CHARACTERISTICS OF CARDIORESPIRATORY FUNCTION DURING SLEEP RELATED TO DEPRESSION AND ANTIDEPRESSANT MEDICATION USE

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Abstract

Through a series of original research articles, this thesis explores the characteristics of autonomic cardiac regulation and respiratory function during sleep in association with depression and antidepressant medication use and validates a novel diagnostic biomarker of depression. Cardiorespiratory dysfunction during sleep may contribute to the increased risk of developing cardiovascular disease amongst individuals with depression. Sleep represents a unique physiological state shielded from many external confounding factors and may be a more relevant window to observe the effects of depression on cardiorespiratory function. In a first study, we found that depression was associated with abnormal autonomic modulation of cardiac activity during sleep. Specifically, depression was associated with reduced heart rate variability compared to healthy controls, and this difference was most prominent during sleep as compared to wake, which may indicate impairments in the parasympathetic modulation of the cardiac sinoatrial node. Secondly, we validated a machine-learning algorithm that uses patterns of heart rate during sleep to identify depression. This algorithm was found to have 79.9% classification accuracy, based on the differences in autonomic modulation associated with distinct mental states. The algorithm was highly generalizable across different depression subgroups and thus may be useful as an adjunct diagnostic tool. Finally, we found that the use of antidepressants, particularly serotonergic agents, was associated with worse sleep-related respiratory disturbances compared to non-medicated individuals with depression and those using non-serotonergic antidepressants. We proposed that depression-related alterations in serotonin receptor expression and binding may shape the response of the respiratory system to the use of serotonergic agents. Considering the high comorbidity between depression and sleep-related breathing disturbances and their impact on cardiovascular health, this has great clinical implications for the management

of depression. Taken together, these results show that depression is associated with several sleep-related abnormalities in terms of cardiorespiratory function, which may represent a valid biomarker of depression.

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1) **Saad M**, Ray LB, Bradley-Garcia M, Palamarchuk IS, Gholamrezaei A, Douglass A, Lee EK, Soucy L & Robillard R. Autonomic modulation of cardiac activity across levels of sleep depth in individuals with depression and sleep complaints. Under Review, *Psychosomatic Medicine.*

2) **Saad M**, Ray LB, Bujaki B, Parvaresh A, Palamarchuk I, De Koninck J, Douglass A, Lee EK, Soucy L, Fogel S, Morin CM, Bastien C, Merali Z & Robillard R. Using heart rate profiles during sleep as a biomarker of depression. BMC Psychiatry 2019;19:168.

3) Robillard R*, **Saad M***, Ray LB, Bujaki B, Douglass A, Lee EK, Soucy L, Spitale N, De Koninck J & Kendzerska T. Selective Serotonin Reuptake Inhibitor use is associated with worse sleep-related breathing disturbances in individuals with depressive disorders and sleep complaints: A retrospective study. *Co-first authors

Abbreviations

Analysis Of Covariance	**ANCOVA**
Angiotensin II Receptor Blocker	**ARB**
Angiotensin-Converting Enzyme	**ACE**
Apnea Hypopnea Index	**AHI**
Atrioventricular	**AV**
Beck Depression Inventory	**BDI**
Brain-Derived Neurotrophic Factor	**BDNF**
Body Mass Index	**BMI**
Cardiovascular Disease	**CVD**
Central Autonomic Network	**CAN**
Central Pattern Generator	**CPG**
Centre D'étude Des Troubles Du Sommeil	**CETS**
Chronic Mild Stress	**CMS**
Confidence Interval	**CI**
Conformité Européenne	**CE**
Coronary Artery Disease	**CAD**
Diagnostic and Statistical Manual Of Mental Disorders	**DSM**
Electrocardiogram	**ECG**
Electroencephalogram	**EEG**
Electromyogram	**EMG**
Electrooculogram	**EOG**
Heart Rate	**HR**
Heart Rate Variability	**HRV**
Heartbeat-Evoked Potential	**HEP**
High Frequency	**HF**
Inter-Beat Interval	**IBI**
Low Frequency	**LF**
Minimum Blood Oxygen Saturation	**SpO_2**
Monoamine Oxidase Inhibitor	**MAOI**
Montreal Archive Of Sleep Studies	**MASS**

Myocardial Infarction	**MI**
National Sleep Research Resource	**NSRR**
Non-Rapid Eye Movement	**NREM**
Noradrenergic Reuptake Inhibitor	**NRI**
Noradrenergic/Specific Serotonergic Antidepressant	**NaSSA**
Norepinephrine-Dopamine Reuptake Inhibitor	**NDRI**
Obstructive Sleep Apnea	**OSA**
Rapid Eye Movement	**REM**
Respiratory Disturbance Index	**RDI**
Respiratory Event Related Arousal	**RERA**
Reversible Monoamine Oxidase Inhibitor	**RIMA**
Root Mean Square of Successive Differences	**RMSSD**
Rostral Anterior Cingulate Cortex	**rACC**
Royal Ottawa Mental Health Centre	**ROMHC**
Respiratory Sinus Arrhythmia	**RSA**
Selective Serotonin Reuptake Inhibitor	**SSRI**
Serotonin	**5-HT**
Serotonin Antagonist and Reuptake Inhibitor	**SARI**
Serotonin-Norepinephrine Reuptake Inhibitor	**SNRI**
Sinoatrial	**SA**
Sleep Onset Latency	**SOL**
Slow-Wave Sleep	**SWS**
Standard Deviation	**SD**
Standard Deviation of Normal-to-Normal Intervals	**SDNN**
Suprachiasmatic Nucleus	**SCN**
Total Sleep Time	**TST**
Tricyclic Antidepressant	**TCA**
Upper Airway Resistance Syndrome	**UARS**
Wake After Sleep-Onset	**WASO**
Western's Brain & Mind Institute Sleep Research Laboratory	**BMISRL**

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Chapter 1 - General Introduction

1.1 The link between depression and cardiovascular disease

Depression is a multi-faceted psychological disorder characterized by significant behavioral, physiological and cognitive changes, affecting both mental and physical health. The lifetime prevalence of depression is estimated to be 20% globally(1), but depression is projected to become one of the leading causes of the global burden of disease by 2030, along with ischemic heart disease(2). As the two leading causes of disability worldwide, depressive disorders and cardiovascular diseases have a well-established relationship. There is a substantially higher risk of developing coronary artery disease (CAD)(3,4) and myocardial infarction (MI)(5) in those with depression, as compared to the general population. In fact, a prospective study found that the relative risk of developing CAD or MI in men who reported clinical depression at baseline was at least 2 times greater than non-depressed individuals(4). Another prospective cohort study reported that individuals with major depression were 2.7 times more likely to die from ischemic heart disease compared to non-depressed individuals over a median follow-up period of 8.5 years(6). Also, the risk of developing heart disease is directly related to the severity of the depressive disorder(7). Depression is not only a risk factor for cardiovascular disease, but also an independent predictor of poor prognosis for individuals who experience an adverse cardiovascular event(8). Specifically, new onset depression following MI is associated with increased cardiac mortality(9). In fact, the impact of depression on survival following a myocardial infarction is as detrimental as factors such as left ventricular dysfunction or prior MI(10).

Several factors tied to depression may underlie the increased risk of cardiovascular disease amongst this population. Some of the proposed mechanisms include the use of antidepressant

medications, hyperactivation of the hypothalamic-pituitary-adrenal axis, increased immune system activation, oxidative stress, and behavioural factors such as non-adherence to cardiovascular medication and physical inactivity(11–20). Moreover, abnormalities in autonomic nervous system activity altering cardiac rhythms may predispose depressed individuals to the development of arrhythmias, hypertension, congestive heart failure, and sudden cardiac death(21,22). Also, the high comorbidity between depression and sleep-related breathing disorders such as sleep apnea warrants further investigation due to their long-term consequences on cardiovascular health. The following sections will address the regulation of cardiovascular and respiratory function, the sleep profile of depression, the links between cardiorespiratory function during sleep, depression, antidepressant medication use, and cardiovascular disease, as well as the potential use of heart rate profiles during seep as an objective physiological biomarker of depression.

