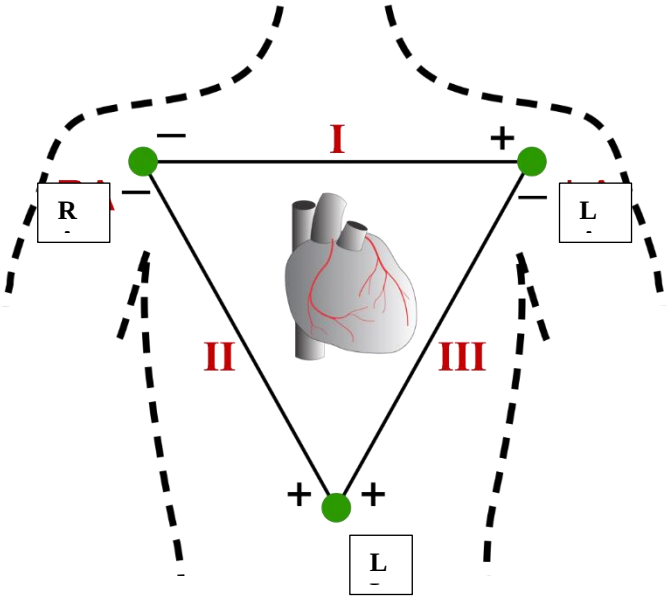
unit of change in blood pressure (measured in millimetres of mercury) (Lehrer, 2007). Since HRV is the variation in time between heartbeats, higher levels of gain of BRs contribute to higher levels of HRV (Lehrer et al., 2003).

In the last thirty years, technological advanced, established standards, and research guidelines increased the interest in HRV in the field of psychophysiology (Berntson et al., 1993; Laborde et al., 2017; Malik et al., 1996). Moreover, HRV parameters are found valuable for understanding the relationship between brain and body, given that the parasympathetic nervous system has been found to be relevant for self-regulation mechanisms with links to cognitive, affective, social processes, and general health (Shaffer et al., 2014; Thayer et al., 2009). Therefore, in the next section, I better explain the measurement techniques and methods of analysis of the cardiac signal to obtain HRV parameters.

1.2.3. Methods of measurement and analysis of HRV

The gold standard for obtaining HRV measurements is through EGC equipment. However, in recent years, photoplethysmograph sensors have become more widespread in research and clinical contexts for the assessment of HRV (Ishaque et al., 2021). Both methods allow for obtaining interbeat interval (IBI) data, the starting point for calculating HRV parameters (Shaffer et al., 2014). The ECG was typically measured using electrodes applied in the chest following different types of configurations: the standard and most used configuration in psychophysiological research is the three-lead ECG (Einthoven's triangle placement) (*Figure 1.10*).

Figure 1.11. ECG electrode placement according to Einthoven's triangle. The ECG is detected from three available electrical dipole activities (bipolar leads). Notes: RA: Right arm; LA: Left arm; LL: Left leg.

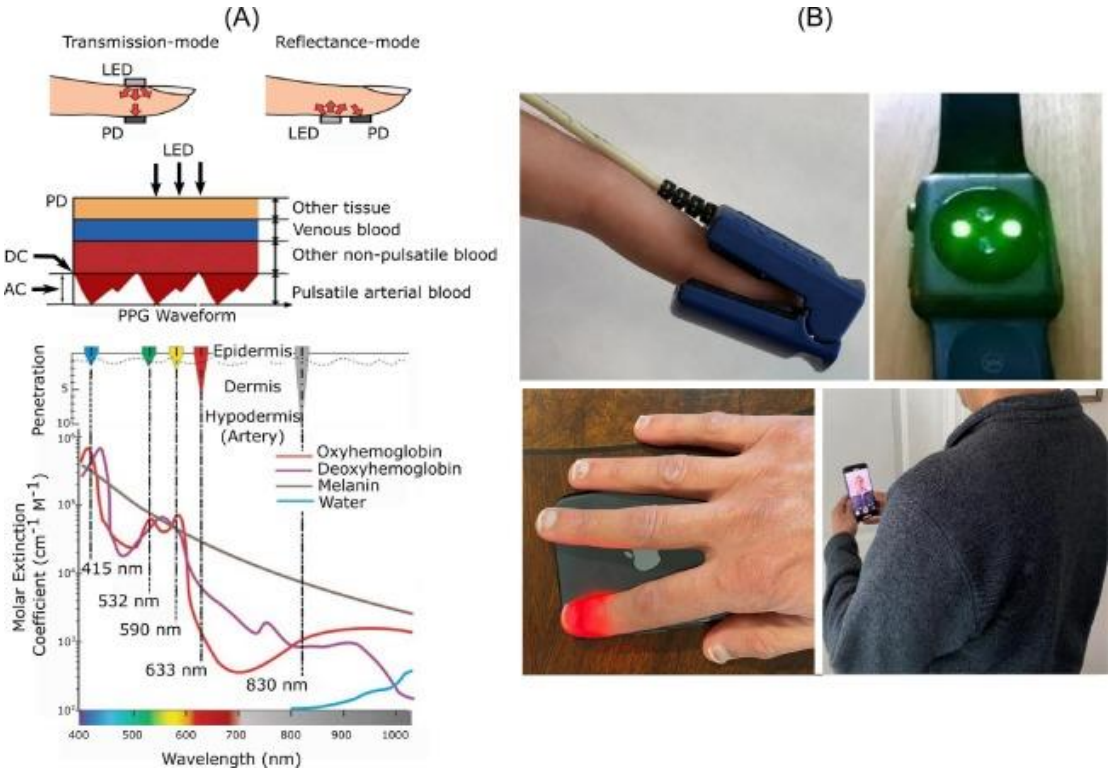


In the distal configuration, the ECG electrodes are applied to the two arms and the left leg (Sarlo & Pennisi, 1998). However, to avoid movement artefacts, the proximal configuration is widely used: two electrodes are located over the right and left coracoid processes, and the third electrode is on the 5th left intercostal space (Sarlo & Pennisi, 1998; Shaffer et al., 2014). In these types of configurations, the heart's electrical activity was registered through a bipolar lead (i.e., the electrical activity of one electrode is compared to another). The lead I configuration has the positive electrode on the left coracoid process and the negative electrode on the right coracoid process. It, therefore, measures the electrical potential difference between the coracoid process. In the lead II configuration, the positive electrode is on the 5th left intercostal space, and the negative electrode is on the right coracoid process. Finally, the lead III configuration has the positive electrode on the 5th left intercostal space and the negative electrode on the left coracoid process. In the research context, the lead II configuration is the most utilized since the two electrodes detect the cardiac signal in parallel with the primary vector of ventricular depolarization. As a result, the cardiac registration provides wider R waves – one of the waves of the QRS complex – that help a more accurately IBI extraction from the ECG (Quintana et al., 2016; Sarlo & Pennisi, 1998). In clinical settings, unipolar leads (i.e., the electrical activity of one electrode is compared to a reference point that averages electrical activity) are common, and a typical configuration is a 12-lead ECG with six limb leads and six precordial leads (Ishaque et al., 2021).

Photoplethysmography (PPG) is the most common alternative to the ECG measurement of the cardiac cycle. It can be used to derive an approximation of the beat-to-beat heart period and thus calculate HRV parameters. The PPG method relies on transforming the pulsatile waveform of microvascular blood flow from a peripheral site on the body (e.g., the fingertip, earlobe, or toe) into a series of beat-to-beat intervals (BBIs) (Hertzman, 1938). This occurs via a simple device consisting of a light-emitting diode (LED) and a photodetector (PD); the presence of the systolic beat produces a perturbation in the light's absorbance, which is identified as a pulse beat (Mukkamala et al., 2022). There are two basic configurations used in PPG: the transmission-mode – in which the perfuse tissue is placed between LED and PD – and the reflectance-mode – in which the LED and PD are placed side-by-side near the skin (*Figure 1.11*.). Th PPG signal consists of two different components: a large quasi-static component (i.e., DC component) corresponding to the light diffusion through tissues and non-pulsatile blood layers, and a small pulsatile part (i.e., AC component) due to the light diffusion through the arterial blood (Allen, 2007). Despite the ECG method being considered more accurate, especially with cardiac signals with frequent abnormal beats, the PPG method is a non-invasive, cost-effective, and simple alternative when different conditions or needs do not allow the registration of the cardiac signal through ECG. Moreover, several studies have shown that when the recordings are

taken during a resting state, the IBI values – and the computed HRV parameters – obtained from ECG and PPG are highly correlated (Jeyhani et al., 2015; Kiran Kumar et al., 2021; Plews et al., 2017; Schäfer & Vagedes, 2013).

Figure 1.12. The PPG principle and current sensors. (A) A light-emitting diode (LED) illuminates tissue, and a photodetector (PD) receives the transmitted or reflected light. The AC component of the measured waveform indicates changes in haemoglobin and, thus, pulsatile arterial blood volume. The signal quality is higher for visible wavelengths due to the absorption characteristics of haemoglobin but better for infrared wavelengths in low signal conditions (e.g., dark skin) due to deeper light penetration. (B) Various forms of PPG sensors are widely available, including conventional finger clips, wristbands, and smartphone cameras for contact or noncontact measurement. Reprinted from Mukkamala, Hahn & Chandrasekhar, Photoplethysmography, Academic Press, 2022, with permission from Elsevier.



Different methods of analysis can be performed for HRV measurement and the chose depends on the aim of the study and the phenomenon of interest. There are three methods: time-domain methods, frequency-domain methods, and methods based on the non-linear dynamics of HR (i.e., non-linear methods) (Laborde et al., 2017). Time domain parameters reflect the overall variability in measurements of IBIs, whereas frequency domain indices reflect the distribution of power (i.e., signal energy) across different frequency bands of the cardiac signal (Malik et al., 1996; Shaffer & Ginsberg, 2017). Non-linear methods differ from the conventional linear methods (time- and frequency-domain methods) because they do not assess the magnitude of variability or fluctuations in some predetermined frequencies but rather the quality, scaling, and correlation properties of the signal

(Malik et al., 1996; Voss et al., 2009). In particular, non-linear parameters are related to the cardiac signal's unpredictability, fractability, and complexity (Huikuri et al., 2003). As explained in *paragraph 1.2.2.*, HRV parameters are affected by the duration of the ECG recording (e.g., 24-h, short-term: 5 minutes, ultra-short-term: < 5 minutes). For instance, the indices obtained from a 24-h recording are not interchangeable with those obtained from a short-term recording due to the different biological and physiological processes that affect 24-h and short-term HRV indices (Shaffer & Ginsberg, 2017). As indicated by Laborde et al. (2017), 24-h HRV indicators cold be interesting for particular study designs or hypotheses. However, due to time constraints and experimental considerations, short-term HRV parameters are the most used in psychophysiology research (Laborde et al., 2017; Malik et al., 1996). More recently, the interest in ultra-short-term HRV parameters has increased, and many studies have started investigating the reliability and validity of these indices compared to short-term ones. Literature report that only a few time-domain HRV parameters (e.g., rMSSD) obtained from time windows short than 5 minutes are as reliable as short-term HRV parameters (Baek et al., 2015; Castaldo et al., 2019; Munoz et al., 2015; Shaffer et al., 2016). However, more replications of comparison studies are needed to understand better which HRV indices could be reliably used when a standard registration of 5 minutes is not possible.

Within the time-domain parameters, the most used in psychophysiology are SDNN, rMSSD, and pNN50. The SDNN (i.e., the standard deviation of the normal IBI, or RR intervals), expressed in ms, reflects the cyclic components responsible for the variability of heart rate (Berntson et al., 1997; Malik et al., 1996). Both SNS and PNS influenced SDNN, and few studies indicate that the accuracy of this parameter is higher for more extended recording periods (e.g., 24 h periods or more) (Malik et al., 1996; Shaffer & Ginsberg, 2017). The rMSSD (i.e., the root mean square of the successive differences between normal heartbeats), expressed in ms, reflects estimates of short-term variability of heart rate, is highly sensitive to the fluctuation of the high frequency of HRV, and is the primary time-domain measure used to estimate the vagal activity on the HR (Berntson et al., 1997; Malik et al., 1996; Shaffer & Ginsberg, 2017). The pNN50 (i.e., the percentage of successive normal IBI that differ by more than 50 ms) is derived from beat-to-beat differences; therefore, it primarily indicates short-term HR variations – as rMSSD (Laborde et al., 2017). The pNN50 is an index of vagal activity, and it is closely correlated with the rMSSD and the high frequency of HRV. However, rMSSD is preferred to the pNN50 for assessing PNS activity due to its statistical robustness and the fact that it provides a better evaluation of RSA (Otzenberger et al., 1998; Shaffer & Ginsberg, 2017).

The frequency-domain analysis provides an understanding of the specific contribution of SNS and PSN to HRV. Through Autoregressive models or Fast Fourier Transformation, the HRV signal is filtered to obtain power distribution across different frequency ranges. As a result, the HRV power

spectrum can be divided into four frequency bands: ultra-low frequency (ULF; ≤0.003 Hz), very low frequency (VLF; 0.0033–0.04 Hz), low frequency (LF; 0.04–0.15 Hz) and high frequency (HF; 0.15–0.4 Hz) (Malik et al., 1996; Shaffer & Ginsberg, 2017). The ULF power, expressed in ms^2, is the less known frequency band, requires an ECG recording period of al least 24-h, and there is no consensus on the physiological mechanism underlying this frequency component (Draghici & Taylor, 2016; Kleiger et al., 2005; Shaffer & Ginsberg, 2017). The VLF power, expressed in ms^2, could be reliably obtained from an ECG recording of at least 5 minutes, reflects sympathetic and parasympathetic inputs on the heart, and could be influenced by the renin-angiotensin, thermoregulatory, and peripheral vasomotor systems (Berntson et al., 1997; Kleiger et al., 2005; Malik et al., 1996; Shaffer & Ginsberg, 2017). The LF power, expressed in ms^2, reflects both sympathetic and parasympathetic cardiac activity and is strongly related to blood pressure regulation (Berntson et al., 1997; Malik et al., 1996). Despite few studies using LF power as an index of sympathetic activity, this tagging is controversial since literature indicated that LF power is modulated by both branches of ANS and baroreflex activity (Billman, 2013; Goldstein et al., 2011). On the other hand, the HF power, expressed in ms^2, primarily reflects cardiac parasympathetic tone (Berntson et al., 1997; Malik et al., 1996). The HF band is frequently called the "respiratory band" because it corresponds to heart rate variations related to the respiratory cycle (Shaffer & Ginsberg, 2017). When breathing rates remain between nine cycles (0.15 Hz) and 24 cycles per minute (0.40 Hz), then HF power reflects vagal tone (Laborde et al., 2017). Moreover, Kleiger et al. (2005) indicated that HF power showed a highly positive correlation with pNN50 and rMSSD, two time-domain parameters that quantify parasympathetic modulation in the heart. The last parameter related to the frequency-domain analyses is the ratio of LF to HF (LF/HF), which was often used as an index of the sympathovagal balance (i.e., the changing relationship between sympathetic and parasympathetic nerve activities) (Heathers, 2014; Shaffer et al., 2014). However, it has been repeatedly shown that LF power is not a pure index of SNS activity; different biological processes and experimental conditions appear to contribute to LF power. Therefore, the LF/HF parameter interpretation as a measure of sympathovagal balance cannot hold (Billman, 2013; Shaffer & Ginsberg, 2017). More studies are needed to understand this parameter's underpinning physiological mechanism.

Lastly, non-linear HRV parameters emphasized the dynamical properties of HRV (Malik et al., 1996; Voss et al., 2009). Examples of these parameters are the entropic measures of HRV as approximate (ApEn) and sample entropy (SampEn), and detrended fluctuation indices (i.e., DFA-α1 and DFA-α2). Entropy parameters provide a measure of regularity and complexity – or unpredictability – of the HRV (Huikuri et al., 2003). Detrended fluctuation parameters are a measure of the correlation between successive RR intervals at different time scales. They are developed to

distinguish between the interval variation generated by the complexity of the cardiac system and those variations due to artefacts or external stimuli (Peng et al., 1998). Non-linear HRV parameters could provide different information about cardiac signals' complexity and non-linear behaviour; however, more validation studies are needed to use these parameters reliably in psychophysiology research (Sassi et al., 2015).

1.3. Heart rate variability and depression

1.3.1. Autonomic dysfunction and psychopathology

Beauchaine and Thayer (2015) defined HRV as "a transdiagnostic biomarker of vulnerability to psychopathology". Although their paper focused only on the HF power of HRV, the literature confirmed that the alteration of different HRV parameters was associated with the development and/or the maintenance of various psychopathologies. For instance, decreased HRV is associated with a higher risk of anxiety disorders (Chalmers et al., 2014), alcohol use disorders (Ralevski et al., 2019), bipolar disorder (Faurholt-Jepsen et al., 2017), and depression (Hartmann et al., 2019; Koch et al., 2019). The main idea underlying different models that explain the association between HRV and mental disorders is that HRV reflects an individual's capacity for flexible and adaptive responding to changing internal and external demands (McCraty & Shaffer, 2015; Porges, 2007; Thayer et al., 2009).

