DEPRESSION AND CARDIOVASCULAR AUTONOMIC CONTROL:

A MATTER OF VAGUS AND SEX PARADOX

Eleonora Tobaldini[a,b*], Angelica Carandina[a,d*], Edgar Toschi-Dias[a,b,c], Luca Erba[a,b], Ludovico Furlan[a,b], Andrea Sgoifo [d], Nicola Montano[a,b].

[a] Department of Internal Medicine, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlínico, Milan, Italy

[b] Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy.

[c] Laboratory of Autonomic and Cognitive Neuroscience - Methodist University of São Paulo, São Paulo, Brazil; Ibirapuera University, São Paulo, Brazil.

[d] Department of Chemistry, Life Sciences and Environmental Sustainability, Stress Physiology Lab, University of Parma, Parma, Italy

*both authors equally contributed to the manuscript

Author for correspondence:

Nicola Montano, MD PhD

Ospedale Maggiore Policlinico

Via Francesco Sforza, 28

Milan - Italy

e-mail: nicola.montano@unimi.it

ABSTRACT

Depression is a well-established stress-related risk factor for several diseases, mainly for those with cardiovascular outcomes. The mechanisms that link depression disorders with cardiovascular diseases (CVD) include dysfunctions of the autonomic nervous system. Heart rate variability analysis is a widely-used non-invasive method that can simultaneously quantify the activity of the two branches of cardiac autonomic neural control and provide insights about their pathophysiological alterations. Recent scientific literature suggests that sex influences the relationship between depressive symptoms and cardiac autonomic dysfunction. Moreover, a few studies highlight a possible sex paradox: depressed women, despite a greater vagal tone, experience a higher risk of adverse cardiovascular events than depressed men. Although there are striking sex differences in the incidence of depression, scanty data on this topic are available. Lastly, studies on the heart-brain axis bidirectionality and the role of sex are fundamental not only to clarify the biological bases of depression-CVD comorbidity, but also to develop alternative therapies, where vagus nerve appears to be a promising target of non-invasive neuromodulation techniques.

Keywords: Depression, Cardiac autonomic control, Heart rate variability, Sex differences, Neuromodulation, Vagal stimulation

CONTENTS

1. INTRODUCTION

The daily exposure to multiple psychosocial stress factors can result in a prolonged and frequent activation of the stress response (McEwen, 2006). Furthermore, worry and rumination can extend stress-related emotional and physiological activation, both in advance of and following stressors (Brosschot et al., 2006). These situations represent significant pathophysiological risk factors and lead to physical and psychological consequences. As a matter of fact, depression is the major stress-related psychiatric disorder. The last official global health estimates reported that the total number of people with depression exceed 300 million and the proportion of the world wide population with depression is rated to be 4.4% (World Health Organization, 2017). When ranked by disability and death combined, depression comes ninth behind killers such as stroke and HIV (Smith, 2014).

But what is the rationale behind this deadly fame? Darwin in 1872, commenting on the work of Claude Berndard, emphasized the close bond between the brain and the heart: "*when the mind is strongly excited, we might expect that it would instantly affect in a direct manner the heart; […] when the heart is affected it reacts on the brain; and the state of the brain again reacts through the pneumo-gastric nerve on the heart; so that under any excitement there will be much mutual action and reaction between these, the two most important organs of the body."* (Darwin, 1990) So, through this intimate connection, psychiatric disorders such as depression not only affect the brain but also involve the heart. Countless evidence from the scientific literature has emphasized the link between cardiovascular disease (CVD) and depression (Carney et al., 2003; Elderon & Whooley, 2013; Freedland et al., 2003; Glassman, 2007; Lett et al., 2004; Penninx et al., 2001; Sgoifo et al., 2015; Zellweger et al., 2004). Several studies, such as "The INTERHEART study", examined modifiable risk factors for acute myocardial infarction in over 25.000 patients from 52 different countries: depression was officially recognized as a coronary heart disease (CHD) risk factor in the 2010 Global Burden of Disease Study (Charlson et al., 2011; Nicholson et al. 2006; Yussuf et al., 2004). Moreover, a wide number of authors reported that either major depressive disorder (MDD) or

significant depressive symptoms with substantial functional impairment are associated with an increased risk of heart failure, stroke, peripheral artery disease and worse adverse outcomes (Grenon et al., 2012; Pan et al., 2011; Rutledge & Linke 2007; Surtees et al., 2008). Depression has also been shown to be an independent predictor of poor prognosis and re-hospitalization among patients with established heart failure (Jiang et al., 2001) and patients with MDD are much more likely to suffer acute cardiovascular sequelae such as myocardial infarction, congestive heart failure and hypertension (Nemeroff & Goldschmidt-Clermont, 2012).