1.2 Autonomic regulation of cardiovascular function

Dynamic flexibility in the modulation of cardiac activity is necessary for cardiovascular health and is regulated by the autonomic nervous system(23). The heartbeat is generated by autorhythmic cells in the sinoatrial (SA) and atrioventricular (AV) nodes, the two pacemakers which initiate action potentials and coordinate the electrical activity of the heart. The impulse is initiated at the SA node, which results in atrial depolarization and contraction, followed by depolarization of the AV node, the AV bundle, the bundle of His and the Purkinje fibers, which ultimately results in ventricular contraction(24). Although this intrinsic conduction system consists of spontaneous depolarizations, the heart is under constant homeostatic regulation by the autonomic nervous system. The interactions of the parasympathetic and sympathetic nervous systems at the level of the SA node are modulated in response to sensory monitoring via

baroreceptors and chemoreceptors. These receptors monitor changes in arterial pressure and blood gas levels, respectively. The baroreceptor and chemoreceptor afferents are relayed via the vagus and glossopharyngeal nerves to the nucleus of the solitary tract, which are then integrated in the hypothalamus and the medullary cardiovascular center in the brainstem(25,26). Input from higher brain centers, as well as from intracardiac neurons, is also integrated to adjust parasympathetic and sympathetic outflow(23).

This afferent information is used for the neuromodulation of the activity of smooth and cardiac muscles via alterations in the activity of sympathetic preganglionic neurons in the upper thoracic spinal cord and parasympathetic preganglionic neurons in the dorsal motor nucleus of the vagus and the nucleus ambiguus. The axons of cardiac sympathetic preganglionic neurons project to the stellate ganglion, which provides the main efferent sympathetic nerve supply to the heart, while the preganglionic parasympathetic neurons innervate the heart via the vagus nerve. The activity at postganglionic noradrenergic sympathetic and cholinergic parasympathetic terminals innervating the sinoatrial node modulates chronotropic functions in the heart, resulting in changes in heart rate and blood pressure(24,27). The binding of norepinephrine to B1 adrenergic receptors, a G-protein coupled receptor, in the SA node results in activation of stimulatory G proteins, leading to a positive chronotropic effect, or increase in heart rate. Conversely, the binding of acetylcholine to muscarinic (M2) receptors leads to the activation of inhibitory G proteins, resulting in a negative chronotropic effect, or slowing of heart rate, and this inhibitory effect occurs on a much faster time scale(28).

According to the neuro-visceral integration model, cardiovascular activity is also modulated by a network of brain structures known as the central autonomic network (CAN). The CAN includes the prefrontal cortex (the anterior cingulate, insular, and ventromedial prefrontal cortices), limbic

areas including the central nucleus of the amygdala and the paraventricular nucleus of the hypothalamus, as well as brainstem structures (the periaqueductal gray matter, the nucleus of the solitary tract, the nucleus ambiguus, the ventrolateral and ventromedial medulla). Several of these regions are involved in the integration of emotional information, and changes in neural activity within these regions are correlated with measures of autonomic cardiac function(29–31). Thus, the CAN is responsible for cardiac regulation in relation to emotional factors(32).

The CAN modulates heart rate via input to the SA node through actions on the autonomic nervous system. Specifically, the orbitofrontal and medial prefrontal cortices tonically inhibit the amygdala via GABAergic neurons. The disinhibition or activation of the central nucleus of the amygdala leads to the suppression of parasympathetic activity and/or the activation of the sympathetic nervous system. This can occur via 1) the activation of sympatho-excitatory neurons in the rostral ventrolateral medulla (directly or indirectly), resulting in an increase in sympathetic outflow, or 2) the inhibition of nucleus ambiguus and dorsal vagal motor nucleus neurons, resulting in a reduction of parasympathetic activity(30). Thus, in addition to the modulation of cardiac activity by hypothalamic-brainstem centers, heart rate is also influenced by central information processing systems(29).

1.3 Dysregulation of autonomic activity in depression

Depression has been associated with hypoactivity in the prefrontal cortex(33–35), which may lead to increased activation of the central nucleus of the amygdala, resulting in an imbalance of parasympathetic and sympathetic modulation of heart rate. Specifically, depression is associated with a loss of vagal modulation and an increase in sympathetic activity, which has been demonstrated through several indices of autonomic function, including heart rate variability (HRV). In addition to the reductions in prefrontal cortex activity levels that may underlie this

autonomic dysregulation, depression is also associated with alterations in functional connectivity. Specifically, there is reduced functional connectivity between the rostral anterior cingulate cortex (rACC) in the medial prefrontal cortex and brainstem regions controlling autonomic activity. Reductions in rACC and brainstem functional connectivity is also associated with reduced cardiac vagal control. Considering the role of the rACC in the modulation of amygdala responses to emotional stimuli, this loss of functional connectivity may result in an inability to appropriately regulate autonomic activity in response to emotional factors in individuals with depression(36).