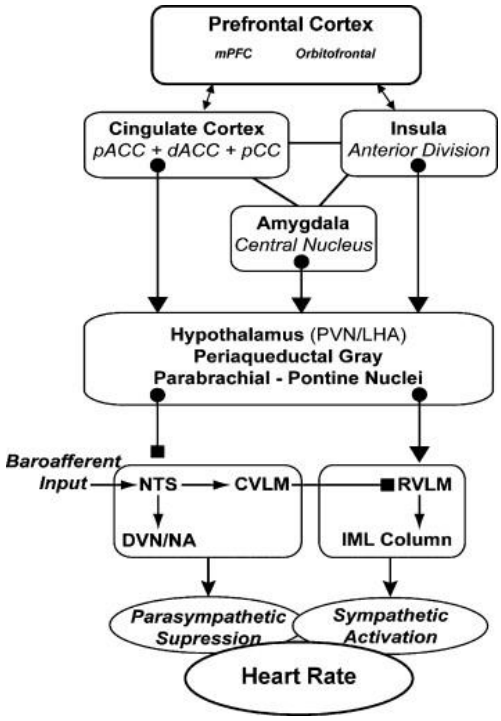
The neurovisceral integration model (Thayer et al., 2009; Thayer & Lane, 2000, 2009) posits that the neural network implicated in the self-regulation and adaptability of psychological processes (i.e., emotional and cognitive regulation) is also related to the regulation of cardiac autonomic activity. Several replicated findings suggested that higher HRV is associated with greater capacity for emotion regulation (Appelhans & Luecken, 2006; Balzarotti et al., 2017; Grol & de Raedt, 2020) and better executive cognitive performance involving attention, working memory, cognitive flexibility, and inhibitory control (Colzato et al., 2018; Forte et al., 2019a; Luque-Casado et al., 2016; Park et al., 2012). The association between the HRV and emotional and cognitive regulation is related to the Central Autonomic Network (CAN) activity (Thayer et al., 2012; Thayer & Lane, 2009).

The CAN consists of cortical (e.g., medial prefrontal cortex, insular cortex), limbic (e.g., anterior cingulate cortex, central nucleus of the amygdala, hypothalamus), and brainstem regions (e.g., periaqueductal grey matter, parabrachial nucleus, the nucleus of the solitary tract) (Benarroch, 1993; Mulcahy et al., 2019; Thayer et al., 2012). The CAN control of cardiac activity derives from the interaction of different neural structures in a feedback-based complex system that leads to ANS modulation that affects heart activity (i.e., increase of HR and decrease of vagally mediated HRV)

(*Figure 1.12.*) (Ernst, 2017; Thayer et al., 2012). Literature shows that CAN activity is also involved in emotional and cognitive regulation, especially the prefrontal cortex and amygdala (Mulcahy et al., 2019; Park & Thayer, 2014; Thayer et al., 2012). The activity of these brain regions modulates human behaviours by the interconnection between higher-level psychological functions, and autonomic regulation of the heart. The CAN integrates the internal and external input, evaluates threat and safety of the situation, and flexibly adjust emotional and executive functions. The output of these neural activity affects the heart through the ANS. Therefore, HRV – especially vagally-mediated HRV – reflects the functional capacity of CAN brain structures that support cognitive and emotional self-regulation (Shaffer et al., 2014; Thayer et al., 2009; Thayer & Lane, 2009).

The model proposed that the non-adaptive and prolonged inhibition of prefrontal cortex activity and the related effect on amygdala drive a disruption on the adaptive and goal-directed behaviours that, in turn, could led to perseverative negative cognition, hypervigilance, and emotional inflexibility and then, to psychopathology (Thayer et al., 2009, 2012). Indeed, the hypoactivity of prefrontal cortex is related with an increase of HR and a decrease of vagally-mediated HRV confirming that associated lower HRV vagal parameters and higher risk of mental disorders (Shaffer et al., 2014; Thayer et al., 2009; Thayer & Lane, 2009).

Figure 1.13. A composite schematic diagram shows the pathways by which the prefrontal cortex might influence heart rate control. The prefrontal, cingulate, and insula cortices form an interconnected network with bi-directional communication with the amygdala. The amygdala is under tonic inhibitory control via prefrontal vagal pathways to intercalated cells in the amygdala. The activation of the central nucleus of the amygdala (CeA) inhibits the nucleus of the solitary tract (NTS), which in turn inhibits inhibitory caudal ventrolateral medullary (CVLM) inputs to the rostral ventrolateral medullary (RVLM) sympathoexcitatory neurons, and simultaneously inhibits vagal motor neurons in the nucleus ambiguus (NA) and the dorsal vagal motor nucleus (DVN). In addition, the CeA can directly activate the sympathoexcitatory neurons in the RVLM. The net effect of pharmacological blockade of the prefrontal cortex would be disinhibition of the CeA, leading to disinhibition of medullary cardio-acceleratory circuits and an increase in heart rate. Reprinted from Neuroscience & Behavioral Reviews, Volume 33 (2), Thayer & Lane, "Claude Bernard and the heart-brain connection: Further elaboration of a model of neurovisceral integration", page 84, 2009, with permission from Elsevier.



A second theory that has been used in the last years to explain the meaning of HRV and the interpretation of the underlying process of ANS is the polyvagal theory (Porges, 1995b, 2007, 2009). This theory draws on an evolutionary model of explanation regarding the neurophysiological development of autonomic regulation. It provides a framework for connecting the neural activation of the vagal system to the experience and expression of social and emotional behaviour.

Porges (Porges, 1995b, 2001, 2007) suggests that mammalian ANS has three hierarchical organised systems: the ventral vagal complex (VVC), the sympathetic nervous system (SNS), and the dorsal vagal complex (DVC) (Porges, 2022). The three subsystems of ANS have different neuroanatomical pathways that lead to peculiar behavioural responses to challenges of the organism. The newest phylogenetic subsystem (VVC) comprises myelinated vagal fibres originating in the nucleus ambiguous that, through the coordination of striated face and head muscles and the regulation of the organs above the diagraphs, promote social expression and engagement (Porges, 2007, 2022). Indeed, the innervation of muscles in the face, larynx, pharynx, oesophagus, soft palate, eyelids, and middle ear are all of crucial importance for communication (e.g. facial expressivity, prosody, and intonation) and perception (e.g., extracting the human voice from background sounds) – and, thereby, also essential prerequisites for social interaction. The SNS is related to fight-or-flight behavioural response, and its efferent originating in the spinal cord innervates both organs above and below the diaphragm (Porges, 2009, 2022). In the DVC, the unmyelinated vagal efferent originating in the dorsal nucleus of the vagus primary innervates organs below the diaphragm (i.e., muscle and glands

of the gut) with few fibres terminating on the heart's sinoatrial node, and its primary behavioural function is immobilisation (Kolacz et al., 2019; Porges, 2022).

When the VVC state is activated in safe conditions, there is an adaptive autonomic balance between SNS and DVC (Porges, 2001). However, when the VVC becomes ineffective (e.g., in threat conditions), the two more phylogenetical archaic subsystems are triggered. The SNS led the organism to actively cope with the environmental challenge through defensive mobilisation behaviour responses (e.g., fight-or-flight behaviours) (Porges, 2007, 2009). In the case of extreme stress or hazardous conditions, the DVCed the organisms to an immobilisation response and conservation of energy through inhibition of metabolic function and passive behavioural responses (e.g., freezing or fainting) (Kolacz & Porges, 2018; Porges, 2001).

The detection of threats and the evaluation of safety play a crucial role in the employment of these systems. The neural processes that determine the level of safety or risk present in the environment have been termed “neuroception” (Porges, 2007, 2022). In order to socially engage with another organism, mammal neuroreceptor circuits have to evaluate the environment as safe and downregulate defensive strategies. When the process of neuroception is disrupted, as in psychopathology, the threat may be mislabelled as more or less dangerous than it should be, and a maladaptive strategy along with inappropriate systems may be employed, leading to behaviours that may be destructive or cause long-term distress (Porges, 2007, 2009). In other words, a chronic dampened function of VVC and the resultant mobilisation (SNS) and immobilisation (DVC) defensive states in non-threat situations provide the framework for the onset of mental health disorders (Kolacz, Dale, et al., 2020; Kolacz et al., 2019).

Other models also explain the relationship between HRV and psychopathology (e.g., the psychophysiological coherence model). However, all these models focused on the PNS activity. The overall idea is that a disruption of vagal tone could be associated with lower adaptability and successful regulation that, in turn, could be related to worst social and emotional functioning and psychological health. Therefore, this thesis will focus on the association between HRV – mainly vagally-mediated HRV parameters – and postpartum depressive symptoms. The topic is critical since, in the last years, literature found an association between vagally-mediated HRV parameters and depressive symptoms in the general population. However, very few studies extend these findings to PPD and no studies used vagally-mediated HRV as a potential biomarker and predictor of higher depressive symptoms after childbirth.

1.3.1. Heart rate variability and depression in the general population

A compelling body of research reported that depression is characterized by lower vagally-mediated HRV (Brown et al., 2018; Dell'Acqua et al., 2020; Hartmann et al., 2019; Koch et al., 2019; Koenig et al., 2016; Schiweck et al., 2019). In their meta-analysis, Kock et al. (2019) considered studies that compared HRV measurements at rest between unmedicated adults with major depression and healthy controls. Results showed that compared to controls, depressed samples showed lower levels of HF power, LF power, rMSSD, SDNN and higher levels of LF/HF ratio, with a greater effect size for rMSSD. These findings supported the idea that depression is characterized by a general alteration of time- and frequency domain measurements of HRV with an important reduction of cardiac vagal control. A recent study corroborates this evidence, showing that lower levels of rMSSD, HF power and LF power might be a diagnostic marker to distinguish between depressive patients and healthy controls (Hartmann et al., 2019). Moreover, when the depressed sample underwent to 2 weeks of antidepressant treatment, they showed lower levels of depressive symptoms and a parallel increase of HF power, supporting the hypothesis of an improvement of symptoms severity of depression in correspondence to an increase of vagal activity. In a successive study, reduced vagally-mediate HRV appears to be a promising indicator of vulnerability to depression (Dell'Acqua et al., 2020). This study aimed to compare HRV parameters in individuals vulnerable to the onset of depression (i.e., individuals with dysphoria and unmedicated past depression) with healthy controls. The results indicated that individuals with at-risk conditions for developing depression showed reduced cardiac vagal modulation (i.e., reduction in both SDNN and HF power parameters) compared to controls. These findings suggested that cardiac vagal modulation could represent a correlate of vulnerability to depression.

Moreover, two longitudinal studies indicated that vagally-mediated HRV was prospectively implicated in the onset of depressive symptoms in a healthy population (Carnevali et al., 2018; Jandackova et al., 2016). For instance, Jandackova et al. (2016) showed that lower baseline HR and higher HRV parameters (i.e., SDNN, rMSSD, HF power, and LF power) were associated with a lower likelihood of symptoms of depression ten years later. However, despite the study's strengths – for instance, the sample did not have depressive symptoms at baseline, and the association between HRV and depression was independent of various sociodemographic and lifestyle covariates – significant results were obtained only for cognitive depressive symptoms and only in male participants. A successive study enhanced these findings reporting that low vagal tone (i.e., rMSSD) was associated with higher depressive symptoms one year later (Carnevali et al., 2018). Moreover, they showed that vagally-mediated HRV mediated the relationship between rumination and depression levels; this seems to indicate that the well-known link between rumination and depressive symptoms could be partly due to the alteration of PNS function.

1.3.2. Heart rate variability and depression in peripartum

The relationship between HRV and depressive symptoms was also investigated in the pregnant population. However, there is an important difference between studies on the general population and pregnant women. During pregnancy, the ANS activity varies widely to maintain the body's health homeostasis and adapt to the new physiological requests of the growing fetus (Abbas et al., 2005; Brooks et al., 2020). Several studies indicated an increase in basal heart rate, a reduction of PNS, and a predominance of SNS activity during the second and third trimester of pregnancy (Balajewicz-Nowak et al., 2016; Fu, 2018; Kuo et al., 2000; Matsuo et al., 2007; Volman et al., 2007) with the restoration of pre-pregnancy ANS activity in the weeks following childbirth (R. L. Brown et al., 2021; Yeh et al., 2009). For instance, Kuo et al. (2000) found a biphasic change in ANS during pregnancy; in particular, ANS is shifted significantly to a lower sympathetic and higher vagal activity in the first trimester and then progressively to a higher sympathetic and lower vagal activity in the second and third trimester. This trend is confirmed in other longitudinal studies (Balajewicz-Nowak et al., 2016; Matsuo et al., 2007). One of the leading causes of the adaptive change of ANS activity seems to be the increase of cardiac output and vasodilatation through pregnancy that increments the workload of the heart, shifting the ANS into a state of a higher SNS and lower PNS activity, as gestational time advances (Fu, 2018; Kuo et al., 2000; Matsuo et al., 2007). After delivery, Brown et al. (2021) reported a significant improvement of vagally-mediated HRV parameters from the third trimester to 4-6 week postpartum, suggesting a returns to vagal tone pre-pregnancy levels in the first period after childbirth (R. L. Brown et al., 2021; G. Y. Chen et al., 1999; Yeh et al., 2009).

Dysfunctional changes in ANS during pregnancy have been investigated directly in relation to depressive symptoms (Kimmel et al., 2021; Shah et al., 2020; Shea et al., 2008) or through other hypotheses (Ecklund-Flores et al., 2017; Rouleau et al., 2016). Shea et al. (2008) examined the association between depression and ANS function during the third trimester of pregnancy by comparing HRV parameters obtained from a 24-h ECG in depressed and healthy pregnant women. Their findings showed that depressed pregnant women reported lower values of SDNN and SDANN (i.e., the standard deviation of the averages of RR intervals in all 5 minutes segments of the entire recording) than the healthy control group, indicative of decreased vagal tone. A successive study – investigating the possible mechanism linking depression and gestational hypertension – corroborates these findings reporting that higher levels of depressive symptoms in the second trimester of pregnancy were associated with lower levels of HF power in the third trimester of pregnancy, that in turn increases the likelihood of gestational hypertension (Rouleau et al., 2016). Another study exploring the effect of pregnancy depressive symptoms on a child's birth weight found that depressive

symptoms and rMSSD in the third trimester of pregnancy were negatively correlated, leading authors to posit that PNS activity is altered by the presence of depressive symptoms during pregnancy (Ecklund-Flores et al., 2017). A recent cross-sectional study reported that higher levels of LF/HF ratio and lower levels of baroreflex sensitivity were associated with depressive symptoms during pregnancy (i.e., between 12 and 30 weeks of pregnancy) (Shah et al., 2020). Despite the difficulty of interpreting the higher levels of LF/HF ratio, lower levels of baroreflex sensitivity confirmed the idea that impaired autonomic modulation is typical in women with prepartum depressive symptoms. Although the literature has supported the association between altered HRV and depression in pregnancy so far, a recent study by Kimmel et al. (2021) found no association between HRV parameters (i.e., SDNN, rMSSD, VLF, LF, HF, and LF/HF ratio) and the presence of a major depressive disorder in pregnant women at the late third trimester of pregnancy. However, authors found that different HRV parameters were associated with other mental health diagnoses. For instance, lower HF power was found for women who met diagnostic criteria for obsessive compulsive disorder, whereas higher LF and LF/HF ration were found for those meeting criteria for social phobia o general anxiety disorder.

1.4. Aims of the present thesis

The main objective of this thesis was to explore the relationship between parasympathetic autonomic activity and mental health, focusing on peripartum depressive symptomatology. In particular, we investigated the role of HRV as an indicator of depressive symptoms during pregnancy and as a predictor of postpartum depressive symptomatology. Literature supported this relationship in the general population, but studies on peripartum samples are scarce. Moreover, the direction of the relationship between HRV and depression is unclear, and no studies investigate the potential of HRV during pregnancy as a predictor of postpartum depressive symptoms. Since all studies reported in this thesis were carried on during the COVID-19 pandemic, we took the opportunity to test the use of remote and online technologies. In the last year, mobile and web-based assessments and interventions have been widespread, and the pandemic social restrictions boosted the trend. So, this thesis could represent a valuable occasion to test the feasibility of using mobile technologies and self-reported questionnaires to assess HRV, a physiological variable that is often measured in person in a laboratory setting. Our target population (i.e., pregnant women) complete the innovative framework of the thesis, considering the scarcity of studies that combine psychological and physiological measures and use eHealth in the peripartum period.

The first study of this thesis validates the use of a commercial Android smartphone application to assess HRV. The study is essential for identifying a reliable remote evaluation of the parasympathetic activity. Many smartphone applications have been developed in recent years to assess cardiac parameters, but validation studies supported very few of them. In the second study, we implemented the use of this application in the main aim of this thesis, namely the investigation of the relationship between HRV and peripartum depressive symptoms. We aimed to understand the role of prepartum HRV in the presence of depressive symptomatology during pregnancy; moreover, to shed light on the direction of the relationship, we explored the impact of HRV during pregnancy in the onset of postpartum depressive symptoms. The third study continued this research line by using a self-reported measure of vagal activity to predict postpartum depressive symptoms. The results of this study are innovative and valuable, considering the test of a physiological index through a questionnaire and the opportunity of measuring the parasympathetic activity in particular conditions (e.g., rural communities, large-scale studies, etc.). Using these tools we aimed to provide new effective measures to assess women health in one of the most important phases of their lives, namely pregnancy.