In the last years, multiple potential behavioural and biological factors have been identified as possible substrates of this dangerous comorbidity. The effects of poor health behaviours have been extensively highlighted in numerous papers (Brummett et al., 2003; Whooley et al., 2008; Win et al., 2011), especially in The Heart and Soul Study (Sin et al., 2016), a prospective cohort study of 1024 subjects with stable coronary heart disease: depressed patients had a 50% greater rate of adverse cardiovascular events than those without depressive symptoms, but the difference was no longer significant following adjustment for smoking, medication adherence and physical activity. Among the pathophysiological pathways that could link depression and CVD, inflammatory processes, enhanced activity of the hypothalamo-pituitary-adrenal (HPA) axis and alterations of the cardiovascular autonomic control play a key role. Most of the evidence demonstrates that one-third of patients with MDD shows elevated peripheral inflammatory biomarkers like c-reactive protein, interleukin-6, interleukin-1β and tumor necrosis factor-α (Baghai et al., 2018; Dowlati et al., 2010). Moreover, a meta-analysis of 22 antidepressant treatment studies found that cytokine levels decreased in response to therapy, along with a reduction in depressive symptoms (Hannestad et al., 2011). In depression-related cardiovascular outcomes inflammation may act as a promotor for the progression of atherosclerosis, inducing endothelial activation and expression of adhesion molecules and vascular endothelial growth factors. The HPA axis hyperactivity may be reciprocally regulated by altered pro-inflammatory pathways, constituting a complex bidirectional biological crosstalk (Baune et al.,

2012). This dysregulation may lead to increased vasoconstriction, heart rate and platelet activation, factors that are directly implicated in the progression to CVD. However, among the possible biological mediators that have been considered to explain the association between depression and CVD, cardiovascular autonomic control dysfunction is the most investigated (Kemp et al., 2012).

2. CARDIAC AUTONOMIC CONTROL IN DEPRESSION

Heart rate variability (HRV) is a very useful non-invasive and sensitive indicator of autonomic impairment. Lowered HRV is a widely recognized prognostic risk factor for adverse cardiovascular events (e.g. myocardial infarction and arrhythmias) as well as cardiac mortality (Carney & Freedland, 2009; Thayer et al., 2010; van der Kooy et al., 2006). HRV analysis in the frequency domain identifies two oscillatory components, namely low frequency (LF) and high frequency (HF), ranging from 0.04 to 0.15 Hz and from 0.15 to 0.4 Hz respectively. The HF band reflects parasympathetic activity and its power is influenced by breathing whereas LF band seems to be produced by both sympathetic and parasympathetic branches, even if its physiological interpretation is still controversial. Finally, the ratio of LF to HF power (LF/HF) provides information about the sympatho-vagal balance (Shaffer & Ginsberg JP, 2017). Alterations of autonomic nervous system that promote vagal withdrawal are reflected in reductions of HRV. It is not surprising that a considerable body of research reports reduced HRV and cardiac parasympathetic indexes, derived both in time and frequency domain analysis, in patients with depression in comparison to healthy controls (Jangpangi et al., 2016; Koch et al., 2019; Nahshoni et al., 2004; Sgoifo et al., 2015). In Kemp's meta-analysis, unmedicated depressed patients displayed reduced HRV compared to control subjects in a standardized short-term resting state condition (Kemp et al., 2012) and Shinba et al. observed that drug-naïve depressed patients without comorbidity showed lower cardiac vagal tone and a shift of the sympathovagal balance towards sympathetic prevalence when compared with healthy age-matched controls during task execution (Shinba, 2017). Depression has been associated with decreased time domain measures

of HRV, including HF and several nonlinear measures, whereas the LF/HF ratio showed a significant increase. Based on these data, we can imagine that the intrinsic mechanisms of regulation of HRV are altered in this pathological condition, both at rest and in response to physiological and psychosocial stimuli (Chen et al., 2017; Koch et al., 2019; Shinba, 2017). However, there is an important bias in all these studies: sex differences were not carefully considered for the analysis.