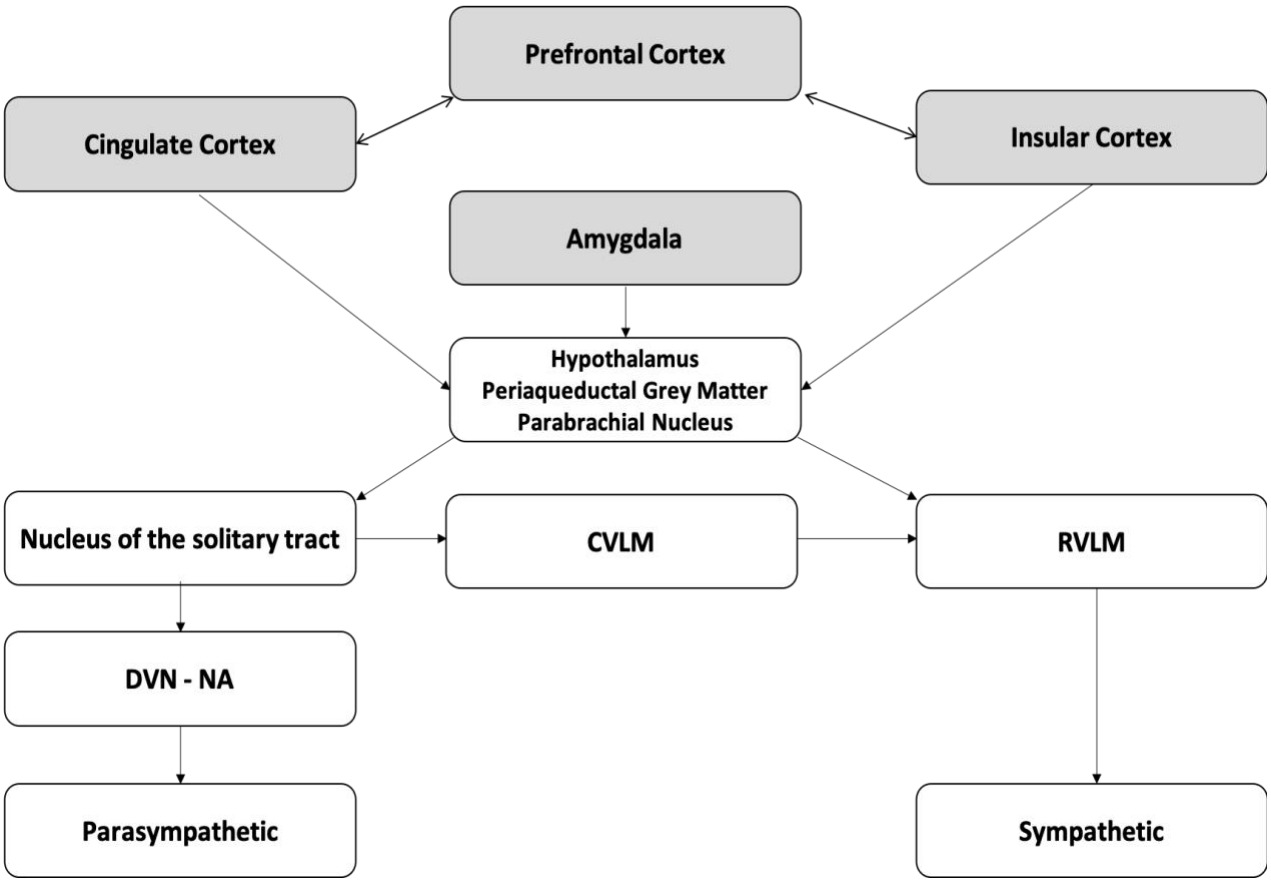

Figure 1. The central autonomic network regulating cardiac activity in relation to depression. The prefrontal cortex (medial and orbitofrontal cortices), as well as the cingulate and insular cortices are connected to the amygdala. The amygdala is under tonic inhibition by the prefrontal cortex. Disinhibition of the central nucleus of the amygdala results in the activation of sympathoexcitatory neurons in the rostral ventrolateral medulla (RVLM). RVLM sympathoexcitatory neurons may also be activated indirectly via inhibition of the nucleus of the solitary tract (NTS), which results in the reduction of inhibitory inputs from the caudal ventrolateral medulla (CVLM) to the RVLM. Vagal motor neurons in the dorsal vagal nucleus (DVN) and the nucelus ambiguus (NA) are also inhibited, leading to an increase in heart rate. Depression is associated with abnormalities in prefrontal, cingulate, insular cortices and amygdala activity and functional connectivity (grey boxes). Sleep loss also impairs prefrontal cortical and amygdala activity. Thus, abnormalities in the central autonomic network linked to both depression and sleep loss may impair autonomic cardiac regulation. Figure adapted from Thayer & Lane (2009) and Sgoifo (2015).

Several interdependent physiological processes operating on distinct timescales, such as respiration, blood pressure regulation, thermoregulation, circadian rhythms, and metabolism, contribute to fluctuations in heart rate. There are indications that most of these processes may be dysregulated in individuals with depression. In terms of measures of autonomic activity, individuals with depression have an increased skin conductance level compared to healthy controls(37), which reflects increased sympathetic nerve activity(38). Conversely, depression is associated with decreased baroreflex sensitivity, which quantifies reductions in heart rate in response to increases in systolic blood pressure, reflecting vagal withdrawal(37). As such, vagal nerve stimulation has been used as an effective treatment of severe depression(39,40). Depression is also associated with abnormalities in cardiorespiratory interaction. The respiratory sinus arrhythmia (RSA) is a measure of the modulation of heart rate by breathing patterns, wherein heart rate increases upon inspiration, and decreases during expiration(41), and serves to improve pulmonary gas exchange efficiency(42,43). Individuals with major depression exhibit reduced task-related RSA reactivity compared to healthy controls(44), and RSA may predict the course of depressive disorders(45). Importantly, RSA is a measure of HRV mediated by

rhythmic variations in vagal modulation of the sinoatrial node due to the central respiratory drive and lung inflation(46).

HRV is a widely used measure of autonomic cardiac modulation, representing the variation in the inter-beat-interval, or the time interval between consecutive heartbeats. The inter-beat interval is measured as the length of time between successive R waves of the QRS complex, reflecting ventricular contraction, in the electrocardiogram (ECG), and is thus termed as the RR interval. Importantly, HRV reflects the dynamic balance between the sympathetic and parasympathetic nervous system's actions at the level of the SA node(23). HRV is an intrinsic characteristic of healthy cardiac functioning, as it reflects the ability to adaptively respond to external and internal stimuli by altering heart rate from beat to beat. Several theoretical perspectives also posit that HRV is a marker of the top-down regulation of cognitive and emotional activity, due to the influences of the CAN on HRV. Importantly, depression is associated with reductions in HRV compared to healthy controls(47–51), and the improvement of depressive severity is associated with a corresponding normalization of frequency-domain HRV parameters, including an increase in high-frequency (HF) power(52).

While most of these studies were observational and therefore did not allow inferring causality, animal studies indicate that depression can actively induce changes in cardiovascular function. In rodents with depressive-like symptoms induced via 4 weeks of chronic mild stress (CMS) exposure, heart rate is elevated, while HRV is reduced, signifying autonomic dysfunction(53). Importantly, these abnormalities in autonomic cardiac regulation may result in cardiac electrophysiological disturbances, and can contribute to arrhythmogenesis(22,54). As such, CMS-exposed rats were found to be more vulnerable to developing chemically-induced ventricular arrhythmias(55).

1.4 Regulation of respiratory activity

Respiration is also automatically controlled and interacts closely with cardiovascular regulation. A cluster of neurons with pacemaker properties in the ventral respiratory column of the medulla known as the pre-Botzinger complex generate the main respiratory rhythm(56). This central pattern generator (CPG) provides the synaptic drives to motor neurons controlling the contraction of respiratory muscles including the intercostal, abdominal, and upper airway muscles. These respiratory-related neurons can be modulated via synaptic inputs from higher brain centers such as the insular cortex, hypothalamus, and amygdala, as well as central and peripheral chemoreceptors and mechanoreceptors which detect changes in blood pH and stretch, respectively(57,58). Moreover, serotonin is an important neuromodulator of respiration, and can have both excitatory and inhibitory effects depending on the profile of serotonin receptor expression of respiratory neurons(59–61). In addition to its role in central respiratory modulation, serotonergic neurotransmission can also alter respiration in response to changes in blood gas and pH homeostasis, due to the chemosensitive nature of 5-HT neurons(62,63). Thus, the impairments in serotonergic neurotransmission associated with depression may result in aberrant regulation of respiratory function. Moreover, considering the sleep-related reduction in serotonergic input to motor neurons regulating upper-airway muscles, abnormalities in respiration may be more apparent during sleep(64).

1.5 Sleep as a unique physiological state

Autonomic functions are distinctly regulated across varying levels of sleep depth and different phases of the circadian cycle. Healthy sleep is crucial to maintaining the homeostasis of both cardiovascular and respiratory functions, and is divided into two main types: rapid eye movement (REM) and Non-REM (NREM) sleep. REM sleep is characterized by higher

frequency and lower amplitude EEG activity (similar to wake), bursts of rapid eye movements, and a loss of muscle tone, while NREM sleep is characterized by lower frequency EEG rhythms. NREM sleep is further divided into three stages based on increasing sleep depth: NREM 1, NREM 2, and NREM 3 (SWS; slow-wave sleep)(65,66). These distinct stages serve different functions, as REM sleep is notably important for emotional memory processing and consolidation(67,68), while NREM sleep, specifically SWS, plays a prominent role in the restoration of synaptic homeostasis (i.e. downregulating synaptic strength to preserve energy)(69–71).

According to the two-process model of sleep regulation, the homeostatic and circadian processes interact to determine the propensity and duration of sleep(72,73). The circadian process is driven by the suprachiasmatic nucleus (SCN) which serves as a 24-hour 'clock' that regulates a range of physiological functions, including heart rate and sleep patterns. The homeostatic process accumulates sleep pressure during prolonged periods of wakefulness, and dissipates this pressure during sleep. Although the exact mechanisms underlying this process are unknown, adenosine has been proposed as an accumulating substance that drives the need to sleep(74,75). The homeostatic process can be indexed by slow-wave brain activity in NREM sleep. Finally, a third process, the ultradian process, determines the cycling of REM/NREM sleep stages(73,76).