2. Study 1: Validation of a smartphone application for the collection of Heart Rate Variability parameters

Study 1 of the paper "Singh Solorzano, C., Violani, C., Grano, C., (2022). Pre-partum HRV as a predictor of postpartum depression: The potential use of a smartphone application for physiological recordings. Journal of Affective Disorders, 319, 172-180. https://doi.org/10.1016/j.jad.2022.09.056"

2.1. Introduction

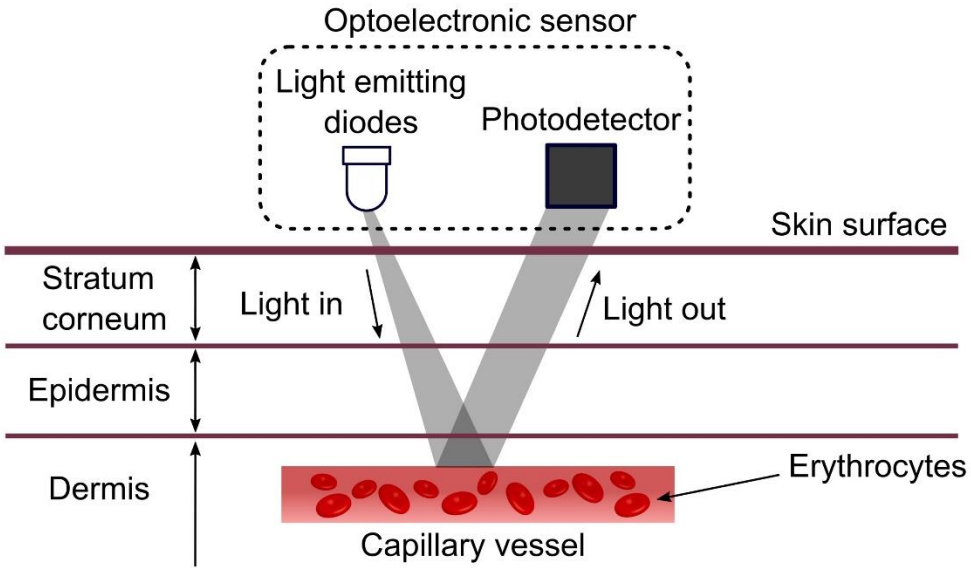
In the last years, the proliferation of smartphones increased the usage of digital content and mobile applications in different contexts (e.g., at home, at school, during free time) and for different purposes (e.g., work, education, health, gaming). Recent statistics reported that the number of current smartphone users worldwide is over 6 billion, with the highest number of smartphone users in China, India, and the United States (Statista Research Department, 2022a). Just in Italy, there are 46,5 million smartphone users, and about 9 out of ten Italian mobile owners prefer smartphones to browse the internet and use digital services (ISTAT, 2019; Statista Research Department, 2022a). Since the increase of the number of smartphone users seems to not slow down in the following years and the ubiquity of mobile technologies in all domains of people's lives, it could be important to investigate and update on the potential applications of these technologies on health.

Mobile Health or mHealth is defined as "medical and public health practice supported by mobile devices, such as mobile phones, patient monitoring devices, personal digital assistants, and other wireless devices" (World Health Organization, 2011) or as "mobile computing, medical sensor, and communications technologies for healthcare" (Istepanian et al., 2007). A more comprehensive definition described mHealth as "the use of any mobile device including mobile phones, smartphones, mobile or phone-based sensors for providing and receiving healthcare services such as healthcare monitoring, diagnosis, management and prediction of diseases" (Iyawa et al., 2020). In the period in which this thesis was written, more than 107,000 mHealth apps were available in the app stores, with an exponential trend in the number of available mobile health apps from 2015 (Statista Research Department, 2022b, 2022c). The main reasons for this increase are related to the economic and convenience aspects. However, most available mHealth apps have been developed without being tested for validity and effectiveness. Indeed, a recent systematic review reported that the level of evidence is currently only sufficient to support the use of apps in a small number of specific clinical situations (Rowland et al., 2020). However, this point did not dampen the use of mHealth apps and even promoted more trials to understand the real value and reliability of mHealth applications. Due to the current technology development and advances, neglecting the use of smartphones in the health context could be a missed opportunity to improve the health care system. Considering the potential

information a smartphone can collect should lead to more investigations and studies on the topic. Indeed, smartphones' ability to carry different embedded or external sensors – apart from a simple collection of self-reported measures –might allow their use as a valuable tool for self-assessment and monitoring common psychological and physiological parameters. Moreover, using technologies, including voice, text messaging, video, and the internet, could improve the quality, make it more convenient, and improve the effectiveness of different psychological and educational interventions (Fiedler et al., 2020; Marcolino et al., 2018).

The smartphone's camera could be an excellent sensor to quickly record cardiac activity with low equipment requirements through contact photoplethysmography (PPG) technology (De Ridder et al., 2018). The main idea of PPG was to assess blood volume changes caused by pressure changes related to the cardiac cycle through a light source to illuminate the subcutaneous tissue and a photodetector to detect the changes in light intensity (Allen, 2007; Jonathan & Leahy, 2010). Smartphones could be used to perform PPG by replacing the photodetector with the digital red-green-blue (RGB) camera and using the flashlight as a light source (*Figure 2.1.*). As explained in *paragraph 1.2.3*, HR and HRV parameters could be derived from a PPG registration's beat-to-beat intervals (BBIs). Literature indicated that a few time- and frequency-domain HRV parameters derived from PPG smartphone camera registration are similar to the same parameters derived from RR intervals (RRIs) of an ECG – the golden standard (Bánhalmi et al., 2018; Bolkhovsky et al., 2012; Guede-Fernández et al., 2020; Holmes et al., 2020; Moya-Ramon et al., 2022; Peng et al., 2015; Plews et al., 2017; Zhang et al., 2021). For instance, Plews et al. (2017), Holmes et al. (2020), and Moya-Ramon (2022) showed that the short-term rMSSD at rest collected with commercial iPhone smartphone applications (i.e., HRV4Training, Welltory) had an acceptable agreement with the same parameters derived via ECG. Moreover, other studies reported similar or better findings using non-commercial PPG smartphone applications using Android (Guede-Fernández et al., 2020; Lenskiy & Aitzhan, 2013; Peng et al., 2015; Zhang et al., 2021) or iOS (Bánhalmi et al., 2018; Bolkhovsky et al., 2012) mobile operating systems.

Figure 2.1. Working principle of PPG collection through a smartphone (reflectance-mode PPG). Figure from (Moraes et al., 2018).



The assessment of HRV through the smartphone camera could be an attractive opportunity for developing different and multidimensional psychological and medical care models. However, more proof of feasibility, validity, and accuracy of the different apps is needed to make using these mHealth technologies profitable and cost-effective. Furthermore, using smartphones for collecting HRV data is currently limited due to the lack of robustness and reliability of these apps in practical scenarios. Apart from the need for more validation studies, the operative system of the smartphones (e.g., IOS, Android), the different software designed to process the smartphone PPG signal, the low frame sampling rate of smartphones camera, and the difficulty accessing raw PPG data are all source of randomness and instability of the HRV parameters collected by smartphone apps (Laborde et al., 2017; Liu et al., 2020b).

This study aimed to investigate a commercial smartphone application's validity in assessing a time-domain HRV index (i.e., rMSSD). This time-domain index was chosen because it is one of the most appropriate HRV measures for short-term and ultra-short-term recordings (Y. S. Chen et al., 2020; Malik et al., 1996; Munoz et al., 2015), is widely used in literature (Khazan, 2013), reflects the cardiac vagal influence and is highly correlated with other HRV parasympathetic parameters (Shaffer & Ginsberg, 2017), and is less influenced to variability in respiration than other HRV indices (Penttilä et al., 2001; Thayer et al., 2012). Therefore, we assessed the reliability and accuracy of a free Android commercial smartphone application for recording rMSSD compared with an electrocardiogram (ECG).

2.2. Methods and Materials

2.1.1. Participants

A total of 35 university students voluntarily took part in the study (mean age = 26.43, standard deviation = 6.56). Almost all participants were females (85.7%), and the average weight and height were 62.63 kg (SD = 10.52) and 1.69 m (SD = 0.08), respectively. Exclusion criteria included current cardiovascular and metabolic diseases.

2.1.2. Procedures

Before the laboratory session, participants were requested to avoid alcohol consumption, caffeine-containing substances, and smoking on the same day of the appointment. In the first part of the laboratory session, participants gave written informed consent and were administered a demographic interview. Moreover, they were provided with an explanation and demonstration of how to use the PPG smartphone application. In particular, the participant had time to familiarise themselves with the PPG application and carried out some registration trials. To collect the most reliable data, they had to place the fingertip of the right hand's index to cover both the smartphone camera and flash. Moreover, the participants were given instructions to improve the signal quality, such as not moving their hands or body during the registration and avoiding hard contact pressure on the smartphone camera and flash when performing measurements.

Then, participants were seated in an upholstered chair in a quiet room. After the ECG sensors were attached and a smartphone with the PPG application mentioned above was provided, the cardiac signal was recorded at rest, simultaneously by the ECG and the application over a period of two minutes for each participant. Short-term recording (<5 minutes) has been reported to be a reliable method to measure time-domain HRV indices both for parameters resulting from ECG (Baek et al., 2015; Shaffer et al., 2016) and PPG smartphone applications (Y. S. Chen et al., 2020; Christien Li et al., 2019; Coppetti et al., 2017). The devices were activated manually to avoid possible synchronisation errors between the instruments. All participants signed an informed consent form. The study was approved by the Institution Review Board of the Psychology Department, Sapienza University of Rome (Prot. n. 0000024).

2.1.3. Measures

ECG was collected using a ProComp5 Infiniti amplifier and BioGraph Infiniti software (Thought Technology Ltd., Montreal, Quebec). The ECG was recorded from three Ag⁄AgCl electrodes that were positioned on the participant's chest in a modified lead II configuration. The

physiological signal was recorded continuously for 2 min while participants were seated comfortably in a quiet room. Impedance was kept below 5 kΩ, and each ECG signal was amplified, band-pass filtered (0.3–100 Hz) and sampled at 1000 Hz. The RR intervals (RRI) were extracted, and Kubios HRV Analysis Software 3.4.1 (Matlab, Kuopio, Finland) was used to inspect raw data. Ectopic beats and artefacts were removed and replaced with the interpolated adjacent RR interval values (threshold = 0.45 seconds or "very low"). Then, the same software was used to calculate the root mean square of successive difference between NN intervals (rMSSD) in ms.

After a training session, the physiological signal was recorded for 2 minutes from the smartphone (Xiaomi Redmi Note 7) at the same time as the ECG recording through the use of the application Heart Rate Variability HRV Camera. This application uses contact PPG technology to detect heartbeats by analysing changes in light absorption related to fluctuations of beat-by-beat capillary blood volume (Christien Li et al., 2019; Schäfer & Vagedes, 2013). The sampling rate of the smartphone camera was 30 Hz, and the smartphone application performed a 100 Hz interpolation to improve the accuracy of raw collected data. Then, the application analysed the raw beat-to-beat interval (BBI) data and computed the rMSSD in ms using the standard formulas for this HRV time-domain index (Jokic et al., 2016; Malik et al., 1996). However, the application did not have a system to inform the user whether the collected raw data were of sufficient quality or not. Therefore, a visual inspection of the graphs provided by the app (*Figure 2.2.*) was carried out by the researcher to identify signals with high noise or movement artefact (i.e., low-quality physiological registrations) through the analysis of the distributions of values in the plot with the course of heart rate over time and in the Poincaré plot (Chua et al., 2008; Stein et al., 2005). In the plot with the course of heart rate over time, linear and quasi-periodic waves without values outside the biologically plausible range of 20-220 beats per minute must be seen in the signal. In the Poincaré plot, an ellipsoid or mildly comet-shaped distribution of points aligned at the centre of the plot must be seen in the signal. An example of a good-quality signal is shown in *Figure 2.2*. If the measured signal was of low quality, participants were asked to repeat the experiment after a pause of 5 minutes. Examples of two bad-quality signals are shown in *Figure 2.3.*

Figure 2.2. An example of graphs plotted by "Heart Rate Variable HRV Camera" after the end of a two-minute physiological registration with good quality. The application reported: a plot with the course of heart rate over time (at the top left); the Poincaré plot (at the middle left); a plot with the distribution of beat-to-beat intervals over time (at the bottom left); a power spectrum density graph of the HRV (at the top right); a power spectrum density graph of the HRV obtained by autoregressive method (at the bottom right).

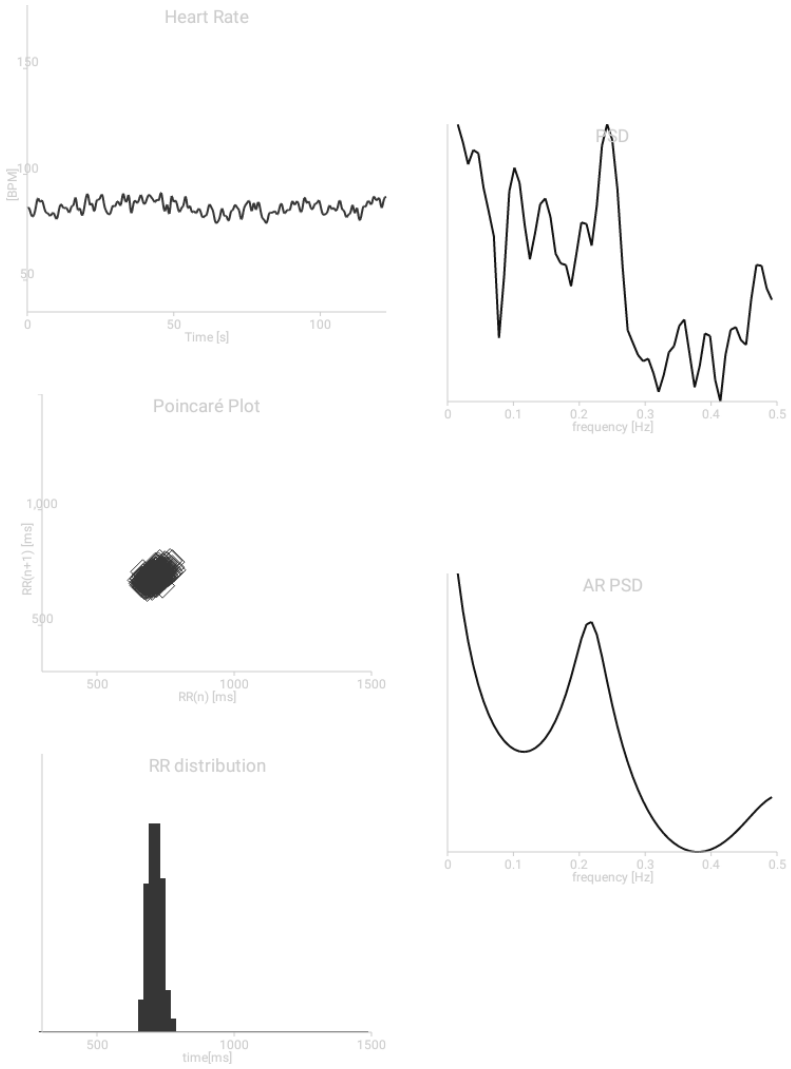
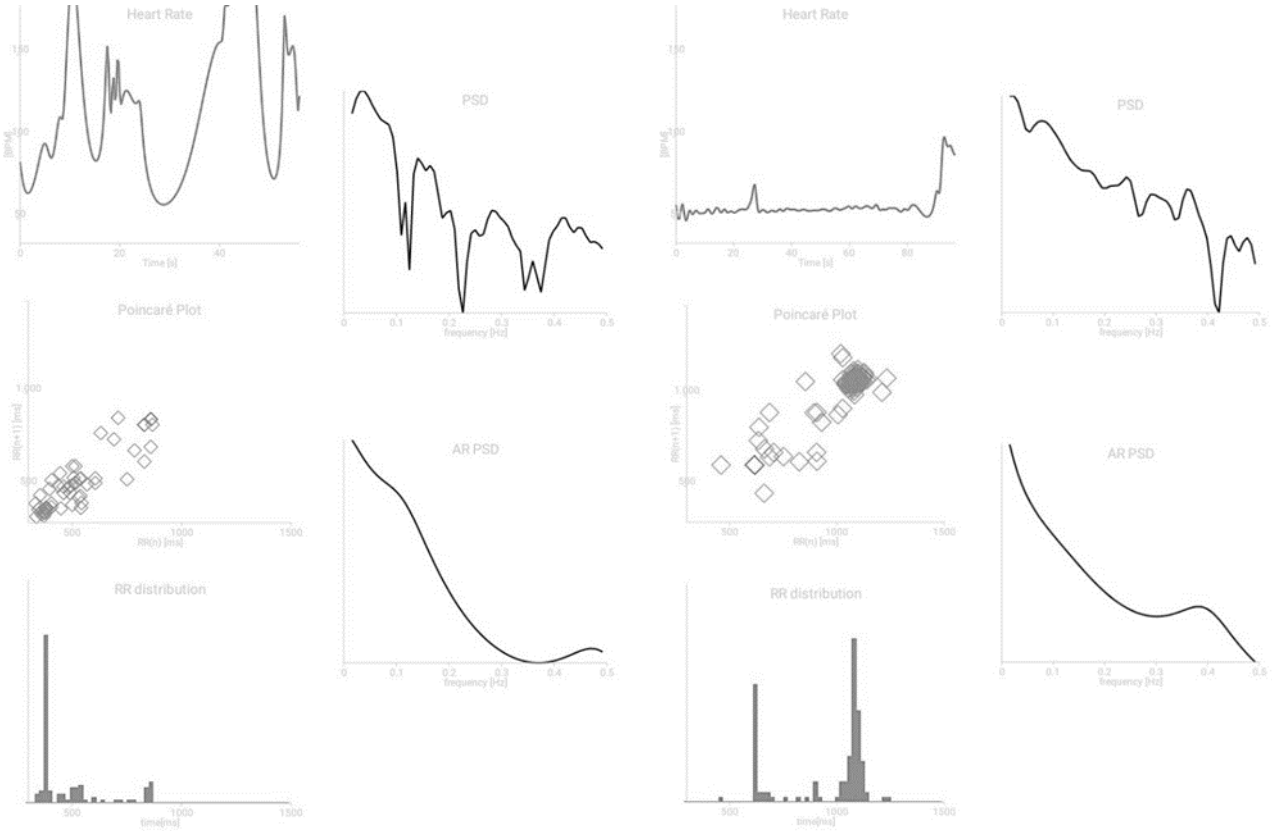


Figure 2.3. Two examples of graphs plotted by "Heart Rate Variable HRV Camera" after the end of a two-minute physiological registration with bad quality. At left is an example of a PPG signal with few movement artefacts throughout the registration, as indicated by an irregular plot with the course of heart rate over time and an unreliable Poincaré plot. At the right is an example of a PPG registration in which the smartphone did not correctly collect the cardiac signal, as indicated by a quasi-linear plot with the course of heart rate over time and an unreliable Poincaré plot.