2.1. SEX DIFFERENCES IN THE RELATIONSHIP BETWEEN HRV AND DEPRESSION

As to sex differences, the first relevant element is the different prevalence of depression in women versus men: women are about twice as likely to develop depression during their lifetime (Bromet et al., 2011; Lucht et al., 2003, Seedat et al., 2009). In 2010, depression global annual prevalence was 5.5% and 3.2% for women and men respectively. Furthermore, women seem to manifest more somatic symptoms of depression than men (Silverstein et al., 2013). The finding of similar prevalence ratios in all developed countries suggests that the differential risk is indicative of a biologically based sex difference. Studies on the short allele variant of the serotonin transporter-linked polymorphic region (5-HTTLPR), which is associated with higher susceptibility to the development of depression in response to environmental stress, identified this interaction more frequently in women than men (Gressier et al., 2016; Sharpley et al., 2014; Uher & McGuffin, 2010). Specific forms of depression-related disorders, e.g. premenstrual dysphoric disorder, postpartum depression and postmenopausal depression, led to hypothesize the existence of a correlation between female hormonal fluctuations and depression. Moreover, females and males seem to have similar rates of depression before puberty and at ages older than 65 years (Bebbington et al., 2003; Burcusa & Iacono, 2007; Cyranowski et al., 2000). From a large number of existing studies (Broderick & Korteland, 2002; Hampel & Petermann, 2005; Johnson & Whisman, 2014; Jose & Brown, 2008; Lopez et al., 2009; Peled & Moretti, 2007; Tamres et al., 2002), higher propensity for ruminative thinking in women has been proposed as a

possible explanation for sex differences in prevalence rates of depression, as well (Nolen-Hoeksema, 2012).

Sex differences do not occur only in terms of prevalence of the disease but also in terms of disease features. In particular, there are evidences about a sex effect on the relationship between depressive symptoms and cardiac autonomic function. Depressed women are reported to have higher vagally mediated cardiac control compared to depressed men (Chambers & Allen, 2007). Garcia et al. evaluated cardiac autonomic control through passive tilt test in treatment-naive young adults with a first episode of major depression and without any comorbid psychiatric disorder. They found that young depressed males had significantly lower HRV during passive orthostatic challenge in comparison to healthy age-matched control men, whereas there were no significant alterations in the autonomic function of depressed women. They reported a more robust association of depressive symptoms with poor cardiac vagal control and sympathetic predominance among depressed males than females (Garcia et al., 2012). Similar results have been obtained by Chen et al.: mildly depressed elderly men exhibited prominent sympathetic predominance compared to the control group, that resulted mainly from diminished HF power and preserved LF power. In contrast, since both HF and LF were attenuated among more depressed elderly males, sympathovagal balance showed no differences in spite of profound vagal withdrawal. There were still no differences in HRV between all depressed elderly female subgroups and the respective age-matched control group (Chen et al., 2010). These results seem to imply a pervasive decline of cardiac autonomic function in depressed men, but not in depressed women. Recent research studies have verified the existence of sex differences in the association between depressive symptoms and cardiac autonomic dysfunction in a non-clinical population, as well. Higher scores in daily depressive symptoms were associated with a decreased circadian variation pattern of vagal activity in men but with increased circadian variation pattern in the female group. In particular, a higher average amount of sadness experienced in daily life was associated with higher levels of lnHF power in women (Jarczok et al., 2018a; Verkuil et al.

2015). A cross-lagged analysis over a 10-year period in the Whitehall II study revealed that higher scores in vagal indexes at baseline are associated with a lower likelihood of depression incidence in men but not in women (Jandackova et al., 2016). Further evidence also comes from animal models. Within a population of 42 adult female *Macaca fasciucularis* in a laboratory setting, Jarczok et al. observed that females classified as behaviourally depressed showed higher vagal cardiac control compared to non-depressed counterparts (Jarczok et al., 2018b).

A possible interpretation of sex differences in cardiac autonomic dysfunction of depressed patients derives from the neurovisceral integration model (Thayer & Lane, 2009; *Figure 1*). A reduction of grey matter volume in ventromedial prefrontal cortex (vmPFC) has been found in unmedicated male patients with major depressive disorder, but not in the female counterpart (Yang et al., 2017). This brain area exerts an inhibitory control over amygdala activity and stronger vmPFC-amygdala connectivity predicts higher vagally mediated HRV (Sakaki et al., 2016). In addition, depressed females but not depressed males were found to have a reduced amygdalar volume when compared with sex-matched control subjects (Hastings et al., 2004).