The regulation of heart rate and respiration varies across sleep stages. During NREM sleep, there is a decrease in subcortical and cortical brain activity, and an increase in baroreflex sensitivity(77) and cardiopulmonary coupling(78), signifying a greater role for afferent peripheral regulation rather than central modulation of cardiac and respiratory function(79), as well as an increase in parasympathetic modulation(29). Moreover, increasing sleep depth is marked by progressively increasing parasympathetic activity. Specifically, HF HRV has been found to undergo a

progressive increase from NREM 1 to NREM 3, while respiration becomes deeper and less frequent with increasing sleep depth(80–82). Conversely, REM sleep is marked by increased central control of respiration and cardiac modulation(79), as well as a shift in the sympathovagal balance towards sympathetic predominance(29,78,82,83). Accordingly, low frequency (LF) HRV is increased during REM, compared to NREM sleep. Respiratory frequency is also increased during REM, compared to NREM sleep(80–82),

In addition to the distinctions in autonomic activity across levels of sleep depth, sleep provides a unique window to observe physiological changes due to the reduced impact of confounding factors present during the wake state. Sleep is relatively shielded from the behavioural factors, and constant cognitive and emotional processing that modulate autonomic activity during wake. Thus, the effects of depression on cardiorespiratory function may be more easily observed during sleep. Moreover, considering the abnormal sleep profile of depression, depression may exert varying effects on cardiorespiratory function across different types of sleep (REM vs. NREM), as well as across levels of sleep depth.

1.6 The sleep profile of depression

Alterations in sleep neurophysiology are one of the core symptoms of depression and are detrimental to cardiovascular and autonomic function. The sleep profile of depression has been extensively investigated using electroencephalography. Polysomnographic findings in individuals with depression show reduced total sleep time (TST), increased sleep onset latency (SOL), fragmented sleep, and reduced sleep efficiency (SE). There are also significant changes in sleep architecture, wherein REM onset latency is shortened, while REM duration and REM density are increased(84,85). Importantly, SWS (deep sleep) is often reduced, and there are abnormalities in the pattern of slow wave activity across sleep cycles, which is a marker of the homeostatic process

driving sleep pressure(85–89). The amount of slow wave activity normally decreases across sleep cycles, due to diminishing sleep propensity. However, this observation is reduced in individuals with depression, reflecting a disruption in the homeostatic sleep process(90,91). Moreover, the use of antidepressants has a significant impact on sleep neurophysiology. Specifically, most antidepressants, including selective serotonin reuptake inhibitors (SSRIs), directly suppress REM sleep(92), and disrupt sleep continuity(93–95). Considering the negative effects of serotonin on respiratory function in animals(96–98), SSRIs may also have an impact on sleep-related breathing disturbances, but this remains to be formally investigated.

1.6.1 Autonomic function during sleep in depression

In terms of autonomic cardiovascular function during sleep, there is limited research amongst individuals with depression. A study assessing the circadian pattern of heart rate in psychiatric illness found that depression was associated with a rapid drop in heart rate upon sleep onset, which progressively increased to wake levels across the night, whereas healthy individuals exhibited a consistently lower heart rate throughout the night(99). Another study found reduced HRV amongst individuals with depression compared to healthy controls during REM sleep(100). A second study investigated non-linear indices of HRV in individuals with depression and found reduced complexity in heart rate during REM sleep, compared to healthy controls(101). Collectively, these studies suggest that the autonomic modulation of cardiac activity may be impaired across the sleep period as a whole and during REM sleep in depression, however, this remains to be investigated across varying levels of sleep depth and across sleep states (i.e. NREM vs REM).

1.6.2 Sleep-related breathing disturbances in depression and the role of antidepressant use

There is a high comorbidity between depression and sleep-related breathing disorders, such as obstructive sleep apnea (OSA)(102). In fact, the prevalence of sleep-related breathing disorders in individuals with a diagnosis of major depressive disorder has been reported to be approximately 18%(103–105). According to a large-scale cross-sectional study, individuals with depression were 5 times more likely to have OSA compared to the general population(103).

OSA is characterized by recurrent upper airway obstruction that causes partial or complete cessation of breathing (hypopneas and apneas, respectively). These disruptions in ventilation result in oxygen desaturation and carbon dioxide accumulation in the blood, and autonomic distress leading to increases in heart rate and blood pressure. Moreover, OSA is associated with grey matter atrophy of the orbital frontal cortex, anterior cingulate cortex, and amygdala, which may lead to emotional dysfunction(106). OSA is also associated with altered functional connectivity between various brain regions involved in emotional regulation, including the insular and cingulate cortices, the hippocampus, and the amygdala(107).

Prospective studies report an increased risk of depression following the development or worsening of OSA(108,109). Although the mechanisms underlying this relationship are not fully elucidated, serotonin may be a linking factor due to its role in both depression and respiratory function. For instance, animal studies have demonstrated that intravenous injection of serotonin generates apneas, while serotonin antagonists reduced the amount of sleep apnea(110,111). Importantly, depression is associated with abnormalities in serotonin receptor expression and activity levels(112–116). Also, serotonergic neurotransmission is key in regulating genioglossus muscle activity via the hypoglossal nerve, which affects upper airway patency. Thus, an important factor to consider in the relationship between depression and OSA is the use of serotonergic antidepressants, which are known to impact sleep(117) and may exacerbate respiratory

dysfunction(118) as well as directly influence cardiovascular function(119–121). Thus, the interactions between depression-related abnormalities in sleep and serotonergic neurotransmission may shape the response of the respiratory system to the use of serotonergic agents, which could contribute to the increased comorbidity between depression and sleep-related breathing disorders. The relationship between antidepressant use and sleep-related respiratory function has not yet been examined amongst individuals with depression, and warrants investigation, notably considering the negative effects of sleep-related breathing disturbances on cardiovascular health.

1.7 Interactions between depression, sleep, and cardiorespiratory function

In summary, there may be complex and reciprocal relationships between depression, antidepressant use, cardiorespiratory function during sleep, and cardiovascular disease. The abnormalities in sleep architecture and cardiorespiratory function associated with depression and antidepressant use may have independent and additive effects on cardiovascular health and on the course of depressive disorders. It is necessary to explore these underlying relationships in order to uncover the effects of depression and related factors on cardiac outcomes.

1.8 The need for a biomarker of depression

Currently, the diagnosis of depression relies upon a subjective method of identifying symptoms consistent with the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria, which may lead to diagnostic error. In fact, diagnostic sensitivity for depression amongst general practitioners has been suggested to be as low as 47.3%(122). Moreover, the DSM-5 Field Trials found that the interrater reliability for the diagnosis of major depression amongst clinicians was in the questionable range [Cohen's kappa = 0.25 CI(0.13-0.36)](123). Therefore, there is an ongoing search for an objective physiological biomarker to aid not only with the diagnosis of depression, but also with its clinical course and treatment monitoring. HRV has been proposed as

a unique, multi-systemic marker of both neural and cardiac function. Combined with the sleep architecture alterations associated with depression, patterns of HRV across varying sleep stages may represent a unique and accurate physiological marker of depression.

1.9 Objectives

The present thesis addressed the links between depression, antidepressant use, and cardiorespiratory function during sleep. More specifically, the main objectives were threefold:

1. Assess the autonomic modulation of cardiac function during sleep in individuals with depression and sleep complaints vs. healthy controls (Chapter 2)

    1.1. Compare heart rate and time-domain parameters of HRV across wake and different sleep states (NREM and REM)

    1.2 Compare heart rate and time-domain parameters of HRV across wake and varying levels of sleep depth (NREM 1, NREM 2, and NREM 3)

2. Validate the accuracy of an automated heart-rate profiling algorithm for the identification of depression (Chapter 3)

    2.1. Determine the generalizability of this algorithm across depression subgroups stratified by potential confounding factors

3. Examine the link between antidepressant use and sleep-related breathing disturbances in individuals with depression and sleep complaints (Chapter 4)

    3.1 Compare sleep-related breathing disturbances in individuals with depression vs. depression combined with antidepressant use vs. controls (non-medicated, non-depressed)

3.2 Compare sleep-related breathing disturbances in individuals with depression using serotonergic vs. non-serotonergic antidepressants vs. no antidepressants

3.3. Assess the interactions between the type of sleep (NREM and REM) and sleep-related breathing disturbances across the groups of interest

Chapter 2 – Autonomic modulation of cardiac activity across levels of sleep depth in individuals with depression and sleep complaints

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Abstract

Objective: We assessed mean heart rate (HR) and heart rate variability (HRV) across wake, rapid eye movement (REM) and non-rapid eye movement (NREM) sleep, and across varying levels of NREM sleep depth in individuals with depression and sleep complaints.