2.1.4. Statistical analysis

Descriptive data of measured variables were presented as means and standard deviations. Mean RRI (i.e., the mean of the time intervals elapsing between two consecutive waves of the cardiac signal), mean BBI (i.e., the mean of the time interval elapsing between two consecutive beats of the PPG signal), and rMSSD recording both with ECG and PPG were logarithmically transformed before statistical analyses to normalise their distribution. To assess differences between measures recorded with PPG and ECG, independent t-tests were used. Cohen's *d* was used to determine the magnitude of the mean differences (J. Cohen, 2013). Cohen's *d* was interpreted as trivial (0.0-0.2), small (0.2-0.6), moderate (0.6-1.2), large (1.2-2.0), and very large (>2.0) (Hopkins et al., 2009). Intraclass correlation coefficients (ICC) with a two-way random model were used to evaluate the agreement between the values provided by the smartphone app to ECG. An ICC value between 0 to 0.30 was considered small, 0.31 to 0.49 moderate, 0.50 to 0.69 large, 0.70 to 0.89 very large, and 0.90 to 1.00 near-perfect (Hopkins et al., 2009). Lastly, Bland-Altman plots were formed to identify the upper and lower limits of agreement (LoA) of the indices as determined by the two different instruments (Bland & Altman, 1986). In addition, the quality of agreement was calculated as the ratio of half the 95% LoA length and the mean of average values of the parameter measured with the PPG and ECG. As suggested by Schäfer & Vagedes (2013), a ratio less than 0.1 was considered a "good" agreement, a ratio between 0.1 and 0.2 was considered a "moderate" agreement, and a ratio greater than 0.2 was

considered an "insufficient" agreement. For all analyses, the level of significance was set at $p < 0.05$. Statistical analyses were conducted using IBM SPSS Statistic version 27 (SPSS Inc., IBM, Armonk, NY, USA) and Microsoft Excel 2019 (Microsoft Corp.).

2.3. Results

Table 2.1. reported raw means (M) and standard deviations (SD) of the mean RRI, mean BBI, and the HRV time-domain index (i.e., rMSSD) of interest. There were no significant differences between the values recorded with ECG and the PPG smartphone app, and the effect sizes (i.e., Cohen's *d*) were considered trivial. Furthermore, all ICC values were nearly perfect (from 0.99-1.0), so there was a high agreement between the parameters provided by ECG and the PPG smartphone application.

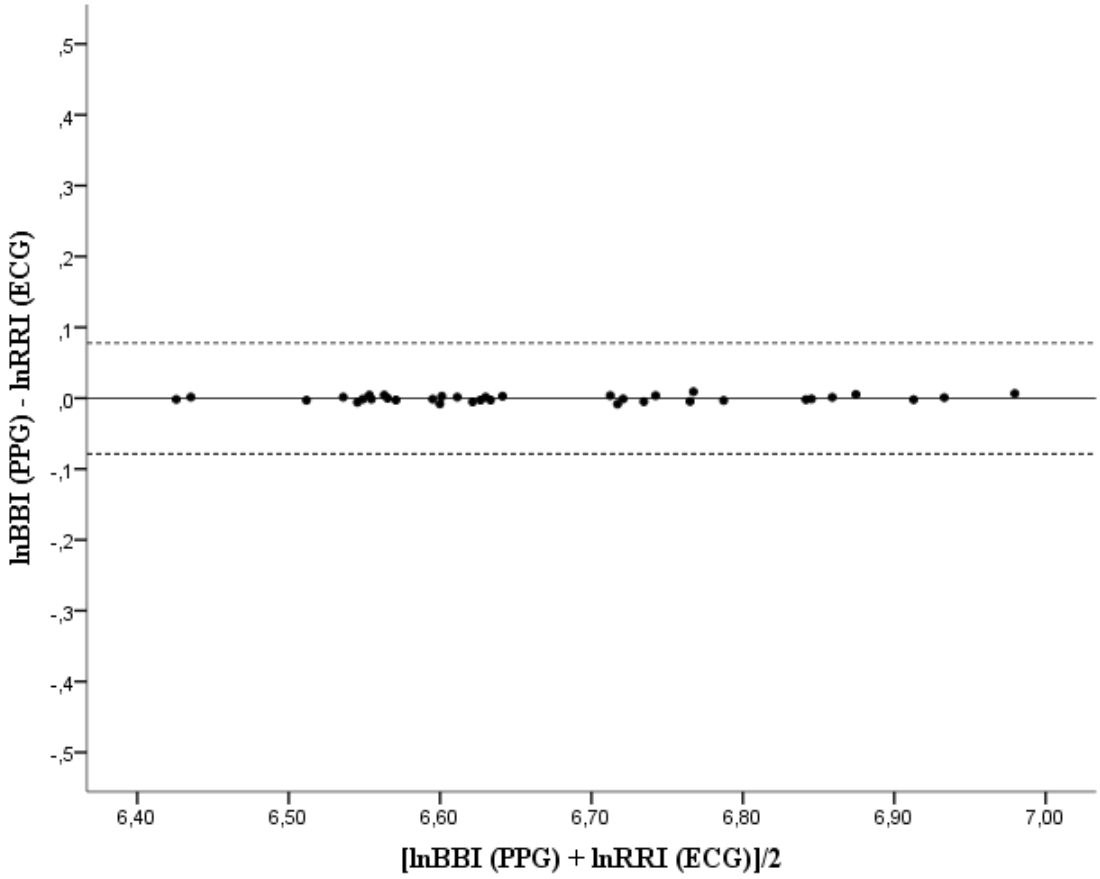
Table 2.1. Comparison of ECG and PPG measurement of RRI, BBI, and rMSSD index.

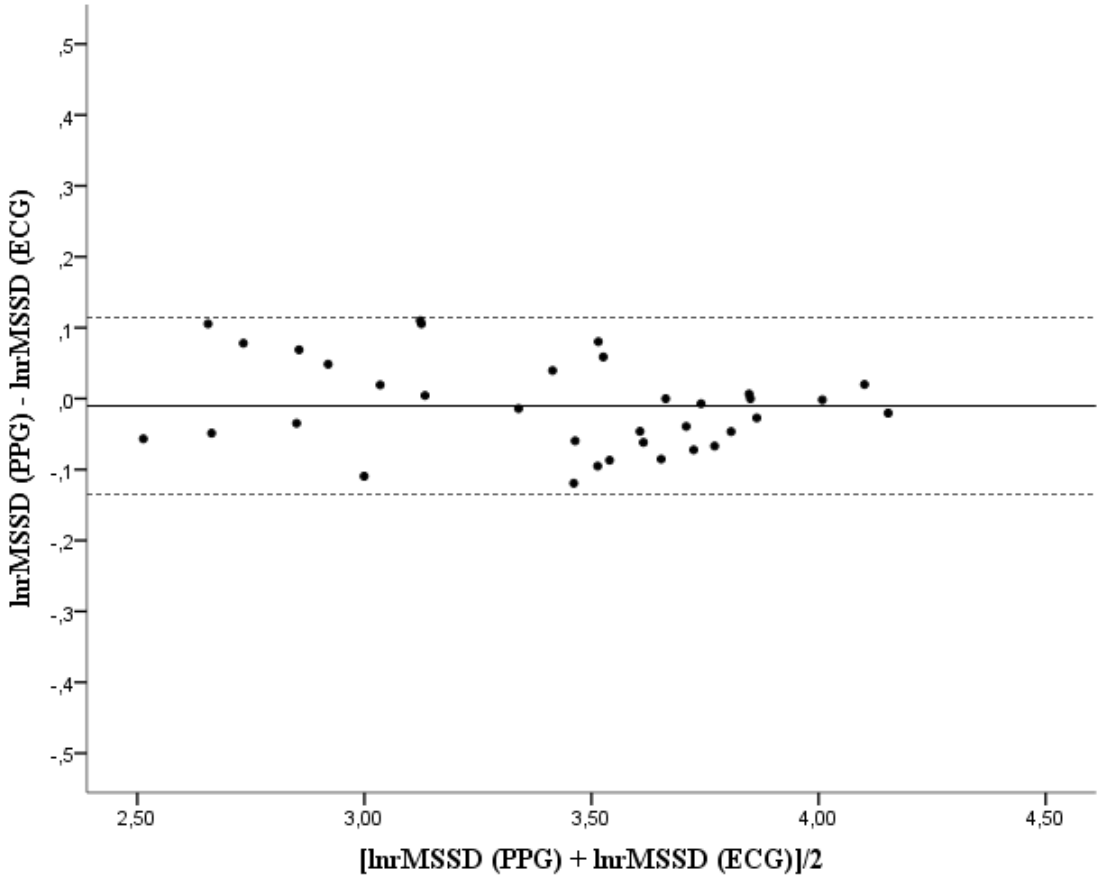
Cardiovascular variables	**Mean (SD)**	**Cohen's *d* (95% CI)**	**ICC (95% CI)**	**Ratio of agreement**
Mean RRI or BBI (ms)				
ECG	798.97 (116.24)	0.003 (-0.466;0.471)	1 (1;1)	0.012
PPG app	798.74 (117.01)			
rMSSD (ms)				
ECG	33.48 (13.71)	0.023 (-0.446;0.491)	0.995 (0.990;0.997)	0.036
PPG app	32.94 (13.23)			

Notes. Results for ECG and PPG application are reported as the Mean (Standard Deviation) of raw values.

Bland-Altman graphs of the differences between the ECG and PPG measurements plotted against their means are reported in *Figure 2.4.* All plots showed relatively narrow values of mean difference in mean RRI/BBI (mean bias = -0.001, upper LoA = 0.078, lower LoA = -0.079) and rMSSD (mean bias = -0.010, upper LoA = 0.114, lower LoA = -0.135). Moreover, all ratios showed a "good" agreement between the two measuring methods. Therefore, the two recording systems showed high levels of agreement in the measurement of the analysed indexes.

Figure 2.4. Bland-Altman analysis comparing the log transformation of mean RRI/BBI (lnRRI/lnBBI) and rMSSD (lnrMSSD) values from the PPG smartphone application measurements with ECG. The solid line represents the mean bias, whereas the outside dashed lines represent the 95% limits of agreement.


lnBBI (PPG) - lnRRI (ECG)
,5
,4
,3
,2
,1
,0
-,1
-,2
-,3
-,4
-,5
6,40
6,50
6,60
6,70
6,80
6,90
7,00
[lnBBI (PPG) + lnRRI (ECG)]/2


lnrMSSD (PPG) - lnrMSSD (ECG)
,5
,4
,3
,2
,1
,0
-,1
-,2
-,3
-,4
-,5
2,50
3,00
3,50
4,00
4,50
[lnrMSSD (PPG) + lnrMSSD (ECG)]/2

2.4. Discussion and conclusion

In this first study, our results reported the validity and reliability of the short-term rMSSD measured via the "Heart Rate Variability HRV Camera" commercial application compared with the standard ECG assessment. Indeed, the trivial Cohen's *d* effect size, the nearly perfect ICC, and the "good" Bland-Altman ratio between ECG and PPG recording indicated an excellent accuracy of the smartphone application used in measuring the time-domain index of interest (Schäfer & Vagedes, 2013).

In line with our findings, other studies reported the validity and reliability of other contact PPG smartphone applications in collecting this HRV index (Christien Li et al., 2019). For instance, Plews et al. (2017) showed that the 1-minute ultra-short-term rMSSD collected with an iPhone commercial smartphone application (i.e., "HRV4Training") had an acceptable agreement with the same index derived via ECG. In addition, the same application displayed strong reliability in measuring different rMSSD values within the same day and between two different days (Holmes et al., 2020). Furthermore, another PPG smartphone commercial application implemented in an iPhone (i.e., Welltory) showed good validity and reliability in the measure of rMSSD during short (i.e., 5 minutes) and ultra-short (i.e., 1 minute) recording in both supine and seated positions (Moya-Ramon et al., 2022).

Moving into an Android programming environment, Guede-Fernández et al. (2020) found that their Android smartphone application can accurately measure the standard deviation of the R-R intervals (i.e., SDNN) and rMSSD. However, other studies found different results. For instance, a study compared time-domain, frequency-domain, and nonlinear HRV parameters computed from 5-minutes ECG and PPG Android camera smartphone acquisitions found that only frequency-domain parameters from PPG were in good agreement with those calculated from ECG; the rMSSD parameter showed insufficient agreement (Peng et al., 2015). In another similar study, Zhang et al. (2021) used their Android smartphone application to measure different time-domain and frequency-domain HRV parameters and to compare them with the same parameters derived from ECG. Their found that all HRV parameters obtained from the PPG were strongly correlated with the results of the ECG measurement with very small differences and within acceptable ranges of error, except rMSSD and HF (i.e., High-Frequency power) (Zhang et al., 2021). However, comparing these studies is complicated by the use of non-commercial smartphone applications and different algorithms to extract beat-to-beat intervals (BBI) from PPG signals.

Our study extended these findings showing the availability of a free commercial smartphone application (i.e., "Heart Rate Variability HRV Camera") that could be used to reliably assess one of the most widely used parameters of HRV. The findings could be relevant for eHealth (i.e., "the use

of information technology, including the Internet, digital gaming, virtual reality, and robotics in the promotion, prevention, treatment and maintenance of health") (Borrelli & Ritterband, 2015) and mHealth fields. In recent years, the advancement and spread of new technologies have promoted the use of smartphone-based software and online intervention in health services (Messner et al., 2019; Rowland et al., 2020). As a result, smartphone applications have vast potential and, nowadays, are used to support clinical diagnosis, enhance patient adherence and compliance with treatment, act as standalone digital therapeutics, and deliver disease-related education (Ferretti et al., 2019; Messner et al., 2019; Yerrakalva et al., 2019). Furthermore, the COVID-19 pandemic social restrictions led to a sudden increase in the development and use of eHealth and mHealth services in many countries since the need to monitor patients and deliver healthcare services remotely (Adetunji et al., 2022). Implementing these new technologies is strictly related to the ability of these systems to collect data correctly and to the effectiveness of the monitoring and treatment implemented via pc, tablet, smartphone or other portable devices. For instance, mHealth showed high usability and good efficacy in increasing physical activity and healthy eating (Domin et al., 2021; Fiedler et al., 2020), in the self-management of hypertension (Li et al., 2020), in the management of diabetes (Mao et al., 2020), in the prevention and recovery of coronary heart diseases (Xu et al., 2021), and in the monitoring and treatment of mental health disorders (Lecomte et al., 2020; Seppälä et al., 2019). Furthermore, a recent review reported increased availability of smartphone applications evaluating heart rate, HRV, and atrial fibrillation (Christien Li et al., 2019). These applications could have an essential role in remote cardiovascular health monitoring; however, there is often a lack of studies testing the statistical reliability and validity of collected data compared to the traditional method of cardiac collection data, namely ECG. Our study provides valid data for a mHealth app that could easily be used in patient assessment and implemented in different remote interventions. In addition, HRV parameters are increasingly becoming used in psychological research due to their relation with cognitive and emotional variables (Forte et al., 2019; Mather & Thayer, 2018). Therefore, the use of this smartphone application is not limited to a measurement of a cardiovascular health index, but it could be used within a global psychophysiological assessment. This aspect could be helpful to psychology professionals that would add a valuable physiological measure to their clinical self-reported assessments. In addition, psychology researchers could use the application to freely assess HRV remotely for research reasons (e.g., ecological studies) or particular conditions (e.g., world pandemics, participants living in rural and remote areas, etc.).