Sex-related differences in HRV have generally been reported in the normal population (Koenig & Thayer, 2016). Women show larger vagal modulation, despite they are characterized by a higher HR relative to men. However, these differences seem to disappear with aging, especially from the age group of 55–64 years (Voss et al., 2015). Furthermore, some authors demonstrated an increased HRV in postmenopausal women with estrogens replacement therapy compared to women without hormone therapy (Liu et al., 2003; Neves et al., 2007; Pikkujämsä et al., 2001). Lastly, estrogens receptors have been localized throughout the central autonomic network (McEwen et al., 2012). This evidence suggests a possible role of estrogens in the female protective mechanism against the autonomic alterations associated with depression. In addition, the vagal predominance observed in depressed women could in part be due to the differential coping strategies that male and female subjects show in response to chronic stressors (namely, fight-or-flight vs. tend-and-befriend response, respectively)

(Taylor et al., 2000). In fact, a greater oxytocin release in response to stress has been found in women than in men (Taylor et al., 2000). Oxytocin-type neurons from the paraventricular nucleus synapse on cardiovagal neurons in the nucleus of the solitary tract, the dorsal motor nucleus of the vagus, and the nucleus ambiguous (Coote, 2013; Koenig and Thayer, 2016) and their excitation ultimately determines an increase in vagal outflow. Moreover, the effects of oxytocin have been found to be significantly enhanced by estrogens (Taylor et al., 2000).

All the above-mentioned evidence signals the need for additional studies to understand more about sex differences in the cardiac autonomic control of depressed patients. This goal could provide new insights into the etiopathogenesis of depression and promote the development of sex-specific antidepressant therapies.

2.2. SEX DIFFERENCES IN DEPRESSION-CARDIOVASCULAR DISEASE COMORBIDITY

The current state of art seems to highlight a great sex paradox in depression and cardiovascular disease comorbidity. Although vagal activity is negatively associated with CVD risk and mortality in both healthy and clinical subjects (Jarczok et al., 2018a; Thayer et al., 2010), depressive symptoms have been associated with an increased risk of adverse cardiovascular events more in women than in men (Bucciarelli et al., 2019; Möller-Leimkühler, 2007). Shah et al. found that depressive disorders predict cardiovascular disease outcomes and increase risk of death in women aged $\leq$ 55 but not in postmenopausal women and men (Shah et al., 2014). Furthermore, data from two cross-sectional surveys (Community Mental Health Epidemiology Study and Third National Health and Nutrition Examination Survey) revealed that young adult females with depression may be at excess risk of premature cardiovascular-related death over a 15-year follow-up period (Shah et al., 2011; Wyman et al., 2012). Possible pathophysiological mechanisms that could explain the highest incidence of CVD in depressed women, despite the cardioprotective role of the vagus, are ascribed to: i)

inflammatory processes; ii) hormonal dysregulation; iii) poorer health behaviour; iv) metabolic derangement (Bucciarelli et al., 2019; Webb et al., 2017). Several authors have highlighted a strong connection between hormonal dysregulation and impaired inflammatory response in female depressed patients. As a matter of fact, circulating estrogens stimulate the T- and B-lymphocytes, with a greater immune and inflammatory response than men. Moreover, estrogens increases IL-1 secretion by macrophages and depressed women have increased eosinophil reactivity compared to men, which may be explained by the presence of estrogens receptor alpha (ERα) on their surface. Elevated serum levels of IL-8, IFN-γ and leptin were found in the blood of depressed women when compared to healthy controls and IL-6, TNF-α and IL-1β levels are mainly elevated in the blood of depressed women compared to depressed men, suggesting that these pro-inflammatory markers are sex-specific in MDD patients. In general, estradiol appears to be linked to suppression of pro-inflammatory cytokine production, such as reduced expression of IL-6 and TNF-α, and increased production of anti-inflammatory cytokine IL-10 (Bucciarelli et al. 2019, Dudek et al. 2019, Webb et al. 2017). However, further complicating this relationship is estradiol dose, as higher concentrations are linked to anti-inflammatory responses, whereas low concentrations are associated with pro-inflammatory responses (Mattina et al. 2019). Inflammation has been postulated to play a major role in endothelial damage of the cerebral vasculature in depressed patients (Halaris 2016) and plays a major role in the development of atherosclerosis and atherothrombosis. Thus, hormonal dysregulation, through the activation of pro-inflammatory pathways, is supposed to be a risk factor for the onset of CVD in depresses women. Finally, gonadal steroid receptors, such as ERα and ERβ, are expressed in the endothelial cell layer of the blood-brain barrier suggesting a further and direct involvement of hormones in neurovascular alteration (Dudek et al. 2019).