Methods: Retrospective polysomnographic data was obtained for 25 individuals diagnosed with depression (84% female; mean age = 33.8±12.2 years) and 31 mentally healthy controls (58.1 % female; mean age = 37.2±12.4 years). All were free of psychotropic and cardiovascular medication, cardiovascular disease, and sleep-related breathing disorders. HR and time-domain HRV parameters were computed on 30-second electrocardiography segments and averaged across the night for each stage of sleep and wake.

Results: Compared to the control group, the depression group had higher HR across wake, REM and all levels of NREM depth ($F(1, 51)=6.3$, $p=.015$). Significant group by sleep stage interactions were found for HRV parameters: standard deviation of normal-to-normal intervals (SDNN; $F(2.1, 107.7)=4.4$, $p=0.014$), and root mean square differences of successive R-R intervals (RMSSD; $F(2.2, 113.5)=3.2$, $p=.041$). No significant group difference was found for SDNN or RMSSD during wake (all $p\geq.32$). However, compared to the control group, the depression group had significantly lower SDNN in REM ($p=.040$) and all NREM stages (all $p\leq.045$), and lower RMSSD during NREM 2 ($p=.033$) and NREM 3 ($p=.034$).

Conclusions: This study suggests that the abnormalities in autonomic cardiac regulation associated with depression and sleep problems are more prominent during sleep, especially NREM sleep, than during wake. This may be due to abnormalities in parasympathetic modulation of cardiac activity.

1. Introduction

Individuals with depression are at increased risk of developing cardiovascular diseases (CVD) as compared to the general population(12,124). Several factors tied to the pathophysiology of depression may contribute to poor cardiac outcomes. For instance, autonomic alterations, increased inflammation, dysregulation of the hypothalamic-pituitary-adrenal axis, and behavioral factors such as tobacco use or low levels of physical activity may all mediate the increased risk of CVD in people with depression(11,12,14,125). Sleep abnormalities are likely to interact with many of these factors, including autonomic regulation of cardiac activity, and may thus modulate the cardiovascular profile of depression.

Depression is linked to reduced baroreflex sensitivity and increased variability in ventricular repolarization time, which are both reflective of autonomic dysfunction and predictors of CVD(126,127). In the wake state, compared to healthy controls, individuals with depression have: i) increased muscle sympathetic nervous system activity(128); ii) elevated plasma cortisol and norepinephrine levels(8,129–131), suggestive of sympathetic hyperactivity; iii) less power in the high frequency (HF) range of heart rate variability (HRV), suggesting decreased cardiac vagal activity(101); and iv) lower standard deviation of normal-to-normal intervals (SDNN) and lower root mean square of successive RR interval differences (RMSSD), reflecting a reduction in overall variability and vagal activity(47,48,50,51,132). However, these findings are not entirely consistent, with some studies reporting no significant differences in HF power or time-domain measures across depression and control groups(47,133,134), or attributing significant differences to the effects of antidepressants(135). During wake, heart rate (HR) is affected by various behavioural and cognitive factors, which may add noise to the signal and could partly explain some

of these inconsistent findings. Given the absence of these factors during sleep, the observable effects of depression on HRV may be more easily identified in this state(136).

Depression-related sleep abnormalities are likely to interact with the autonomic regulation of cardiac activity, and may thus modulate the cardiovascular profile of depression(137). In healthy individuals, sleep onset is characterized by a rapid reduction in HR, which remains relatively low throughout the night and sharply rises upon awakening(99). Compared to pre-sleep wakefulness, non-rapid eye movement (NREM) sleep is accompanied by an increase in HF HRV, due to increases in vagal modulation, and a reduction in low frequency (LF) HRV(138–140). Evidence from direct sympathetic nerve recordings(141,142), plasma catecholamine levels(143), and HRV indices suggest an increase in parasympathetic activity during NREM sleep, and a shift towards sympathetic dominance during rapid eye movement (REM) sleep. Specifically, HF HRV is higher in NREM compared to REM sleep, while LF HRV is higher in REM than NREM sleep(138,139,144,145). Within NREM sleep, some studies found a progressive increase in HF HRV from NREM stage 1 (NREM1) to NREM stage 3 (NREM3) sleep(139,146,147), while others reported reduced cardiac vagal modulation during NREM3 compared to NREM stage 2 (NREM2) sleep(148,149). Considering these normal fluctuations in autonomic function across sleep stages, depression-driven abnormalities in both cardiovascular regulation and sleep neurophysiology may interactively influence HR responses to the progression of sleep stages across the night. From this perspective, dynamic changes in HR and HRV across sleep stages may reflect cardiovascular responses to endogenously driven variations in physiological state.

Limited studies have assessed sleeping HRV in depression(100,101). Pawlowski and colleagues (2017) report increased HR and reduced SDNN, RMSSD, LF-power, and HF-power during REM sleep in depressed individuals compared to healthy controls, but they did not assess these

parameters during NREM sleep(100). More recently, Kwon et al. (2019) reported lower HR complexity during REM sleep in individuals with depression as compared to healthy controls(101). They also observed lower SDNN in the depression group during pre-sleep wakefulness, but did not find significant group differences in any stage of sleep. However, this study(101) combined NREM stage 1 (NREM1) and NREM2 sleep, and thus did not differentiate between the varying levels of sleep depth. Thus, the present study aimed to: i) compare the sensitivity of sleep states (wake, REM and NREM sleep) to depression-related abnormalities in HR and HRV, and ii) assess autonomic cardiac regulation across the progression of NREM sleep depth (wake, NREM1, NREM2, and NREM3) in individuals with depression and sleep complaints.

2. Methods

2.1 Cases

As part of a retrospective study conducted at the Sleep Disorders Clinic of the Royal Ottawa Mental Health Centre (ROMHC), a systematic review of medical charts was conducted to identify patients who underwent polysomnography between 2006 and 2016 and met the criteria described below.

Depression group. To be included in the depression group, patients had to have a documented history of a depressive syndrome (*e.g.*, major depression, dysthymic disorder, depressive disorder not otherwise specified), and current depressive symptoms on the Beck Depression Inventory (BDI-II $\geq$14;40) around the time of their sleep assessment. Patients included in this sample were free of other psychiatric comorbidities, except for anxiety disorders.

Control group. All patients included in the control group had no history of mental or neurological disorders, and were asymptomatic on the BDI-II (score <14). A psychologist reviewed and classified all diagnostic information for mental disorders and a neurologist reviewed and classified all CVD diagnoses.

Patients from both groups were systematically excluded if they met any of the following criteria: Apnea-Hypopnea Index (AHI) $\geq$5 events per hour or a Respiratory Disturbance Index (RDI) $\geq$15, a body mass index (BMI) $\geq$29kg/m^2, any history of CVD, and use of any psychotropic, chronotropic, or sleep-related medications at the time of polysomnography. This retrospective study was approved by the Human Research Ethics Board of the Royal Ottawa Health Care Group.

2.2 Procedures

All patients filled out the BDI-II, underwent height and weight measurement to determine BMI, and underwent diagnostic level 1 polysomnography at the ROMHC Sleep Clinic.

2.2.1 Polysomnographic Recordings

A registered sleep technologist placed electrodes according to the 10-20 system with: 3 scalp electroencephalogram (EEG) channels (F3, C3 and O1), ground and reference channels, right and left electrooculograms (EOG), 2 chin and leg electromyograms (EMG), and 2 ECG channels. Respiration was monitored with an airflow cannula (pressure transducer), nasal-oral thermistor, respiratory effort via thoracic and abdominal respiratory belts, and blood oxygen saturation via an oximeter probe on the finger. Sleep stage scoring was manually performed by registered sleep technologists in accordance with the clinical scoring guidelines established by the American Academy of Sleep Medicine(65). The following sleep variables were then computed for descriptive purposes: total sleep time (TST), sleep onset latency, REM latency, and percentage of

time spent in NREM stage 1, NREM stage 2, NREM stage 3 (slow wave sleep), and rapid eye movement (REM) sleep. TST was calculated as the total time spent asleep between "lights off" and "lights on" tags. Sleep stage percentages were calculated as the percentage of time between "lights off" and "lights on" scored as NREM1, NREM2, NREM3, and REM divided by TST.