Findings have to be read considering some limitations. First, although literature reported a good agreement between ECG and smartphone PPG measurements (Christien Li et al., 2019; de Ridder et al., 2018), a few motion artefacts (e.g., hand movements) might corrupt the physiological

signal registered with a smartphone and lead to an instrument measurement error. To our knowledge, none of the previous studies that compare smartphone PPG with ECG completely solved the problem. Moreover, the research does not know the data correction methods implemented by the "Heart Rate Variability HRV Camera" application. Therefore, in this study, the subjects were instructed to sit in an upholstered chair and place the fingertip of the right hand's index to cover both the smartphone camera and flash. Moreover, the participants were told not to move their hands or body during the registration and to avoid hard contact pressure on the smartphone camera and flash when performing measurements. We also gave time to participants to familiarise themselves with the PPG application and carried out some registration trials. If we detect any artefact, we ask participants to repeat the recording with the application. Therefore, we tried to minimise motion artefacts during the recording phase to provide the application algorithm with the most cleaned PPG signal. However, this procedure is not the most practical in daily life recording, so smartphone applications with efficient motion-resistant algorithms are required. Second, we have considered the source of the PPG signal. The periodic systolic and diastolic heart activity causes blood to enter arteries and return from veins, forming the blood circulation system. The spreading of heart pulsation along arterial blood vessels and the blood flow to peripherical arteries form the PPG signal. Therefore, the BBI derived from PPG signal lag relative to the RRI derived from ECG and, consequently, the computation of HRV parameters from BBI might produce errors. This could be a reason for the non-perfect correspondence between HRV parameters obtained from the two methods. Even though we must remember this asynchronism between the smartphone PPG and ECG signal, the error is negligible, and the time-domain HRV index seems not to be affected as much (Gil et al., 2010; Selvaraj et al., 2008). However, since the biological processes that led to a PPG signal are different from those involved in an ECG signal, we have to consider that the HRV parameters computed by PPG are also affected by many other body sources of variability (e.g., blood pressure, chronic disease, etc.) (Yuda et al., 2020). Third, we only tested the application on an Android environment, so our findings were not generalizable to iOS smartphones. However, two commercial apps are validated with iOS systems (i.e., "HRV4Training" and "Welltory"). To our knowledge, this is the first study that tested the validity and reliability of a commercial Android application. Finally, 86% of our sample was composed of females. Although there are no physiological mechanisms by which biological sex should affect the comparison between the two recording systems, the current study did not have adequate homogeneity between men and women to test it, as it was beyond the scope of the current study.

Despite the limitations, this study provides a reliable and valid tool to remotely and freely measure rMSSD parameters using an Android smartphone. Moreover, using a robust statistical approach to compare rMSSD parameters (e.g., Bland-Altman ratio) increases our results' validity

(Vagedes 2013). Following the increase in the use and request of mobile technologies in healthcare services, the “Heart Rate Variability HRV Camera” application could offer an accessible and non-invasive alternative to assess HRV for clinical or research purposes. In the next chapter, we explore the measurement of rMSSD during the peripartum period using this application to explore the relationship between HRV and depressive symptoms during pregnancy and after childbirth.

3. Study 2: Prepartum Heart Rate Variability as a predictor of postpartum depression

Study 2 of the paper "Singh Solorzano, C., Violani, C., Grano, C., (2022). Pre-partum HRV as a predictor of postpartum depression: The potential use of a smartphone application for physiological recordings. Journal of Affective Disorders, 319, 172-180. https://doi.org/10.1016/j.jad.2022.09.056"

3.1. Introduction

Peripartum depressive symptoms are a subset of major depressive disorder in which the "onset of mood symptoms occurs during pregnancy or in the four weeks following delivery" (American Psychiatric Association, 2013). Recent meta-analyses reported that the prevalence of women affected by depression during gestation is about 12% (Woody et al., 2017), and the overall rate increased for postpartum depression (PPD) to 17% (Shorey et al., 2018). PPD can also occur later than four weeks after the delivery, and a trend of increasing prevalence was reported from a few days to more than one year after childbirth (Shorey et al., 2018; Stewart & Vigod, 2016). Moreover, PPD was associated with detrimental effects on both mother and newborn infant's mental and physical health and disruptions in maternal-infant interactions (O'Hara & McCabe, 2013; Slomian et al., 2019). Mothers with PPD often showed increased negative emotionality and reduced newborn care activities (O'Hara & McCabe, 2013; Shorey et al., 2018; Slomian et al., 2019). Reduced maternal caretaking activities (e.g., reduced breastfeeding, decreased bonding and engagement with the infant) can have a negative impact on the development and health of the child (O'Hara & McCabe, 2013; Webber & Benedict, 2019). Some studies reported that children of depressed mothers are more likely to develop cognitive, behavioural, and health-related problems, which may persist into later childhood and adolescence (O'Hara & McCabe, 2013; Slomian et al., 2019). Therefore, identifying risk factors for developing PPD is vital for preventing and early treating depression in pregnant women and promoting the newborn's well-being. One potential biomarker of the development of PPD might be the autonomous nervous system (ANS) function.

The ANS is implicated in heart activity through the influence of sympathetic nervous system (SNS) activity and parasympathetic nervous system (PNS) (Thayer & Sternberg, 2006). Heart rate variability (HRV) is the variation in time between heartbeats and reflects the interaction between the SNS and PNS branches of the heart (Khazan, 2013; Malik et al., 1996). Since the vagus nerve's parasympathetic fibres directly innervate the heart and predominately affect cardiac activity with the withdrawal or stimulation of vagal input (Malik et al., 1996; Porges, 1995a; Thayer et al., 2012), resting vagally regulated HRV is a reliable parameter to measure PNS activity (Khazan, 2013; Thayer & Sternberg, 2006). The ANS is in part implicated in the stress response system (Thayer et al., 2012;

Thayer & Lane, 2000), and a dysfunctional parasympathetic activity might facilitate the fail in the provision of adaptive response to stressors that, in turn, can lead to the onset of emotional disorders (Porges, 1995a; Thayer & Lane, 2000). For instance, a recent meta-analysis reported lower resting HRV in depressed subjects than healthy controls (Koch et al., 2019), and a series of studies indicated that the HRV parameters are important diagnostic indexes of depression severity (Hartmann et al., 2019) and promising biomarkers of vulnerability to the onset of depression (Carnevali et al., 2018; Dell'Acqua et al., 2020). Moreover, HRV biofeedback is a valid and reliable intervention for improving depressive symptomatology nowadays (Pizzoli et al., 2021).

During pregnancy, the activity of maternal ANS varies greatly and adapts to the new physiological requests of the developing foetus (Soma-Pillay et al., 2016). Literature reports a normative increase in PNS activity and a decrease in SNS activity during the first trimester of pregnancy; however, the second and third trimester is characterised by an increase in SNS activity and a decrease in PNS activity (Fu, 2018; Kuo et al., 2000; Matsuo et al., 2007; Stein et al., 1999). In the weeks following the birthchild, the ANS activity should be restored to pre-pregnancy levels (Brown et al., 2021; Yeh et al., 2009). In addition to the specific autonomic adaptations as pregnancy progresses, ANS dysfunctional changes are associated with depressive symptoms in the prepartum period (Ecklund-Flores et al., 2017; Rouleau et al., 2016; Shah et al., 2020; Shea et al., 2008). For instance, reduced parasympathetic activity and sympathovagal imbalance have been reported in pregnant women with depressive symptoms (Shah et al., 2020; Shea et al., 2008), and a reduced HRV was indicated as a potential mechanism in the onset of gestational hypertension (Rouleau et al., 2016) and correlated with high birth weight in the newborns of depressed women (Ecklund-Flores et al., 2017). Moreover, few trials showed that HRV biofeedback might be a promising intervention to reduce depressive symptoms during the peripartum period (Beckham et al., 2013; Kudo et al., 2014). As pregnancy could be a stressful condition (Obrochta et al., 2020), the resulting potential decrease of parasympathetic tone might boost the normative decrease of PNS activity in late pregnancy or avoid the normal parasympathetic restore after childbirth (Brown et al., 2021). This condition could make pregnant women more vulnerable to the development of emotional disorders, such as depressive symptoms. However, the potential role of vagally regulated HRV at rest in the prepartum period as a biomarker of the development of postpartum depression is still unknown.

In the last years, mobile technologies have supported many women in dealing better with physical and mental difficulties during pregnancy and improving their well-being (Chan & Chen, 2019; Iyawa et al., 2021). The COVID-19 pandemic has increased the use of mobile health (mHealth) applications because of their flexibility, convenience, and low cost in remote health monitoring. For instance, recent studies showed the usefulness of mHealth applications in monitoring the

psychophysiological well-being of pregnant women during the COVID-19 pandemic (Niela-Vilen et al., 2021). The smartphone's camera could be an excellent sensor to quickly record cardiac activity with low equipment requirements through contact photoplethysmography (PPG) technology (De Ridder et al., 2018). Recent studies using PPG smartphone applications confirm the well-known relationship between HRV and mental health in the general population (Liu et al., 2020a).

Based on these premises, this study aimed to investigate the role of a time-domain HRV index (i.e., root mean square of successive difference between NN intervals or rMSSD) as a predictor of the onset of postpartum depression. This time-domain index was chosen because it is one of the most appropriate HRV measures for short-term recordings (Chen et al., 2020; Malik et al., 1996; Munoz et al., 2015), is widely used in literature (Khazan, 2013; Koch et al., 2019), reflects cardiac vagal influence, and is less influenced to variability in respiration than other HRV indices (Penttilä et al., 2001; Thayer et al., 2012). In study 1, we assessed the reliability and accuracy of a free smartphone application for recording rMSSD compared with an electrocardiogram (ECG). Therefore, we assess whether rMSSD measured via PPG smartphone application in women during pregnancy could be a potential biomarker of the development of depression in the postpartum period. In line with existing studies on the general population, we hypothesised lower prepartum rMSSD as a predictor of depressive symptoms after childbirth.

3.2. Methods and Materials

3.2.1. Participants

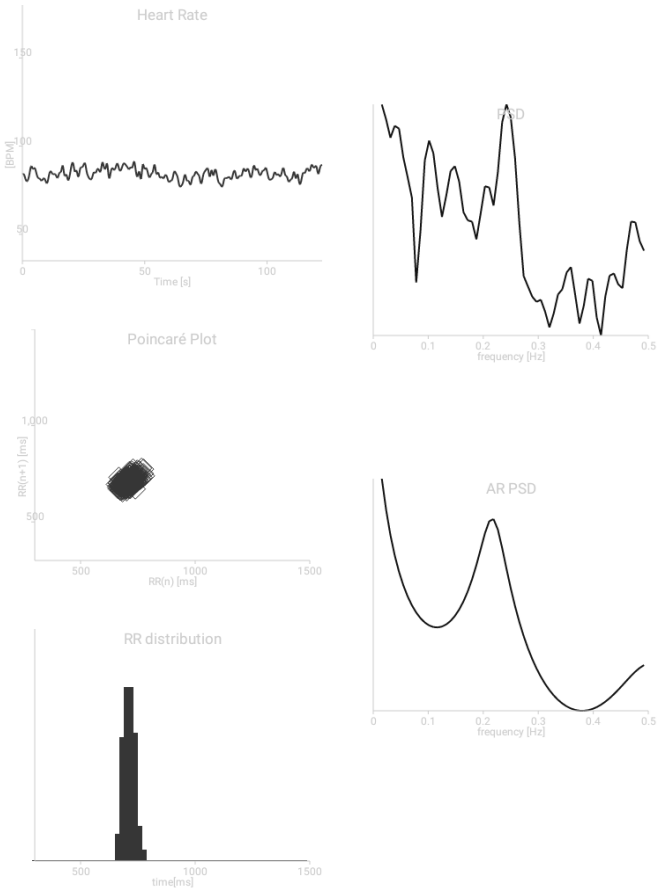
A total of 135 Italian pregnant women (mean age = 31.39 years, standard deviation = 4.27) participated in the prepartum and postpartum assessments. Since the study was conducted during the recent COVID-19 pandemic in Italy (July 2020 – June 2021), participants were recruited from different social media platforms and websites. All pregnant subjects had a singleton fetus. Inclusion criteria were to be at least 18 years of age, to be able to complete questionnaires in Italian and to be in the second or third trimester of pregnancy. Exclusion criteria were substance abuse during pregnancy, current cardiovascular or metabolic disease diagnosis, and current diagnosis or past history of major depression, psychotic disorders, or other severe psychiatric illness. This study was approved by the Institution Review Board of the Psychology Department, Sapienza University of Rome (Prot. n. 0000024), and informed consent was obtained for each participant.

3.2.2. Procedures

Pregnant women were asked to participate in two sessions. The first session took place in the second or third trimester of pregnancy, and the second section in postpartum (one month after

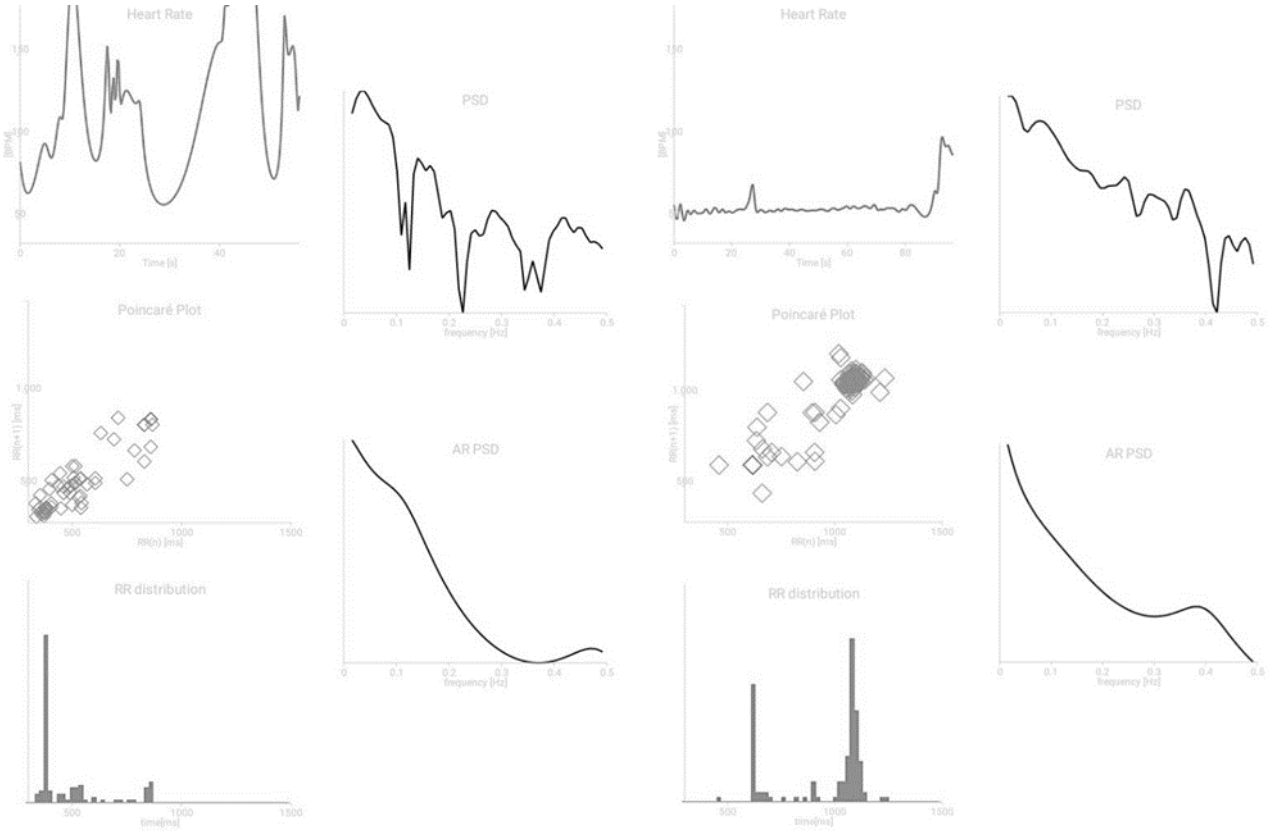
delivery). After explaining the entire study, participants read and signed an online informed consent. Participants were provided with instructions to download the application on their smartphones and performed a contact PPG registration of good quality without movement artefacts. Then, pregnant women were asked to carry out the HRV assessment with the "Heart Rate Variability HRV Camera" smartphone application. Participants were requested to avoid caffeine on the same day as the physiologic measurements. The HRV recording had to take place in the morning hours (9:00 am to 1:00 pm) and consisted of a 2-minute recording in a sitting position with spontaneous breathing patterns throughout. Participants were requested to collect two HRV measurements and send them to a researcher for instant feedback about the quality of the registrations. The application did not have a system to inform the user whether the collected raw data were of sufficient quality or not. Therefore, a visual inspection of the graphs provided by the app (*Figure 3.1.*) was carried out by the researcher to identify signals with high noise or movement artefact (i.e., low-quality physiological registrations) through the analysis of the distributions of values in heart rate plot and the Poincaré plot (Chua et al., 2008; Stein et al., 2005). In the plot with the course of heart rate over time, linear and quasi-periodic waves without values outside the biologically plausible range of 20-220 beats per minute must be seen in the signal. In the Poincaré plot, an ellipsoid or mildly comet-shaped distribution of points aligned at the centre of the plot must be seen in the signal. An example of a good quality signal is shown in *Figure 3.1*.

Figure 3.1. An example of graphs plotted by "Heart Rate Variable HRV Camera" after the end of a two-minute physiological registration with good quality. The application reported: a plot with the course of heart rate over time (at the top left); the Poincaré plot (at the middle left); a plot with the distribution of beat-to-beat intervals over time (at the bottom left); a power spectrum density graph of the HRV (at the top right); a power spectrum density graph of the HRV obtained by autoregressive method (at the bottom right).



If the measured signal was of low quality, participants were asked to repeat the experiment after a pause of 5 minutes. Examples of two bad quality signals have shown in *Figure 3.2*. If the measurement had a bad quality, participants were provided with further suggestions to achieve a good registration and were asked to repeat the HRV measurement. After collecting a good quality physiological signal, participants were able to complete the online questionnaire. Women were asked to complete a second online questionnaire one month after giving birth.