3. THROUGH THE VAGUS NERVE: NON-INVASIVE NEUROMODULATION TECHNIQUES AS ALTERNATIVE THERAPY

The link between cardiovascular autonomic control and MDD seems to be fundamental also in view of new alternative therapies to drug treatment. Although pharmacological antidepressant treatment is the gold standard therapy for major depression, up to 50–60% of patients do not obtain adequate response following a first antidepressant drug treatment and about 40% of depressed patients do not respond to 4 or more conventional treatments and are considered to have treatment-resistant depression (Kemp et al., 2010; Otte et al., 2016; Rush et al., 2006). Moreover, pharmacological, antidepressant treatment doesn't resolve reductions in HRV that have been observed in general population despite decrease in depressive symptoms, suggesting that the pathology might have residual effects on neurophysiological systems. In addition, several studies found that tricyclic antidepressants significantly reduce HRV because of the anticholinergic and α1-adrenergic properties of this class of medication, while the effects on cardiovascular autonomic function of selective serotonin reuptake inhibitors and serotonergic noradrenergic reuptake inhibitors are still debated (Kemp et al., 2010; Koch et al., 2019). In view of such evidence, recent research studies have been focused on trying to develop treatments that could be effective in non-responsive patients and have cardioprotective effects (*Figure 2*). In their review, Iseger et al. proposed a frontal-vagal network that overlaps with the functional areas affected by depression. As a matter of fact, several years of neuroimaging research have shown that the depression-related decrease of metabolism and blood flow in the prefrontal cortex and anterior cingulate and the pathologically increased activity in the subgenual cingulate and amygdala are positively correlated with cardiovascular dysautonomic features. These authors summarized the most promising neuromodulation techniques that target key nodes for both depression and cardiac autonomic control (Iseger et al., 2019). For example, the dorsolateral prefrontal cortex (DLPFC) has been frequently selected in the depression treatment as the most suitable area for non-invasive neurostimulation such as repetitive Transcranial Magnetic

Stimulation (rTMS) and transcranial Direct Current Stimulation (tDCS). It has been hypothesized that the antidepressant effect of DLPFC-stimulation is exerted via trans-synaptic modulation of the subgenual cingulate cortex (sgACC). Lane et al. observed that depressed patients show an altered emotional state shifting due to DLPFC hypoactivity and abnormal sgACC activity, which subsequently leads to altered vagal control. These alterations are positively correlated with the severity of depression and a concurrent increase in vagal indexes occurs when the pathological condition is reversed by a successful treatment (Iseger et al., 2019; Lane et al., 2013). Surprisingly, also the direct stimulation of the Vagus Nerve (VNS) has shown important antidepressant effects and it was officially approved by The Food and Drug Administration in 2005 as an alternative therapy for severely treatment-resistant depression. VNS has clear dose- and time-dependent effects on the brain in key regions implicated in the neurobiology of depression such as prefrontal and cingulate cortex (Carreno & Frazer, 2017; Kosel et al., 2011). An electrode is attached from a pacemaker implanted on the left side of the chest to the left Vagus Nerve in the neck. It has been suggested that impulses from the vagus nerve are transmitted to the following regions: locus coeruleus, raphe nuclei, and nucleus tractus soliarious, which then project to other above-mentioned regions of the brain long thought to be relevant for depression (Carreno & Frazer, 2017). To overcome the potential barriers of applying VNS, which requires surgery, a non-invasive VNS method has been developed. Transcutaneous Vagus Nerve Stimulation (tVNS) stimulates the afferent auricular branch of the vagus nerve located on the surface of the ear and produces a similar effect to classical VNS in reducing depressive symptoms. For instance, tVNS applied for 2 weeks in patients with depression, once or twice for 15 minutes per day, significantly reduced depression scores (Hein et al., 2013). The antidepressant effect as measured by the Beck Depression Inventory (BDI) was very prominent: it showed subjective symptom amelioration in depressed patients of almost 50 % and the effects appeared to be similar to other non-invasive brain stimulation techniques, such as rTMS (Fitzgerald et al., 2006; Frank et al., 2011) and tDCS (Loo et al., 2010). Moreover, 4 weeks of tVNS was found to modulate the resting state functional connectivity between the right amygdala and left DLPFC as