2.3 HRV analysis

ECG signals were visually inspected and artifacts were manually removed using Kubios HRV Premium software (version 2.3; University of Kuopio, Kuopio, Finland; 42). The corrected signals were then individually split into 30-second segments that were temporally aligned with sleep stage scoring epochs, based on their occurrence during EEG-defined wake or sleep stages (NREM1, NREM2, NREM3, and REM) using custom MATLAB scripts (R2017, Mathworks, Inc., Natick, MA). Inter-beat interval (IBI) values were subsequently extracted for each individual segment in MATLAB. Using the ARTiiFACT software (version 2.13; University of Würzburg, Würzburg, Germany; 43), HR and HRV parameters were computed for each segment separately. Mean HR, as well as the following time-domain HRV parameters were calculated on 30-second segments: SDNN (standard deviation of all normal RR intervals), and RMSSD (root mean square of successive RR interval differences). Time-domain variables were selected in order to match the temporal resolution of sleep stage scoring. Several studies(153–155) have assessed the reliability of 30-second recordings in comparison to the gold standard of 5-minute recordings. For instance, the minimum length of data required for the accurate assessment of RMSSD has been proposed to range between 10-30 seconds(153,154), and 30-second recordings have been recommended to evaluate SDNN(155). The resulting HR and HRV parameters were then averaged across all segments in wake and in each sleep stage for every participant.

2.4 Statistical analysis

For descriptive purposes, a chi-square test was used to compare sex distributions across the two groups. Age, AHI, BDI, sleep architecture variables, and the length of available artifact-free ECG data were compared across groups using independent samples t-tests or Mann-Whitney U tests.

Main analyses were conducted for HR and HRV parameters using mixed analyses of covariance (ANCOVA) with one independent factor (group: depression and control) and one repeated measure [sleep states: wake, NREM (*i.e.*, combination of NREM1, NREM2 and NREM3), and REM] while controlling for sex. Similar ANCOVAs were also used to assess group differences across the progression of sleep depth (wake, NREM1, NREM2, and NREM3) while controlling for sex. SDNN and RMSSD were log transformed to improve normality. Huynh-Feldt corrections were used where appropriate. Post-hoc independent samples t-tests were performed to decompose significant group by sleep interactions. All analyses were carried out using the Statistical Package for the Social Sciences (SPSS, version 22.0, IBM Corp, Armonk, NY).

3. Results

3.1 Sample characteristics

Descriptive information is outlined in Table 1. The depression and control groups included 25 (mean age = 33.8 ± 12.2 years) and 31 patients (mean age = 37.2 ± 12.4 years), respectively. There were no significant differences across groups in terms of age, BMI, AHI or sleep efficiency. Although the depression group had significantly less NREM2 [both in absolute (minutes) and relative (as a percentage of total sleep time) values] compared to controls ($p<.050$), there were no significant group differences in the length of artifact-free ECG data compared across all sleep

stages. The depression group had a significantly higher proportion of females (84.0%) than the control group (58.1%; $x^2(1) = 4.4$, p=.036).

3.2 Heart rate and HRV parameters

Mean values and standard deviations for HR and HRV parameters are reported in Tables 2 and 3.

3.2.1 Sleep States (Wake vs. NREM vs. REM)

There was no significant group by sleep state interaction for mean HR. A significant main effect of group revealed that those with depression had higher mean HR than controls (p=.020). A significant main effect of sleep state showed that mean HR was significantly lower during NREM sleep, compared to both wake (p<.001) and REM sleep (p<.001). After controlling for sex differences, the effect of sleep state persisted (p=.001), while the group effect became a trend (p=.056).

There was a significant group by sleep state interaction for SDNN (F(1.9, 97.9)=4.0, p=.023). SDNN was significantly reduced in the depression group compared to controls during both NREM (p=.026) and REM (p=.040) sleep, but not during wake (p=.72). This group difference was somewhat more pronounced in NREM than in REM sleep. This interaction persisted after controlling for sex differences (F(1.9, 97.6)=3.3, p=.043).

There was a significant group by sleep state interaction for RMSSD (F(1.9, 97.9)=3.2, p=.048; Figure 1). The depression group tended to have lower RMSSD than controls during NREM sleep (t(52)=2.0, p=.054), but not during wake (t(52)=0.5, p=.59) or REM (t(52)=1.7, p=.094). This interaction did not persist after controlling for sex (F(1.9, 96.6)=2.2, p=.11). However, a significant main effect of sleep state on RMSSD persisted after controlling for sex (F(1.9, 96.6)=6.0, p=.004).

Overall, RMSSD was significantly lower during REM sleep as compared to both NREM sleep ($p<.001$) and wake ($p=.013$).

3.2.2 Sleep Depth (Wake vs. NREM1 vs. NREM2 vs. NREM3)

There was no significant group by sleep depth interaction for mean HR. However, there were significant main effects of group ($F(1, 51)=6.3$, $p=.015$) and sleep depth ($F(1.7, 87.3)=18.8$, $p<.001$). Compared to controls, the depression group had higher HR ($p<.050$). There was a progressive decrease in HR from wake to NREM1 to NREM2, followed by a slight increase in NREM3 (Figure 2). These main effects of group and sleep persisted after controlling for sex differences.

There was a significant group by sleep depth interaction for SDNN ($F(2.1, 107.7)=4.4$, $p=0.014$). The depression group had a significantly lower SDNN compared to the controls in all NREM sleep stages, ($t(51)\geq 2.1$, $p\leq .045$; Figure 2), but not during wake ($t(51)=0.9$, $p=.35$). This interaction persisted after controlling for sex differences ($F(2.1, 104.8)=3.5$, $p=.032$).

There was a significant group by sleep depth interaction for RMSSD ($F(2.2, 113.5)=3.2$, $p=.041$). The depression group had significantly lower RMSSD compared to controls during NREM2 ($t(51)=2.2$, $p=.033$) and NREM3 ($t(51)=2.2$, $p=.034$), but not during wake ($t(51)=1.0$, $p=.32$) or NREM1 ($t(51)=1.7$, $p=.090$). After controlling for sex differences, this interaction did not persist ($F(2.2, 111.6)=2.1$, $p=.12$), but a significant main effect of sleep depth persisted ($F(2.2, 111.6)=6.7$, $p=.001$). Overall, RMSSD was significantly higher during NREM1 compared to wake ($p=.042$), and significantly lower during NREM3 compared to NREM2 ($p=.007$).

4. Discussion

Based on retrospective data from non-medicated people with depression referred to a sleep clinic, this study suggests that some of the HRV abnormalities related to depression and sleep problems are more prominent during REM and NREM sleep than during wake, with slightly more prominent abnormalities during NREM sleep.

HRV is controlled by the central autonomic network, which acts on the cardiac sinoatrial node via the stellate ganglion and vagus nerve. Prefrontal cortical areas (the medial prefrontal cortex and the orbitofrontal cortex) tonically inhibit the amygdala, which has connections to medullary cardioacceleratory circuits. Under conditions of stress or threat, certain areas of the prefrontal cortex become less active, resulting in amygdala disinhibition which leads to the suppression of parasympathetic activity and to sympathetic hyperactivity, as reflected by an increase in HR and decrease in HRV(30,156–158). Importantly, depression is associated with prefrontal hypoactivity, and increased activation of the amygdala related to prolonged emotional processing(35,159). Moreover, sleep deprivation is associated with a reduction in the prefrontal control of limbic activity, and an increased amygdala response to negative emotional stimuli(160). Thus, the neural correlates of depression may directly contribute to the observed dysfunction in autonomic activity, or indirectly via the neural effects of sleep loss. Importantly, both REM and NREM sleep are associated with reductions in prefrontal cortical activity compared to wake(161), which may explain our finding of reduced HRV associated with depression most prominent during sleep.