Figure 3.2. Two examples of graphs plotted by "Heart Rate Variable HRV Camera" after the end of a two-minute physiological registration with bad quality. At left is an example of a PPG signal with few movement artefacts throughout the registration, as indicated by an irregular plot with the course of heart rate over time and an unreliable Poincaré plot. At the right is an example of a PPG registration in which the smartphone did not correctly collect the cardiac signal, as indicated by a quasi-linear plot with the course of heart rate over time and an unreliable Poincaré plot.



3.2.3. Measures

Predictor variable: rMSSD

The root mean square of successive difference of NN intervals (i.e., rMSSD) expressed in ms was computed by the smartphone application using the standard formulas (Jokic et al., 2016; Malik et al., 1996). rMSSD has been used previously in many studies about stress and mental well-being in the pregnant population as an indicator of cardiac parasympathetic activity (Braeken et al., 2017; R. L. Brown et al., 2021; Shea et al., 2008; Tung et al., 2021). Higher scores of rMSSD indicated higher vagally regulated HRV.

Outcome variable: Depressive symptoms

The Edinburgh Postnatal Depression Scale, EDPS (Cox et al., 1987), is a 10-item self-report scale that assesses the levels of depressive symptoms in the previous week. Responses to each statement are scored on a 4-point Likert scale (from 0 to 3). The total score ranged from 0 to 30, with higher scores indicating a greater frequency of depressive symptoms. It has been shown to be a reliable instrument for screening depressive symptoms during pregnancy and the postnatal period (Bergink et al., 2011; Levis, Negeri, et al., 2020; Sit & Wisner, 2009). The Italian validation study of the questionnaire suggested a clinical cut-off of 12 to identify the presence of postpartum depression (Benvenuti et al., 1999). In the current study, Cronbach's alphas were $\alpha = 0.85$ (prepartum assessment) and $\alpha = 0.86$ (postpartum assessment).

Descriptive variables and covariates

Participants' age, education, annual income, marital status, gestational age (in months), and parity were recorded. Education was classified into six groups ranging from low to high levels of education, whereas annual income was classified into five groups ranging from low to higher income per year. Marital status, gestational age, and parity were measured as binary variables (married/cohabiting, second/third trimester, and primiparous/multiparous, respectively). Body mass index (BMI) was calculated based on the participant's self-reported height and weight.

3.2.4. Statistical analysis

Descriptive data are expressed as means ± standard deviations (SD) or as the number of participants with the percentage in parenthesis. Summary scores were created for EDPS, and paired *t*-test was used to explore the change in depressive symptoms from the prepartum to the postpartum period. The prepartum rMSSD was logarithmically transformed before statistical analyses to normalise its distribution. Association between depressive symptoms at prepartum and postpartum and rMSSD at prepartum were assessed using Pearson's *r*, and all results are reported as Pearson's *r* and *p*-value. A hierarchical linear regression model (P. Cohen et al., 2014; Field, 2009) was built to assess the relationship between prepartum rMSSD (as the predictor variable) and postpartum depressive symptoms. Age, education, pregnancy trimester, prepartum BMI, and depressive symptoms during pregnancy were entered into the model as covariates (Step 1 of the model). These factors were included as covariates since they are known to be associated with postpartum depression (Guintivano et al., 2018; Hutchens & Kearney, 2020). Prepartum rMSSD was then entered at Step 2 to see if it explained any additional variance over and above covariates (P. Cohen et al., 2014). Variance inflation factor (VIF) values and tolerance values were generated for all regression models to assess multicollinearity, and the assumption was not violated (VIF <10 and tolerance >0.1). Results are presented as standardised beta coefficients. The significance level was set to $p < 0.05$, with a precise *p*-value reported for all test results. Statistical analyses were conducted using IBM SPSS Statistic version 27 (SPSS Inc., Armonk, NY, USA).

3.3. Results

General descriptive characteristics of the sample are shown in *Table 3.1*. Pregnant women had an age range between 19 and 41 years. The majority of the participant had a university-level education or higher (59.3%), had an annual income between 15,000 and 55,000 € (75.5%) and were in their first pregnancy (70.4%). The average BMI during pregnancy was 25.59 ± 4.50 kg/m^2 with a range of 16.71 to 39.66 kg/m^2.

Table 3.1. Demographic characteristics of the sample (N = 135)

Variable	Mean ± SD or N (%)
Age	31.39 ± 4.27
Education	
Middle School	6 (4.4)
High School	49 (36.3)
Bachelor	29 (21.6)
Master's degree	33 (24.4)
Post-lauream specialisation courses	12 (8.9)
PhD	6 (4.4)
Marital status	
Married	67 (49.6)
Cohabiting	68 (50.4)
Annual income	
< 15,000 €	22 (16.3)
15,000 – 28,000 €	52 (38.5)
28,001 – 55,000 €	50 (37.0)
55,001 – 75,000 €	6 (4.5)
> 75,000 €	5 (3.7)
Pregnancy Trimester (T1)	
Second trimester (4^{th}, $5^{th,}$ and 6^{th} month)	59 (43.7)
Third trimester (7^{th}, $8^{th,}$ and 9^{th} month)	76 (56.3)
Parity status	
Primiparous	95 (70.4)
Multiparous	40 (29.6)
BMI	
BMI before the pregnancy	23.07 ± 4.31
Prepartum BMI	25.59 ± 4.50
Postpartum BMI	24.63 ± 4.79

Table 3.2. reported the means and standard deviations of the main variables of the study. Depressive symptoms did not change significantly over peripartum period (t = 0.486, p =0.628). Prepartum depressive scores ranged from 0 to 22, with 20% of women above the cut-off. Postpartum

depressive scores ranged from 0 to 27, with 15.6% of women above the cut-off. The 6.7% of the participants were above the cut-off at both prepartum and postpartum. Table 3.2 also shows the correlation between prepartum rMSSD and peripartum depressive symptoms. Prepartum rMSSD was significantly and negatively correlated both with prepartum depression (r = -0.448, $p < 0.001$) and postpartum depression (r = -0.400, $p < 0.001$). A positive significant correlation was found between depressive symptoms at prepartum and postpartum (r = 0.510, $p < 0.001$).

Table 3.2. Correlation between variables of the present study (N = 135).

Variable	Mean	SD	1	2	3
1. Prepartum rMSSD	27.16	12.25	-		
2. Prepartum depressive symptoms	6.96	4.99	-0.448*	-	
3. Postpartum depressive symptoms	6.75	5.03	-0.400*	0.510*	-

* $p < 0.01$

Table 3.3. presents the results of the hierarchical linear regression model examining the association between rMSSD during pregnancy and postpartum depressive symptoms. In Step 1, all covariates were added to the model, and only prepartum depressive symptoms predicted postpartum depressive symptoms (β = 0.555, $p < 0.001$). In Step 2, prepartum depressive symptoms were still associated with postpartum depression (β = 0.447, $p < 0.001$), but also a reduction of prepartum rMSSD was a significant predictor of the development of depressive symptoms after the delivery (β = -0.217, p = 0.010). The final model accounted for 30% of the variance in postpartum depression.

Table 3.3. Regression analyses with postpartum depressive symptoms as dependent variable (N = 135).

Predictor variable	B	S.E.	95% CI	β	*p*
Step 1					
Age	0.123	0.096	[-0.068; 0.314]	0.105	0.204
Education	0.476	0.333	[-0.182; 1.134]	0.117	0.155
Pregnancy trimester	-0.963	0.791	[-2.529; 0.603]	-0.095	0.226
Prepartum BMI	-0.015	0.086	[-0.185; 0.155]	-0.014	0.860
Prepartum depressive symptoms	0.560	0.077	[0.407; 0.713]	0.555	**<0.001**
Step 2					
Age	0.082	0.096	[-0.107; 0.272]	0.070	0.393
Education	0.549	0.327	[-0.097; 1.195]	0.135	0.095
Pregnancy trimester	-1.031	0.775	[-2.564; 0.502]	-0.102	0.186
Prepartum BMI	-0.006	0.084	[-0.172; 0.161]	-0.005	0.947

Prepartum depressive symptoms	0.451	0.086	[0.280; 0.622]	0.447	**<0.001**
Prepartum lnrMSSD	-2.670	1.025	[-4.698; -0.642]	-0.217	**<0.05**

Notes. Bold font indicates statistical significance ($p < 0.05$). Step 1: $F(5,129) = 10.772$, $p < 0.001$, *Adj*. $R^2 = 0.267$. Step 2: $F(6,128) = 10.511$, $p < 0.001$, *Adj*. $R^2 = 0.299$; $R^2_{change} = 0.036$, $p = 0.010$.

3.4. Discussion and Conclusion

This study explored the link between prepartum HRV and postpartum depression. Using "Heart Rate Variability HRV Camera" smartphone application in the measure of short-term rMSSD, we assessed the role of this vagal time-domain HRV index during pregnancy as a predictor of depressive symptoms after childbirth. The results indicated that lower levels of rMSSD during the prepartum period predicted higher levels of depressive symptoms in the postpartum period. To our knowledge, these findings are the first to assess the role of prepartum rMSSD as a predictor of postpartum depression; moreover, the study supports the use of smartphone technologies as valuable tools in the monitoring and self-management of women in the peripartum period.

The study evidenced that prepartum rMSSD was negatively associated with depressive symptoms before and after the delivery. The association between depressive symptoms and vagal withdrawal was corroborated by previous reports (Ecklund-Flores et al., 2017; Rouleau et al., 2016; Shah et al., 2020; Shea et al., 2008), although measures were evaluated only during pregnancy and not in the postpartum. Two of these studies (Ecklund-Flores et al., 2017; Shah et al., 2020) found a significant correlation between rMSSD and depressive symptoms. In contrast, Shea and colleagues (2008) did not find a significant association between rMSSD and depressive symptoms during pregnancy. However, a reduced parasympathetic activity measured with other HRV indices (i.e., lower levels of SDNN, SDANN – the standard deviation of the averages of NN interval in all 5 minutes segments of the entire recording – and higher levels of LF/HF – low-frequency/high-frequency ratio – during the sleeping hours) was associated with higher levels of depressive symptoms (Shea et al., 2008). Rouleau and colleagues (2016) used a different index to examine the parasympathetic influence on the heart (i.e., the high-frequency component of HRV, HF), finding an association between depressive symptoms and lower vagal activity. A recent study reported that other mental health disorders, but not depressive symptoms, were associated with altered PNS activity in late pregnancy (M. C. Kimmel et al., 2021).

Finally and most importantly, we found that prepartum rMSSD was a significant predictor of postpartum depressive symptoms. Moreover, the predictive power of this HRV time-domain index remained significant also when controlling for women's prepartum depressive symptoms and other potential covariates. Our findings align with previous evidence showing that initial levels of depressive symptoms strongly increase the risk for depressive symptoms after childbirth (Guintivano

et al., 2018) and, for the first time, highlight the role of rMSSD collected during pregnancy in the onset of depressive symptoms in the postpartum. Importantly, a large proportion of women who reported clinically significant depressive symptoms in postpartum did not report clinically significant prepartum depressive symptoms, indicating that rMSSD could be both an indicator and a predictor of depressive symptoms after childbirth. Therefore, the prepartum rMSSD assessment may also be a useful tool to predict who will have depressive symptoms in order to improve women's mental health while pregnant.

Some studies reported reduced resting HRV as a potential vulnerability biomarker to depression in the non-pregnant population (Carnevali et al., 2018; Dell'Acqua et al., 2020; Jandackova et al., 2016). For instance, the most recent study showed that individuals with dysphoria and past depression had reduced cardiac vagal activity compared to the control group with no current or history of depressive symptoms (Dell'Acqua et al., 2020). Moreover, longitudinally studies reported that reduced rMSSD was associated with depressive symptoms over two years after the first assessment (Carnevali et al., 2018) and that higher HRV was a significant predictor of a lower likelihood of depressive symptoms ten years later (Jandackova et al., 2016). We extend these findings to the pregnant population showing that a reduced resting vagal tone during the second and third trimester of pregnancy could be a vulnerability factor to depressive symptoms at one month postpartum. This literature and our study align with the neurovisceral integration model and the relationship between PNS and the prefrontal cortex (PFC) (Beauchaine & Thayer, 2015). Indeed, PFC was associated with inhibition, control and executive functions that are altered in patients with different psychiatric diagnoses, including major depressive disorder (Mulcahy et al., 2019; Zhou et al., 2020). Since HRV is also a peripherical marker of prefrontal cortex functioning (Beauchaine & Thayer, 2015), it could be an important index for investigating the vulnerability to psychopathology, such as depression. Moreover, during the last two trimesters of pregnancy, there is a normative and adaptive decrease in PNS activity (Kuo et al., 2000; Matsuo et al., 2007) that could be boosted by psychological stress and emotional difficulties during pregnancy (Brown et al., 2021). In depressed pregnant women, dysfunction of a few prefrontal cortex areas has been evidenced (Cheng et al., 2020) that HRV may peripherally capture and express as a dysfunctional parasympathetic activity.

Some limitations of the study need to be acknowledged. First, although literature reported an excellent agreement between ECG and smartphone PPG measurements (Christien Li et al., 2019), few artefacts (e.g., hand movements) might corrupt the physiological signal registered with a smartphone and lead to an instrument measurement error. Second, we considered only rMSSD among all available HRV indexes, so we do not have a complete framework of the relationship between HRV and peripartum depression. Other potentially useful parasympathetic indicators were not available

through the smartphone application (e.g., Coefficient of Variance of RR intervals, CVRR; the number of differences NN intervals greater than 50 m, NN50) or did not show good reliability when compared with the same indicators derived from the ECG recording (e.g., SDNN or HF). Therefore, we preferred to focus only on the rMSSD index since other studies showed its reliability in short-term smartphone collection (Chen et al., 2020; Guede-Fernández et al., 2020; Plews et al., 2017). Third, we assessed depressive symptoms with a self-report questionnaire. Future studies may assess peripartum depression through other clinical tools, such as structured clinical interviews. Fourth, more than half of the women in our sample (59.3%) had a tertiary education, which is similar to the percentages of the female European population (52%), although lower than Italian ones (35%) (OECD, 2021). Future studies may consider more heterogeneous samples with particular attention to including more participants with primary or secondary educational levels as the highest level attained.

Despite the limitations, this study highlights the potential role of the rMSSD index as a valuable, economic, and easily used clinical tool that can identify pregnant women with a higher risk of developing depressive symptoms in the postpartum period. Moreover, using a smartphone application supports findings on the effectiveness of mobile applications for self-management during pregnancy to monitor women's mental and physical health (Iyawa et al., 2021).

Overall, this study showed that a reduced vagal tone, indexed by lower rMSSD, during pregnancy (i.e., second and third trimester) was a predictor of depressive symptoms at one month postpartum. Thus, our findings suggest that the prepartum period offers an important timeframe to implement preventive intervention on vagal modulation to avoid its influence on the prospective generation of postpartum depressive symptoms. Indeed, literature reported increasing evidence of the role of HRV biofeedback in the treatment and prevention of depression (Beckham et al., 2013; Kudo et al., 2014; Pizzoli et al., 2021). Moreover, using a smartphone application to collect rMSSD might promote the remote monitoring of the psychophysiological well-being of pregnant women and the potential implementation of smartphone-delivered intervention for peripartum depression.

4. Study 3: Predicting postpartum depressive symptoms by evaluating self-report autonomic nervous system reactivity during pregnancy

Study of the paper "**Singh Solorzano, C.**, Grano, C. (under review, Journal of Psychosomatic Research). Predicting postpartum depressive symptoms by evaluating self-report autonomic nervous system reactivity during pregnancy."

4.1. Introduction

Depressive symptoms are common in the peripartum period affecting about 20.7% of women during pregnancy (Yin et al., 2021) and 17.2% after childbirth (Wang et al., 2021). The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) classified peripartum depression as depressive symptoms occurring during pregnancy or within four weeks following delivery (American Psychiatric Association, 2013). Postpartum depression (PPD) might result in negative consequences for both mother and infant's well-being and impaired mother-infant interaction (Slomian et al., 2019). For instance, PPD may negatively affect maternal caretaking activities and the mother-child relationship, which in turn may lead to cognitive, behavioural and emotional consequences for the mental health of the child in the short and long-term period (Murray et al., 2011; O'Hara & McCabe, 2013; Verkuijl et al., 2014). Therefore, understanding risk factors for PPD is crucial to prevent adverse health and psychosocial effects on women and minimise poor long-term psychological outcomes in children. One potential marker of the development of PPD might be the autonomous nervous system (ANS) function.