well as to enhance activation of the left insula and these changes were associated with improvement in depressive symptomatology (Fang et al., 2016; Liu et al., 2016). The tVNS seems to be able to alleviate depressive symptoms activating neuroprotective pathways and suppressing the inflammation of the areas involved by pathology (Kong et al., 2018). The molecular process leading to these results could be linked to the activation of α7 nicotinic acetylcholine receptors (α7 nAChRs), expressed on neuronal cells, astrocytes and microglia cells (Pavlov & Tracey, 2005). The tVNS determines an increased release of acetylcholine, massively activates these receptors and finally implements a neuroprotective anti-inflammatory process in the compromised areas, through the PI3K-Atk intracellular pathway, already observed in the inhibition of the peripheral macrophage inflammatory response (Tyagi et al., 2010). Lastly, to the best of our knowledge, the influence of tVNS on cardiovascular autonomic control in depressed patients has not yet been specifically studied. However, in their study on 29 healthy volunteers aged ≥ 55 years, Bretherton et al. found that 2 weeks of daily tVNS improve measures of vagal tone and some aspects of quality of life, mood and sleep, which are all aspects affected by depression. Importantly, findings showed that improvements in measures of autonomic balance were more pronounced in participants with greater baseline sympathetic prevalence (Bretherton et al., 2019). In addition, tVNS performed on 48 healthy participants significantly increased HRV, promoting a shift in cardiac autonomic function toward parasympathetic predominance (Clancy et al., 2014). To fill this literature gap, further investigations are needed to analyse the possible cardioprotective role of the tVNS in depressed patients.

All these non-invasive neuromodulation techniques modulate the entire frontal-vagal network rather than just the local stimulation target. Thus, prolonged stimulation causes anatomical and functional changes in the central nervous system and promotes the remodelling of damaged neuronal circuits.

Previous studies support gender-related differences in pharmacokinetics and pharmacodynamic properties of antidepressant medications (LeGates et al. 2019) and men and women with chronic depression show different responsivity to and tolerability of various antidepressant classes including

SSRIs, norepinephrinergic tetracyclic antidepressant and tricyclic antidepressant. However, only few studies have assessed the gender differences in the antidepressant effect of new neuromodulation techniques (D'Urso et al. 2017; Figiel et al. 1998; Conca et al. 2000; Brunoni et al. 2016) and authors reported that gender was not a significant predictor in determining non-invasive neuromodulation efficacy. Nevertheless, Kedzior and colleagues revealed in their meta-analysis, which included 54 sham-controlled trials between 1997 and 2013, that gender might be a positive predictor of response as studies showing good antidepressant response to rTMS had mostly female patients (Kedzior et al. 2014). To the best of our knowledge, only one paper (Huang et al. 2008) highlighted a gender effect in the therapeutic response to rTMS: while no difference was observed between male and premenopausal female patients, 68.8% and 70.6% respectively, postmenopausal women did not respond at all. They also found that greater improvement in depression score was associated with a higher estradiol/progesterone ratio in premenopausal women, suggesting an important role of female hormones in the therapeutic response.

4. CONCLUSION

Depression and cardiovascular disease currently represent two of the most common causes of disability and mortality. Women seem to experience depressive disorders with a double incidence than men. The latest studies have shown that depression in otherwise healthy subjects seems to increase the risk of cardiovascular disease more strongly in young women, despite a higher vagally-mediated heart rate variability. However, this sex paradox is still unresolved due to the lack of studies in sex-balanced populations and randomized clinical studies including a larger number of women. To the best of our knowledge the majority of research is correlational and does not longitudinally examine the effects of depression on cardiac autonomic control and in particular on HRV. Moreover, most studies present mixed gender groups and only a few of them considers gender differences in the analysis of results. Finally, it is difficult to analyse any adaptations related to the disease alone since