In the present study, mean HR was found to be significantly higher in individuals with depression, as compared to controls, during wake and across all levels of sleep depth. This confirms that the depression-related autonomic dysfunction observed in the wake state in previous studies persists during sleep. Moreover, the significant differences in HR observed across sleep stages were in line

with known fluctuations in autonomic function related to sleep. In both groups, mean HR was higher during wake and REM sleep, as compared to NREM sleep. This finding can be explained by parasympathetic dominance during NREM sleep, which decelerates HR(29,137,138).

Moreover, our results suggest that the depression profile of HRV changed across sleep stages. This was in contrast to our finding that individuals with depression had higher overall mean HR. Both the sympathetic and parasympathetic branches of the autonomic nervous system contribute to SDNN(162–164). A significant interaction was found whereby there was no significant group difference in SDNN during wake, while a significant group difference was apparent during both NREM and REM sleep. These effects were slightly more prominent during NREM than REM sleep. This group difference persisted across all levels of sleep depth, emerging in NREM1 and persisting across both NREM2 and NREM3 sleep. Also, the depression group had a decrease in SDNN from wake to NREM sleep, while the control group did not, which may also point to the absence of a surge in vagal activation during NREM sleep, resulting in a loss of overall variability. Thus, the effects of depression on autonomic cardiac modulation are most prominent during sleep, more specifically NREM sleep, suggesting that the depression-related reduction in overall variability may be more heavily influenced by parasympathetic modulation. Moreover, the assessment of sleep stage-specific HRV across different sleep cycles throughout the night may reveal further impairments in autonomic cardiac regulation in individuals with depression.

Group differences in RMSSD widened with increasing sleep depth, becoming significant only during NREM2 and NREM3 (Figure 2). Since RMSSD is thought to be parasympathetically modulated(162–164), this supports the notion that abnormalities in parasympathetic modulation may play an important role in the overall reduction in HRV in individuals with depression. Also, the RMSSD was higher during NREM sleep compared to wake, in the control group, representing

an increase in vagal modulation. Conversely, this effect was not apparent in the depression group. This is reminiscent of post-myocardial infarction patients who do not present the normal surge in parasympathetic activity, as indexed by HF power, during NREM sleep(165). The absence of the surge in vagal activation during NREM sleep may thus represent a risk for adverse cardiovascular events in individuals with depression. Additionally, vagus nerve stimulation has been found to have antidepressant effects in individuals with treatment-resistant depression, further reinforcing the role of impaired parasympathetic cardiac modulation in depression(166). However, further research is required to compare autonomic cardiac regulation across different types of depression and levels of depressive severity.

It is worth noting that, in the present study, the effects of depression on mean HR and RMSSD during sleep seemed to be strongly modulated by sex, as some group differences were no longer significant after controlling for differences in sex distributions. This is in line with the results of a meta-analysis that showed significant reductions in SDNN, along with increased HR in females compared to males(167). This could be influenced by sex differences in the neural control of the heart. For instance, amygdala activity and HRV are positively correlated in women, and negatively correlated in men(168). However, the relationship between depression and cardiac autonomic dysfunction is more robust in males compared to females(169–171). While the sample size of the current study was too small to enable direct sex-comparisons, this highlights the need for larger studies to evaluate how sex influences the effects of depression on HR during sleep.

Depression is also associated with increased activation of inflammatory pathways, which interacts with autonomic function(172). A study assessing the effects of an acute inflammatory challenge in healthy individuals found significant increases in the LF/HF HRV ratio upon administration of an inflammatory vaccination model(173). Interestingly, the inflammatory effects of this vaccine

on autonomic function were mediated via components of the central autonomic network which are also involved in affective processing and mood disorders, like the anterior cingulate cortex. Moreover, increased levels of inflammatory markers such as fibrinogen, interleukin-6, and C-reactive protein are associated with reduced HRV in depressed individuals with CVD(174,175). This relationship between inflammatory markers and HRV has also been found in non-depressed individuals(176,177). Additionally, in healthy individuals, increased vagal activity is associated with anti-inflammatory effects that reduce the production of pro-inflammatory cytokines(178). Thus, a potential physiological mechanism underlying autonomic impairment may involve the increased levels of inflammatory cytokines in individuals with depression.

The autonomic dysfunctions observed in depression have important prognostic implications for CVD, as well as for the course of depressive disorders. Prospective studies in individuals free of CVD found that reduced HRV at baseline predicted an increased risk of adverse cardiac outcomes, including the development of coronary heart disease, as well as increases in all-cause mortality(21,179–181). Clinical depression is also associated with a relative risk of 2.7 for the development of coronary heart disease in initially physically healthy individuals(182). Other studies have found that low HRV is related to ruminative thinking(183,184), which is associated with worse depressive symptoms and increased number and duration of depressive episodes(185,186). Importantly, both rumination and low HRV are associated with inadequate inhibitory control by the prefrontal cortex and increased reactivity of the amygdala(184,187,188). Moreover, the successful application of biofeedback techniques to increase HRV in depressed individuals is associated with improvements in subjective mood, further reinforcing the notion that HRV may have an impact on the course of depressive disorders(189). Of note, the negative effects of depression-related sleep disturbances on cardiac autonomic activity may also contribute to poor

cardiovascular and depression outcomes. Chronic sleep deprivation is associated with impaired autonomic modulation reflected by reduced HRV(190). Moreover, insomnia is also commonly accompanied by reduced HF HRV(137). Thus, the increased risk of CVD in individuals with depression may be mediated via direct effects of depression on autonomic activity, as well as indirectly via comorbid sleep problems.

5. Limitations

Firstly, this study was based on patients with sleep complaints who were referred to a specialized sleep disorders clinic. Thus, this sample may not be representative of the general population with depression. However, sleep problems are highly comorbid with depression and, considering the potential interactions between sleep disturbances and the pathophysiology of depression for autonomic functions, this represents an important subgroup to investigate. Furthermore, both groups were sourced from the same clinic, and we were able to rule out individuals with significant sleep-disordered breathing. Secondly, the two groups had unequal sex distribution. Although we attempted to control for this statistically, the findings suggest some considerable modulation of certain HRV variables by sex. Finally, we were unable to compute frequency-domain measures of HRV such as HF power, due to the use of 30-second windows of ECG data. Although this limited our analyses of the parasympathetic modulation of cardiac activity, we were able to align our time-domain HRV measures to sleep stage epochs which increased the resolution of our analyses and allowed us to conduct our analyses with more data points.

6. Conclusion

The current study assessed autonomic cardiac modulation, indexed by HR and HRV across sleep stages, in individuals with depression and sleep complaints compared to controls with sleep complaints. Depression-related autonomic dysfunctions appear to persist, and, in some cases, be

more prominent during sleep. This persistent imbalance in autonomic function may worsen the increased risk of cardiovascular morbidity and mortality in individuals with depression. Thus, further research is required to identify the underlying pathophysiological mechanisms by which this may occur. Prospective studies are also required to determine whether abnormal profiles of sleep-derived HR and HRV can normalize following the treatment of depression.