The ANS plays a crucial role in maintaining homeostasis through afferent and efferent neural pathways that allow the coordination between brain and body in threat and safety situations (Jänig, 2006; Kolacz et al., 2019). Polyvagal Theory (Porges, 1995b, 2001, 2007) suggests that mammalian ANS has three hierarchical organised systems: ventral vagal complex (VVC), the sympathetic nervous system (SNS), and the dorsal vagal complex (DVC) (Porges & Carter, 2012). The three subsystems of ANS have different neuroanatomical pathways that lead to peculiar behavioural responses to challenges of the organism. The newest phylogenetic subsystem (VVC) comprises myelinated vagal fibres originating in the nucleus ambiguous that, through the coordination of striated face and head muscles and the regulation of the organs above the diagraphs, promote social expression and engagement (Kolacz et al., 2019; Porges & Carter, 2012; Porges, 2007). The SNS is related to fight-or-flight behavioural response, and its efferent originating in the spinal cord innervates both organs above and below the diaphragm (Porges & Carter, 2012). In the DVC, the unmyelinated vagal efferent originating in the dorsal nucleus of the vagus primary innervates organs below the diaphragm with few fibres terminating on the heart's sinoatrial node, and its primary behavioural

function is immobilisation (Kolacz et al., 2019; Porges & Carter, 2012). When the VVC state is activated in safe conditions, there is an adaptive autonomic balance between SNS and DVC (Porges, 2001). However, when the VVC becomes ineffective (e.g., in threat conditions), the two more phylogenetical archaic subsystems are triggered. The SNS led the organism to actively cope with the environmental challenge through defensive mobilisation behaviour responses (e.g., fight-or-flight, (Porges & Carter, 2012; Porges, 2007). The DVC, in the case of extreme stress or hazardous conditions, led the organisms to an immobilisation response and conservation of energy through inhibition of metabolic function and passive behavioural responses (e.g., freezing or fainting, (J. Kolacz & Porges, 2018; S.W. Porges, 2001). A chronic dampened function of VVC and the resultant mobilisation (SNS) and immobilisation (DVC) defensive states in non-threat situations provide the framework for the onset of mental health disorders (Kolacz et al., 2019; Kolacz, Dale, et al., 2020). Many studies and meta-analyses reported a significant relationship between physiological autonomic dysregulation and depressive symptoms (Hartmann et al., 2019; Koch et al., 2019; Shinba, 2017). As regards self-reported measures, Cabrera and colleagues (2018) reported that destabilised self-reported ANS reactivity was associated with self-reported mental psychiatric disorders in the general population. A recent study corroborated this finding showing the mediational role of dysfunctional self-reported ANS activity in the relationship between prior adversity experiences and mental health in the general population (i.e., depressive symptoms, post-traumatic stress disorder symptoms, and COVID-19-related worry) (Kolacz, Dale, et al., 2020).

The ANS activity varies during pregnancy to maintain the body's healthy homeostasis and adapt to the new physiological requests of the growing fetus (Abbas et al., 2005; Brooks et al., 2020). Several studies showed an increase in basal heart rate and a predominance of sympathetic activity during the second and third trimesters of pregnancy (Fu, 2018; Kuo et al., 2000; Volman et al., 2007) and the restoration of pre-pregnancy ASN activity in the weeks following delivery (R. L. Brown et al., 2021; Yeh et al., 2009). Dysfunctional changes in ANS during pregnancy have been investigated in relation to depressive symptoms (M. C. Kimmel et al., 2021; Kishan et al., 2021; Shah et al., 2020; Shea et al., 2008). For instance, higher sympathetic reactivity and lower vagal modulation during pregnancy were related to depressive symptoms in the peripartum period (Kishan et al., 2021; Shah et al., 2020; Shea et al., 2008), though Kimmel and colleagues (2021) did not find a significant relationship between ANS activity and depressive symptoms in late pregnancy. No studies investigated the relationship between self-reported autonomic function and depressive symptoms during pregnancy and of self-reported autonomic function as a potential predictor of postpartum depression. Given the evidence of ANS dysregulation in the pathophysiological mechanisms of depression in the general population (Hartmann et al., 2019; Kolacz, Dale, et al., 2020) and the

normative adjustments of ANS during pregnancy (Brooks et al., 2020), we argue that a dysfunctional and maladaptive autonomic response in this period can increase the likelihood of emotional disorders concurrently and after the childbirth (Brown et al., 2021; Porges, 1995b; Thayer & Lane, 2000).

Based on this premise, this study aimed to examine the impact of prepartum self-reported autonomic reactivity on the development of depressive symptoms during pregnancy and after childbirth. In particular, we hypothesised that a dysfunctional self-reported autonomic reactivity during pregnancy would predict higher prepartum and postpartum depressive symptomatology.

4.2. Methods and Materials

4.2.1. Participants

A total of 287 pregnant women volunteered to participate in a two-phase longitudinal study after providing their online informed consent. Data were collected during the COVID-19 pandemic in Italy (July 2020 – January 2022). Data from women who withdrew from the study in the second phase were omitted from the final analyses. Therefore, the final sample was composed of 170 women. Eligible participants included women over 18 starting from the second trimester of pregnancy who can complete questionnaires in Italian. Exclusion criteria were self-reported substance abuse during pregnancy, current cardiovascular or metabolic disease diagnosis, current diagnosis or history of major depression, psychotic disorders, or other severe psychiatric illness. This study was approved by the Institution Review Board of the Psychology Department, Sapienza University of Rome (Prot. n. 0000024).

4.2.2. Procedures

Pregnant women were asked to participate in two sessions. The first session took place in the second or third trimester of pregnancy, whereas the second section took place in the postpartum period (one month after delivery). Pregnant women were recruited through different social media platforms and blogs. After explaining the entire study, participants read and signed an online informed consent. Then, they completed an online questionnaire. After childbirth, participants were contacted again by email or social media and asked to complete a second online questionnaire.

4.2.3. Measures

Predictor variable: self-reported autonomic reactivity

Prepartum self-reported experience of the autonomic nervous system reactivity was assessed using the Italian version of the Body Perception Questionnaire Short Form (BPQ – SF) (Cabrera et al., 2018; Cerritelli et al., 2021). The autonomic reactivity domain of the questionnaire (20 items)

included the Supradiaphragmatic Reactivity Subscale (15 items), which reflects the control of ventral vagal complex (VVC) on visceral organs above the diaphragm (e.g., "My heart often beats irregularly"), and the Subdiaphragmatic Reactivity Subscale (6 items), which reflect the control of dorsal vagal complex on organs below the diaphragm (e.g., "After eating I have digestive problems") (Cabrera et al., 2018; Kolacz et al., 2018; Porges, 2001). One item ("I feel like vomiting") is included in the score of both subscales (Kolacz et al., 2018). Items of the scales measured the frequency of each sensation on a 5-point Likert-type scale ranging from 1 ("never") to 5 ("always"). The total score for each subscale was obtained by the sum of the items. Higher scores on both subscales indicate destabilised autonomic reactivity. The BPQ-SF showed good psychometric properties and consistent factors structure across different samples (Cabrera et al., 2018; Cerritelli et al., 2021; N. Wang et al., 2020) and high scores for BPQ – SF subscales were previously associated with lower flexible respiratory sinus arrhythmia (RSA) (Kolacz et al., 2022) and the presence of mental health disorders (Cabrera et al., 2018; Kolacz, Dale, et al., 2020). In the current sample, Cronbach's alphas were $\alpha = 0.86$ (Supradiaphragmatic Reactivity Subscale) and $\alpha = 0.76$ (Subdiaphragmatic Reactivity Subscale).

Outcome variable: Depressive symptoms

Depressive symptoms were assessed using the Patient Health Questionnaire – 9 (PHQ – 9) (Kroenke et al., 2001), a widely-used measure that evaluates the frequency of depressed mood over the past two weeks using a 4-point Likert-type scale ranging from 0 ("not at all") to 3 ("nearly every day"). Total scores range from 0 to 27, with higher scores indicating more depressive symptoms. The PHQ-9 was used to assess prepartum and postpartum depression showing good sensitivity and specificity in screening for peripartum depressive symptoms, with a clinical cut-off score of 10 (Flynn et al., 2011; Gjerdincjen et al., 2009; L. Wang et al., 2021). In the current study, Cronbach alpha was $\alpha = 0.72$ at prepartum assessment and $\alpha = 0.75$ at postpartum assessment.

Descriptive variables and covariates

Participants' age, nationality, education, annual income, marital status, gestational age (in months), and parity were recorded. Education was classified into six groups ranging from low to high levels of education, whereas annual income was classified into five groups ranging from low to higher income per year. Marital status, gestational age, and parity were measured as binary variables (married/cohabiting, second/third trimester, and primiparous/multiparous, respectively). BMI was calculated based on the participant's self-reported height and weight.

4.2.4. Statistical analysis

Analyses were conducted using IBM SPSS Statistic version 27 (SPSS Inc., Armonk, NY, USA). In order to examine whether participants recruited in the prepartum assessment differed or not

from those who completed the study, independent t-tests and $\chi 2$ tests were used. Women were compared on age, education, annual income, parity, BMI, supradiaphragmatic reactivity, subdiaphragmatic reactivity and prepartum depressive symptoms. Descriptive statistics are expressed as means (M) ± standard deviations (SD) or as the number of participants (N) with the percentage in parenthesis. Summary scores were computed for Supradiaphragmatic Reactivity Subscale, Subdiaphragmatic Reactivity Subscale, and PHQ – 9. Raw total scores of autonomic reactivity subscales were transformed into T total scores as suggested by the BPQ manual for parametric analyses (Kolacz, Dale, et al., 2020; Kolacz et al., 2018; Kolacz, Hu, et al., 2020). Paired t-tests were used to explore the change in depression from the prepartum to the postpartum period. Associations between study variables were assessed using Pearson's *r*, and all results are reported as Pearson's *r* and *p*-value. Hierarchical linear regression examined the association between prepartum autonomic reactivity measured through Supradiaphragmatic and Subdiaphragmatic Reactivity Subscales and postpartum depressive symptoms. The adjusted model included age, education, annual income, parity, prepartum BMI and prepartum depressive symptoms as covariates. Variance inflation factor (VIF) values and tolerance values were generated for the regression model to assess multicollinearity, and the assumption was not violated (VIF < 10 and tolerance > 0.1). The significance level was set to $p < 0.05$, with a precise *p*-value reported for all test results.

4.3. Results

Of the initial sample of 287 pregnant women recruited for the prepartum assessment, 117 did not participate in the postpartum assessment one month later, leaving a final sample of 170, resulting in a 59.2% participation rate. Compared to the women who completed assessments at both time points, those who did not complete the postpartum assessment were more likely to have high prepartum supradiaphragmatic reactivity ($t(285) = 2.771$, $p = 0.006$). The two groups did not differ for any other variable, namely age ($t(285) = -1.229$; $p = 0.220$), education ($t(285) = -1.075$; $p = 0.283$), annual income ($\chi^2(4) = 3.088$, $p = 0.543$), parity status ($\chi^2(1) = 0108$, $p = 0.743$), BMI ($t(285) = 0.150$; $p = 0.881$), prepartum subdiaphragmatic reactivity ($t(285) = 1.387$; $p = 0.167$), and prepartum depressive symptoms ($t(285) = 1.962$; $p = 0.063$).

The sociodemographic characteristics of the sample are presented in *Table 4.1*. Pregnant women had an age range between 19 and 46 years. The large majority were Italian (97.6%), had at least a high school education (95.9%), had an annual income over 15,000 € (84.1%), and were at the first pregnancy (70.0%).

Table 4.1. Demographic characteristics of the sample (N = 170)

Variable	Mean ± SD or N (%)
Age	31.58 ± 4.23
Nationality	
Italian	166 (97.6)
Other Countries	4 (2.4)
Education	
Middle School	7 (4.1)
High School	52 (30.6)
Bachelor	45 (26.5)
Master's degree	40 (23.5)
Post-lauream specialization courses	17 (10.0)
PhD	9 (5.3)
Marital status	
Married	88 (51.8)
Cohabiting	82 (48.2)
Annual income	
< 15,000 €	27 (15.9)
15,000 – 28,000 €	64 (37.6)
28,001 – 55,000 €	62 (36.5)
55,001 – 75,000 €	11 (6.5)
> 75,000 €	6 (3.5)
Pregnancy Trimester (T1)	
Second trimester (4^{th}, $5^{th,}$ and 6^{th} month)	78 (43.7)
Third trimester (7^{th}, $8^{th,}$ and 9^{th} month)	92 (56.3)
Parity status	
Primiparous	119 (70.0)
Multiparous	51 (30.0)
BMI	
BMI before the pregnancy	23.64 ± 6.04
Prepartum BMI	25.99 ± 6.29
Postpartum BMI	25.03 ± 6.17

Depressive symptoms did not change significantly over peripartum period (t = 0.532, p =0.596). Postpartum depression scores ranged from 0 to 22, with 8.8% of women above the cut-off score of 10. Table 2 reports the correlations of the main variables of the study. Prepartum supradiaphragmatic reactivity (M = 50.49, SD = 6.79) and subdiaphragmatic reactivity (M = 52.93,

SD = 7.43) were significantly and positively associated with both prepartum (M = 6.11, SD = 3.22) and postpartum (M = 5.97, p = 3.53) depressive symptoms (*Table 4.2*).

Table 4.2. Correlation between variables of the present study (N = 170)

Variable	1	2	3	4	5	6	7	8
1. Age	-							
2. Education	.353*	-						
3. Annual income	.164^	.227*	-					
4. Parity	.206*	-.150	.061	-				
5. Prepartum BMI	-.048	-.079	-.234*	-.037	-			
6. Prepartum supradiaphragmatic reactivity	-.230*	-.161^	-.020	-.011	.002	-		
7. Prepartum subdiaphragmatic reactivity	-.152^	-.080	-.067	-.041	.018	.547*	-	
8. Prepartum depressive symptoms	-.136	-.135	-.142	.142	-.042	.438*	.453*	-
9. Postpartum depressive symptoms	-.109	-.108	-.047	-.038	-.010	.417*	.337*	.522*

Notes: ^ $p < 0.05$, ***** $p < 0.01$

Table 4.3. presents the results of the hierarchical linear regression model that examined the association between autonomic reactivity during pregnancy and postpartum depressive symptoms. In Step 1, all covariates were added to the model, and only prepartum depressive symptoms were significantly associated with postpartum depressive symptoms (β = 0.540, $p < 0.001$). In Step 2, prepartum depressive symptoms were still associated with postpartum depression (β = 0.438, $p < 0.001$), but also an increase in prepartum supradiaphragmatic reactivity was a significant predictor of the development of depressive symptoms after the delivery (β = 0.215, $p = 0.009$). The final model accounted for 29% of the variance in postpartum depression, with a significant change in explained variance from Step 1 to Step 2 (R^2 change = 0.039, p = 0.011). In addition, the accounted variance in postpartum depressive symptoms was higher when both depressive symptoms and autonomic nervous

system reactivity subscales during pregnancy were considered than when only prepartum depressive symptoms (26%) or only prepartum autonomic nervous reactivity subscales were included (16%).

Moreover, we re-run the same regression analyses considering only women below the PHQ-9 clinical cut-off at prepartum (N=147). Results of the regression analysis still showed a significant change in explained variance from Step 1 to Step 2 (R^2 change = 0.054, p = 0.008), indicating that self-reported supradiaphragmatic reactivity subscale significantly contributed to predicting postpartum depressive symptomatology also in those women who had subthreshold symptoms of depression during pregnancy.

Table 4.3. Regression analyses with postpartum depressive symptoms as the dependent variable (N = 170).

Predictor variable	**B**	**SE.**	**95% CI**	**β**	***P***
Step 1					
Age	-0.003	0.062	[-0.126; 0.120]	-0.004	0.956
Education	-0.082	0.160	[-0.398; 0.234]	-0.038	0.608
Annual income	0.186	0.261	[-0.330; 0.702]	0.050	0.478
Parity	-0.942	0.545	[-2.017; 0.134]	-0.122	0.086
Prepartum BMI	0.009	0.038	[-0.066; 0.085]	0.017	0.806
Prepartum depressive symptoms	0.592	0.075	[0.443; 0.740]	0.540	**<0.001**
Step 2					
Age	0.026	0,062	[-0.096; 0.148]	0.031	0.672
Education	-0.061	0.157	[-0.370; 0.249]	-0.028	0.699
Annual income	0.115	0.257	[-0.393; 0.622]	0.031	0.656
Parity	-0.841	0.535	[-1.898; 0.215]	-0.109	0.118
Prepartum BMI	0.006	0.038	[-0.069; 0.080]	0.010	0.882
Prepartum depressive symptoms	0.479	0.085	[0.311; 0.647]	0.438	**<0.001**
Prepartum supradiaphragmatic reactivity	0.112	0.042	[0.028; 0.196]	0.215	**0.009**
Prepartum subdiaphragmatic reactivity	0.010	0.039	[-0.066; 0.086]	0.022	0.790

Notes. Bold font indicates statistical significance ($p < 0.05$). Step 1: F(6,163) = 11.012, $p < 0.001$, *Adj.* $R^2 = 0.262$. Step 2: F(8,161) = 9.801, $p < 0.001$, *Adj.* $R^2 = 0.294$; $R^2_{change} = 0.039$, $p = 0.011$.

4.4. Discussion and Conclusion

This longitudinal study investigated the link between prepartum self-reported autonomic reactivity and postpartum depression. We found that higher prepartum supradiaphragmatic reactivity predicted higher levels of depressive symptoms in the postpartum period. These findings are the first to evidence the role of self-reported autonomic reactivity during pregnancy as a predictor of postpartum depression. Importantly, this relationship remains significant after controlling for the effect of women's prepartum depressive symptoms and other potential covariates.

In the present study, depressive symptoms remained stable along the peripartum period with no significant differences between pregnancy and postpartum evaluation. This finding is consistent with prior studies that, although the heterogeneity of peripartum trajectories of depressive symptoms, reported similar levels of depression from pre- to postpartum (Kiviruusu et al., 2020; Santos et al., 2017; Wikman et al., 2020). In the present study, the prevalence of women with PPD was 8.8% (i.e., PHQ – 9 score ≥ 10), consistently with other studies that reported prevalence between 7% and 14.2%, using the same questionnaire and cut-offs (Abulaiti et al., 2022; Anokye et al., 2018; Beck et al., 2012; Wang et al., 2021).