antidepressants have a great impact on the cardiovascular autonomic control. Further longitudinal studies are required assess the adaptation of the cardiovascular autonomic control in depressed patients and on the potential sex differences. Therefore, sex differences should be more carefully considered as they can add new insights into the etiopathogenesis of both these pathologies and lead to more effective therapeutic approaches. For instance, the frontal-vagal network proposed by Iseger et al. best highlights the target areas of new neuromodulatory therapies for depression, emphasizing the importance of the bidirectionality of heart-brain axis and the direct or indirect involvement of the vagus. Based on this, it is even more important to consider HRV measures in depression studies as a prognostic factor and in order to assess the influence of neuromodulation on cardiovascular autonomic control. New studies are required to shed further light on the effects of these new antidepressant therapies in relation to sex differences both from the point of view of efficacy and in the evaluation of sex-related differences in the neuromodulation of the areas involved by depression.

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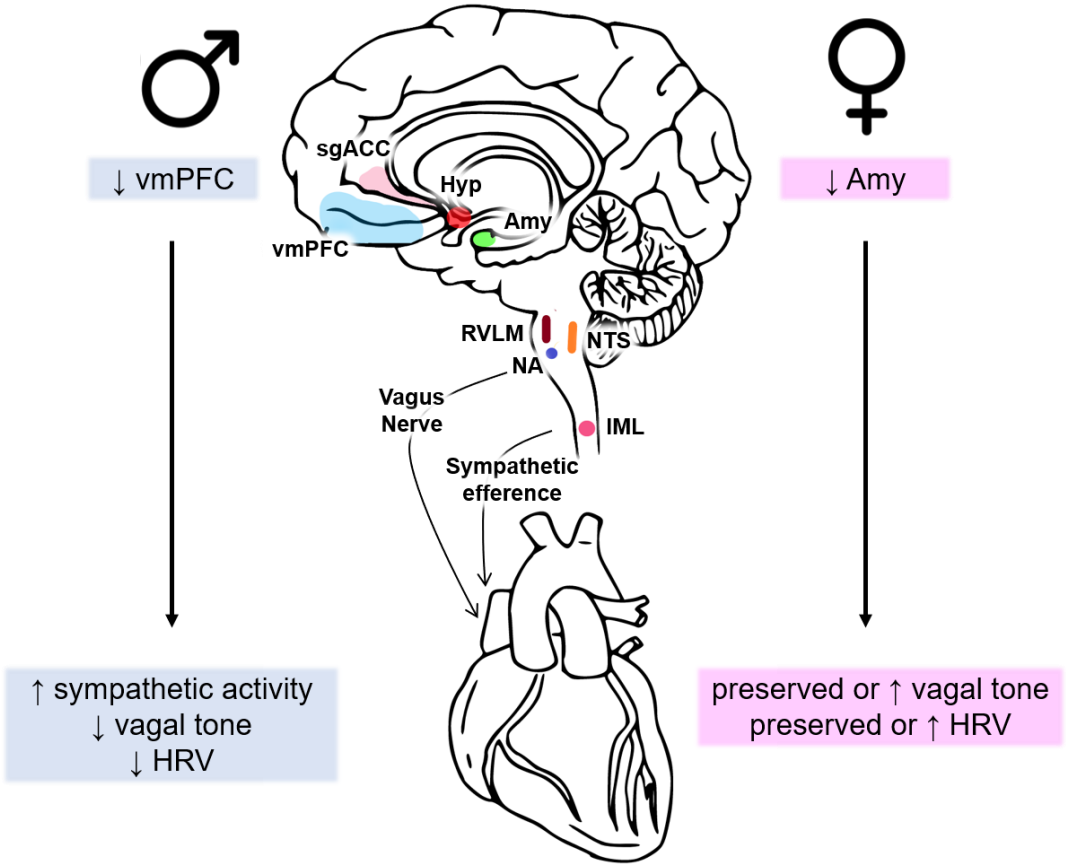

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710 *Figure 1.* **Sex differences in cardiac autonomic control of depressed patients.** Depression affects several functional
711 areas involved in the heart-brain axis. Thus, the cardiovascular autonomic control is altered. Recent studies highlight that
712 sex influences the relationship between depressive symptoms and cardiac autonomic dysfunction. vmPFC: ventromedial
713 prefrontal cortex; sgACC: subgenual anterior cingulate cortex; Amy: basolateral amygdala and the central nucleus of the
714 amygdala; Hyp: hypothalamus (lateral and paraventricular); NTS: nucleus of the solitary tract; RVLM: rostral
715 ventrolateral medulla; NA: nucleus ambiguous; IML: intermediolateral cell column of the spinal cord.

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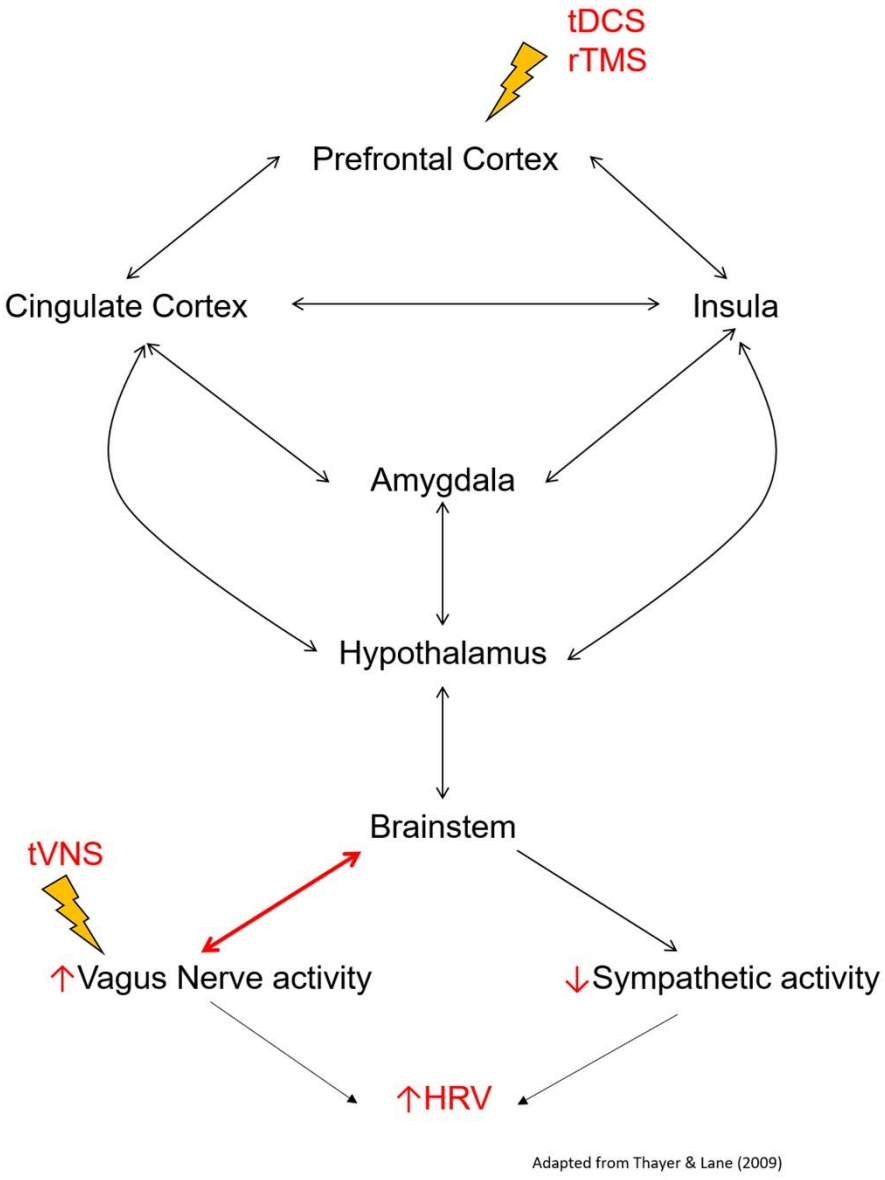

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721 *Figure 2.* **The frontal-vagal network and non-invasive neuromodulation techniques.** Non-invasive neuromodulation
722 techniques, such as repetitive Transcranial Magnetic Stimulation (rTMS), transcranial Direct Current Stimulation (tDCS)
723 and transcutaneous Vagus Nerve Stimulation (tVNS), modulate the entire frontal-vagal network. The prolonged
724 stimulation of vagus nerve or prefrontal cortex remodels the depression-damaged neuronal circuits and determines
725 cardioprotective effects.