For correlations, our findings indicated that self-reported prepartum dysfunctional autonomic reactivity was significantly and positively associated with depressive symptoms before and after childbirth. These findings align with Polyvagal Theory and previous correlational research conducted in the general population, confirming the negative impact of altered self-reported autonomic reactivity on mental health (Cabrera et al., 2018; Kolacz, Dale, et al., 2020; Wang et al., 2020). In particular, significant correlations were reported between destabilised self-reported autonomic reactivity and higher depressive symptoms (Kolacz, Dale, et al., 2020; Wang et al., 2020). However, in previous studies, this relationship was analysed only cross-sectionally. Furthermore, no previous studies evaluated self-reported autonomic reactivity in pregnancy and postpartum. However, prior psychophysiological studies showed that a vagal withdrawal at rest was associated with depressive symptoms during the peripartum (Lin et al., 2019; Shah et al., 2020; Shea et al., 2008). For instance, ANS imbalance favouring sympathetic dominance was significantly related to prepartum depression during pregnancy (Kishan et al., 2021; Shah et al., 2020; Shea et al., 2008) and lowered resting respiratory sinus arrhythmia (RSA) was significantly associated with higher levels of depression during late pregnancy (Lin et al., 2019).

Unlike previous research, our study considers the relationship between self-reported autonomic activity and depression symptoms over time, focusing on pregnant women and evaluating whether dysregulated self-reported autonomic activity during pregnancy was a risk factor for developing postpartum depression. The findings partially confirmed this hypothesis, indicating that

self-reported supradiaphragmatic reactivity during pregnancy, but not subdiaphragmatic reactivity, was a risk factor for developing postpartum depressive symptoms. Additionally, the role of dysfunctional self-reported supradiaphragmatic reactivity during pregnancy in the onset of postpartum depressive symptoms remains significant even after controlling for the effects of self-reported depressive symptoms during pregnancy. Previous studies supported the role of a physiologically measured altered autonomic activity as a potential marker of vulnerability and severity of depressive symptoms in the non-pregnant population (Brush et al., 2019; Dell'Acqua et al., 2020; Hartmann et al., 2019; Rottenberg et al., 2007; Yaptangco et al., 2015). For instance, Brush and colleagues (2019) showed that lower cardiac autonomic balance (i.e., sympathetic predominance) was a significant predictor of current major depression disorder (MDD). Moreover a longitudinally study reported that lower resting RSA was a potential physiological marker of depressive symptoms one year later (Yaptangco et al., 2015). For the peripartum period, only a recent study reported a longitudinal relationship between adverse childhood experience, lower resting RSA reactivity during the second trimester of pregnancy and 1-year postpartum depressive symptoms (Oosterman et al., 2019).

Consistently, our study's findings evidenced that a brief self-reported supradiaphragmatic measure of autonomic dysregulation during pregnancy is predictive of the onset of depressive symptoms one month later. Our findings are in line with Porges's conceptualisation of the role of VVC in stabilising autonomic processes (Porges & Carter, 2012). One specific biomarker of VVC functioning is RSA (Porges, 2007), which is related to the adaptive homeostasis process under safe conditions and the associated social engagement activities; indeed, lower resting levels of RSA were related to emotion dysregulation and behavioural inflexibility that are typical in the psychopathology of many mental disorders (Beauchaine, 2015; Beauchaine & Thayer, 2015; Wagner & Waller, 2020). One of the links between autonomic activity and mental disorders is the prefrontal cortex (PFC) activity (Wagner & Waller, 2020). PFC functioning is altered in patients with different psychiatric diagnoses, including major depressive disorder (Mulcahy et al., 2019; Zhou et al., 2020), and its dysfunctional activity is reflected peripherally by vagal withdrawal indexes (e.g., RSA) (Beauchaine, 2015; Beauchaine & Thayer, 2015). During the last two trimesters of pregnancy, women's SNS activity increases (Fu, 2018; Kuo et al., 2000; Volman et al., 2007) and RSA and parasympathetic nervous system (PNS) activity decreases (DiPietro et al., 2005; Kuo et al., 2000; Matsuo et al., 2007). Few recent studies showed that women reported elevated SNS activity during stressful laboratory conditions in pregnancy (Tung et al., 2021; Vlisides-Henry et al., 2021) (i.e., Trier Social Stress Test). However, a higher sympathetic activation to a stressor is an adaptive autonomic response (Vlisides-Henry et al., 2021) only if it is associated with a higher vagal tone at rest and a faster recovery of

parasympathetic activity after the stressor (Laborde et al., 2018; Porges, 2007). We could hypothesise that stressful conditions and emotional problems related to pregnancy could boost the normative and adaptive changes of autonomic reactivity, increasing the likelihood of a dysfunctional autonomic activity at rest, that in turn, could lead to higher emotional dysregulation and mental health problems (Porges, 2007; Thayer & Lane, 2000). Postpartum depressive symptoms might arise when the restoration of pre-pregnancy autonomic function is compromised due to retuning of ANS to defence states during pregnancy. These ANS changes might persist after childbirth, affecting the homeostatic function of the body and increasing the likelihood of emotional problems (Porges, 2001, 2007). More research is needed on the pregnant population to clarify the psychophysiological mechanism at the basis of the relationship between the ANS function and depressive symptoms.

In cross-sectional studies on the general population, higher self-reported subdiaphragmatic reactivity was associated with greater depressive symptoms (Wang et al., 2020) and other psychological disorders (Cabrera et al., 2018). We found this association in the correlation analyses, but the effect of subdiaphragmatic reactivity on postpartum depressive symptoms in the final regression model was not significant. Literature indicated that as the pregnancy progresses, many gastrointestinal complaints of the subdiaphragmatic organs (e.g., nausea, vomiting, constipation) are reduced (Body & Christie, 2016; Zielinski et al., 2015). On the other hand, many cardiovascular and respiratory changes associated with supradiaphragmatic organs begin early in pregnancy, increase throughout the gestation and return to pre-pregnancy levels only after the delivery (Fu, 2018; Jarvis & Nelson-Piercy, 2020; Tan & Tan, 2013; Volman et al., 2007). It is possible that during pregnancy, changes in supradiaphragmatic organs affected more body perceptions than changes in subdiaphragmatic organs. Since the BPQ-SF assesses the person's autonomic reactivity through the functioning of the autonomically-innervated organs, it is possible that the greater impact of physiological changes related to pregnancy on the supradiaphragmatic organs led to a more dysfunctional self-reported autonomic activity. More studies are needed to understand the different roles of supra- and subdiaphragmatic autonomic reactivity on the onset of mental disorders during pregnancy.

Finally, some limits need to be acknowledged. First, depressive symptoms were evaluated through a self-reported measure. Therefore, there is the possibility that women may over-or under-estimate their depressive symptomatology. However, it has to be said that the instrument used is well-validated with structured clinical interviews and is broadly used in the pregnant population. Second, in the present study, we focused on a sample of pregnant women from the general population. Future studies on pregnant women with major depressive disorders may shed further light on the dysfunctional processes involving supra- and subdiaphragmatic autonomic reactivity. Nonetheless,

the study has several strengths. The prospective design allows us to identify self-reported autonomic reactivity as a predictor of postpartum depressive symptoms and contributes to evidence of the specific role of supradiaphragmatic reactivity. Generally, autonomic nervous system reactivity is assessed in laboratory conditions or using wearable sensors. Considering that the self-reported measure used may be more easily and freely available and administered, the BPQ could provide a reliable measure of autonomic nervous reactivity in large-scale studies and in all those conditions in which an in-person physiological evaluation is impossible. Interestingly, postpartum depressive symptoms were better predicted when both self-reported prepartum depressive symptoms and autonomic nervous system reactivity were considered together, indicating that both scales uniquely contributed to predicting postpartum depressive symptomatology. The self-reported autonomic subscales of BPQ evaluate a range of aspects related to the physiological activation that the typical depression screening questionnaires do not include. Beyond the specific symptoms of depression (e.g., sadness, apathy), the autonomic assessment detects information on the physiological and bodily self-regulation responses to emotional and stressful conditions (Porges, 2007; Thayer & Lane, 2009) that may be later reported as depressive symptoms or that may lead to the onset of depressive symptoms (Stange et al., 2017). Therefore, evaluating autonomic nervous system reactivity in combination with self-reported symptoms of depression may help to better screen vulnerable women at risk of developing postpartum depression. Indeed, also, when only prepartum women under the clinical threshold of depression were considered, ANS reactivity contributed to predicting postpartum depressive symptoms. Unfortunately, the relatively small number of women who developed postpartum depressive symptoms did not allow us to evaluate whether self-reported autonomic regulation during pregnancy could discriminate between those who remained asymptomatic and those who became symptomatic. Population studies are foreseen to answer this question.

Overall, this longitudinal study indicates that dysfunctional self-reported supradiaphragmatic reactivity during pregnancy (i.e., second and third trimester) was a significant predictor of postpartum depressive symptoms at one month, after controlling for prepartum depressive symptoms. This may help more precisely target interventions aimed to reduce the threat-responsive autonomic reactivity at rest and promote interventions aimed to increase cues of safety which may help to decrease ASN defensive responses. More studies are needed to understand how pregnancy affects the self-reported autonomic reactivity and the pathophysiological pathways that lead to postpartum depression. This is fundamental to finding novel interventions to support and help women during this crucial transition.

5. General discussion and conclusions

5.1. Summary and discussion of key findings

This PhD thesis aimed to assess the role of prepartum autonomic nervous system (ANS) activity as an indicator of depressive symptoms during pregnancy and as a predictor of depressive symptoms after childbirth. Growing scientific literature shows that HRV and autonomic activity are strictly related to the onset and maintenance of depressive symptoms in the general population (Dell'Acqua et al., 2020; Koch et al., 2019). However, few studies investigated this relationship in the pregnant population, with mixed findings (M. C. Kimmel et al., 2021; Shah et al., 2020; Shea et al., 2008). The COVID-19 pandemic allowed us to explore remote and self-reported ways to measure ANS activity. Despite the standard gold to measure cardiac activity and derived autonomic parameters remaining ECG, using new technologies and questionnaires to assess physiological activity could be a significant step forward to their higher use in eHealth assessments and interventions.

The first study (*Chapter 2*) aimed to assess the validity of an Android commercial smartphone application to measure HRV (i.e., "Heart Rate Variability HRV Camera") in the general population. Studies on the validation of contact PPG smartphone applications are very few and predominately focused on using iOS systems and non-commercial applications (Christien Li et al., 2019). Therefore, it was a need for rigorous validation studies that compared HRV parameters (e.g., rMSSD) derived from a traditional assessment (i.e., ECG) and those computed from a PPG freely available mobile application (Schäfer & Vagedes, 2013). Our result indicated the validity and reliability of a short-term parameter of HRV (i.e., rMSSD) measured via the "Heart Rate Variability HRV Camera" application compared with the standard ECG assessment. Indeed, the trivial Cohen's *d* effect size, the nearly perfect ICC, and the "good" Bland-Altman ratio between ECG and PPG recording indicated an excellent accuracy of the smartphone application used in measuring rMSSD. These findings align with other validity studies of contact PPG smartphone applications and provide a new free tool that could be implemented in eHealth screening or intervention programmes.

In *Chapter 3*, we report an implementation of the "Heart Rate Variability HRV Camera" in a real-life setting. In particular, our longitudinal study aims to assess the association between rMSSD and depressive symptoms during pregnancy and the role of the same HRV parameter as a predictor of depressive symptoms after childbirth. This study could help to disentangle the mixed findings on the association between HRV and depression in the pregnant population (M. C. Kimmel et al., 2021; Shah et al., 2020; Shea et al., 2008) and show evidence of a potential prospective relationship between prepartum parasympathetic activity at rest and postpartum depressive symptoms. Our result showed

that short-term rMSSD collected with a contact PPG smartphone application is associated with the presence of depressive symptoms during pregnancy. Moreover, the same HRV parameter could be a valuable prepartum biomarker to detect women with higher depressive symptoms at postpartum, also controlling for depressive symptoms at prepartum. Thus, our findings suggest that the prepartum period offers a vital timeframe to implement preventive intervention on vagal modulation to avoid its influence on the future generation of postpartum depressive symptoms. Indeed, literature reported increasing evidence of the role of HRV biofeedback in the treatment and prevention of depression (Pizzoli et al., 2021). Moreover, using a smartphone application to collect rMSSD might promote the remote monitoring of the psychophysiological well-being of pregnant women and the potential implementation of smartphone-delivered intervention for peripartum depression.

Our third study (*Chapter 4*) investigated the potential use of a self-reported measure of autonomic activity (i.e., supradiaphragmatic and subdiaphragmatic subscale of the Body Perception Questionnaire - BPQ) as an indicator and predictor of peripartum depressive symptomatology. A recent study validated the two BPQ subscales mentioned above as a measure of autonomic flexibility (Kolacz et al., 2022); therefore, we tested the association between self-reported ANS activity and depressive symptoms during pregnancy and after delivery. Our results showed that prepartum supradiaphragmatic and subdiaphragmatic reactivity (i.e., altered autonomic activity) were significantly and positively associated with both prepartum and postpartum depressive symptoms. However, further analyses only detect prepartum supradiaphragmatic reactivity as a predictor of postpartum depressive symptoms, also controlling for depressive symptoms at prepartum. In particular, it seems that the altered autonomic activity of the organs above the diaphragm could predict higher levels of depressive symptoms after childbirth. Overall, this study indicates that dysfunctional self-reported supradiaphragmatic reactivity during pregnancy was a significant predictor of postpartum depressive symptoms. This may help more precisely target interventions aimed to reduce the threat-responsive autonomic reactivity at rest and promote interventions aimed to increase safety cues, which may help decrease ASN dysfunctional responses.

5.2. General conclusions

Altogether, the findings of these studies suggest that:

1) mHealth technologies could play an essential role in future management and treatment programmes addressing people's health needs. The reliable assessment of cardiac parameters (e.g., heart rate, RRI, rMSSD) through free and accessible smartphone applications could improve a medical screening for cardiac or other physical diseases, but also – and more intriguing for us – could lead to a more comprehensive assessment of psychophysiological health in different samples. The

HRV parameters have been increasingly used as biomarkers of different mental health disorders in the last few years. Therefore, the remote collection of this physiological data allows us to develop ecological studies better to understand the relationship between daily stressors and HRV. It also provides clinicians with a tool to improve the quality of their interventions and collect data in real-time.

2) Lower parasympathetic activity during pregnancy (i.e., lower levels of rMSSD) is an indicator of depressive symptoms during pregnancy and – more interesting for preventive mental health programmes – a predictor of postpartum depressive symptoms up to a month after the delivery. More studies are needed to bring significant evidence for this cross-sectional and prospective association. However, this finding reflects on the peripartum population what psychophysiological literature already knows about the significant association between HRV and depression. Indeed, HRV biofeedback or other mind-body treatments that improve parasympathetic activity showed their efficacy in reducing mental health disorders and improving psychological well-being in the general population. By providing evidence of the strict and prospective relationship between HRV and depressive symptoms, our study might be a flourishing starting point for the implementation of intervention based on a modulation of HRV to manage depressive symptomatology during pregnancy and to prevent their onset in the postpartum period.

3) Altered self-reported autonomic activity of supradiaphragmatic organs is an indicator of depressive symptoms during pregnancy and a predictor of postpartum depressive symptoms up to a month after the delivery. The result of an association of self-reported non-adaptive ANS reactivity and depression in part overlaps our findings about HRV as a predictor of postpartum depressive symptoms. Indeed, using rMSSD – a predominantly parameter of parasympathetic activity – could be considered a part of the assessment of the ANS activity. However, in this case, we used a self-reported questionnaire to assess data traditionally collected by a sensor (e.g., PPG sensor) or specific physiological instruments (e.g., ECG). Therefore, considering that the self-reported measure used may be more easily and freely available and administered, the BPQ could provide a reliable measure of autonomic nervous reactivity in large-scale studies and in all those conditions in which an in-person physiological evaluation is impossible. Clearly, the autonomic self-reported measure could not replace a physiological assessment of ANS through a "traditional" sensor. The main reason is that despite the sensor-based measure and the self-reported measure of ANS reflecting different aspects of sympathetic and parasympathetic activity. For instance, HRV parameters like rMSSD or HF power are indices of nearly pure vagal activity at rest. However, other HRV parameters are more related to sympathetic activation (e.g., VLF power), other to sympathovagal balance (e.g., HF/LF ratio), and other related to other aspects of cardiac variability (e.g., non-linear parameters). Conversely, the self-

reported autonomic measure pool information over many innervation targets, and it is impossible that reflect the dynamic function of only one ANS system. Moreover, the self-reported assessment was filled with thinking about their own perception of particular body symptoms that are strictly related to a dysregulated or non-functional activation of ANS. Therefore, the collected data could be limited by memory and attention bias. However, our results intriguingly indicate the association between an autonomic disruption of organs above the diaphragm and depressive symptoms both at prepartum and postpartum. The specificity of the result allows us to hypothesise an alteration of the autonomic activity of supradiaphragmatic organs in pregnant women (e.g., heart, lungs) as normal physiological changes in pregnancy confirmed (e.g., higher heart frequency, more difficulties in respiration). In turn, if the ANS activity was not restored to pre-pregnancy levels after the delivery, this could affect sympathetic and parasympathetic activity. As shown throughout this PhD thesis, ANS activity and mental health are strictly related, so the altered ANS activity could lead to more depressive symptoms in the postpartum. Our result shows that a self-reported measure of autonomic activity could capture the dysfunctional ANS activity, setting itself as a promising tool to assess the experience of autonomic symptoms that can be utilized for clinical monitoring and treatment. More studies are needed using this self-reported tool and physiological measurements to clarify which aspects of ANS could be reflected by a simple measure of autonomic symptoms.

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