Table 1. Characteristics of depression and control groups

	Depression mean ± SD	Control mean ± SD	U/t/X^2	p
Subjects (n)	25	31	-	-
Age (years)	33.8 ± 12.2	37.2 ± 12.4	1.0	.30
Females (%)	84.0	58.1	4.4	.036
BMI (kg/m^2)	24.2 ± 2.6	24.1 ± 2.8	-0.1	.91
AHI (events/hour)	0.8 ± 1.0	1.0 ± 1.2	363.5	.69
BDI	22.6 ± 9.5	7.0 ± 4.3	0.0	.001
Sleep Efficiency (%)	88.2 ± 10.0	85.9 ± 9.2	306.0	.18
TST (min)	396.6 ± 52.3	390.0 ± 48.2	-0.5	.63
WASO (min)	41.1 ± 43.4	55.2 ± 40.1	271.5	.056
SOL (min)	13.4 ± 10.4	10.8 ± 10.2	314.0	.226
NREM1 (min)	61.0 ± 46.2	45.9 ± 28.5	309.5	.20
NREM2 (min)	196.9 ± 52.7	226.8 ± 46.4	2.3	.028
NREM3 (min)	61.9 ± 45.4	50.6 ± 33.2	-1.1	.29
REM (min)	76.9 ± 31.7	66.7 ± 20.1	308.0	.19
%NREM1 (%TST)	16.0 ± 12.9	12.2 ± 8.6	322.0	.28
%NREM2 (%TST)	49.5 ± 10.5	58.0 ± 9.1	3.2	.005
%NREM3 (%TST)	15.3 ± 10.9	12.8 ± 8.2	-1.0	.33
%REM (%TST)	19.2 ± 7.3	17.0 ± 4.2	-1.4	.17
REM Latency (min)	169.6 ± 186.8	140.4 ± 127.2	369.5	.97

SD: Standard deviation, BMI: Body Mass Index, AHI: Apnea-Hypopnea Index, BDI: Beck Depression Inventory, TST: Total Sleep Time, WASO: Wake After Sleep Onset, SOL: Sleep Onset Latency

Table 2. HR and HRV across sleep states

Parameter	Sleep	Depression	Control	Group*Sleep		Sleep Effect		Group	
		mean ± SD	mean ± SD	F	p	F	p	F	p
Mean HR[a]	Wake	67.5 ± 9.2	62.5 ± 7.9	.04	.95	13.6	<.001	5.7	.020
	NREM	65.3 ± 8.4	60.2 ± 7.4						
	REM	67.6 ± 7.9	62.3 ± 7.7						
SDNN[a]	Wake	47.2 ± 15.4	48.7 ± 16.0	4.0	.023	-	-	-	-
	NREM	42.0 ± 14.1	52.1 ± 17.6						
	REM	41.1 ± 20.3	49.9 ± 16.6						
RMSSD[a]	Wake	41.1 ± 20.3	42.8 ± 18.2	3.2	.048	-	-	-	-
	NREM	39.5 ± 18.1	51.0 ± 23.6						
	REM	33.7 ± 18.4	41.4 ± 19.3						

Means and standard deviations (SD) for heart rate (mean HR), root mean squared of successive differences (RMSSD), and standard deviation of normal RR intervals (SDNN) across wake in the two groups across wake, NREM and REM sleep.

[a]Huynh-Feldt correction.

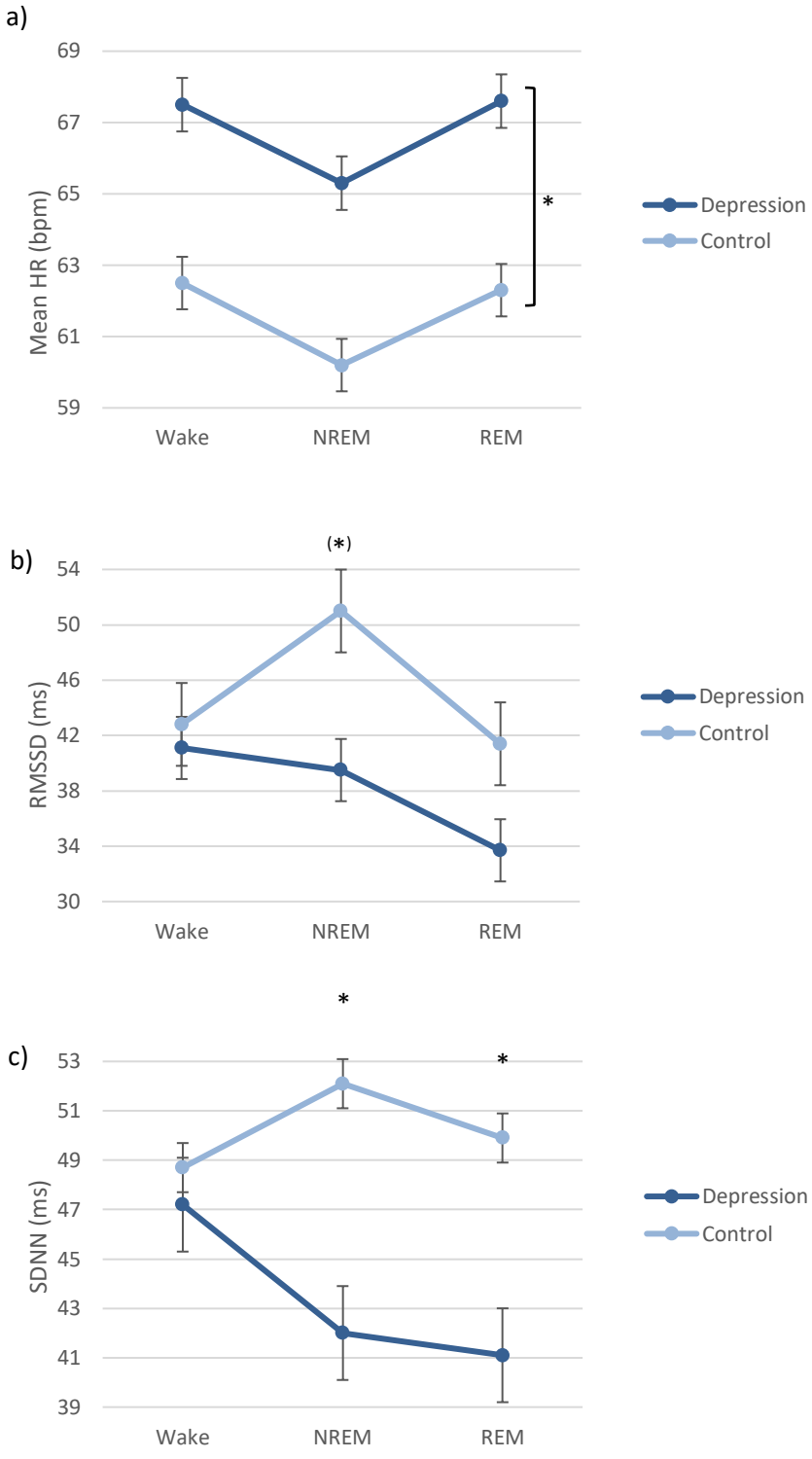
Table 3. HR and HRV across levels of sleep depth

Parameter	Sleep	Depression	Control	Group*Sleep		Sleep Effect		Group	
		mean ± SD	mean ± SD	F	p	F	p	F	p
HR[a]	Wake	68.1 ± 9.2	62.7 ± 8.0	0.5	.57	18.8	<.001	6.3	.015
	NREM1	65.7 ± 8.4	60.6 ± 7.8						
	NREM2	65.4 ± 8.5	59.3 ± 7.4						
	NREM3	66.6 ± 8.8	61.3 ± 7.6						
SDNN[a]	Wake	44.5 ± 15.3	48.3 ± 16.2	4.4	.014	-	-	-	-
	NREM1	46.2 ± 16.9	56.3 ± 19.6						
	NREM2	41.5 ± 16.1	53.0 ± 18.7						
	NREM3	34.3 ± 13.7	45.9 ± 17.6						
RMSSD[a]	Wake	39.3 ± 20.9	42.8 ± 18.5	3.2	.041	-	-	-	-
	NREM1	40.5 ± 19.0	50.2 ± 23.0						
	NREM2	39.2 ± 19.5	53.1 ± 26.0						
	NREM3	36.3 ± 19.2	48.9 ± 24.1						

Means and standard deviations (SD) for heart rate (mean HR), root mean squared of successive differences (RMSSD), and standard deviation of normal RR intervals (SDNN) across wake in the two groups across levels of sleep depth.

[a]Huynh-Feldt correction.

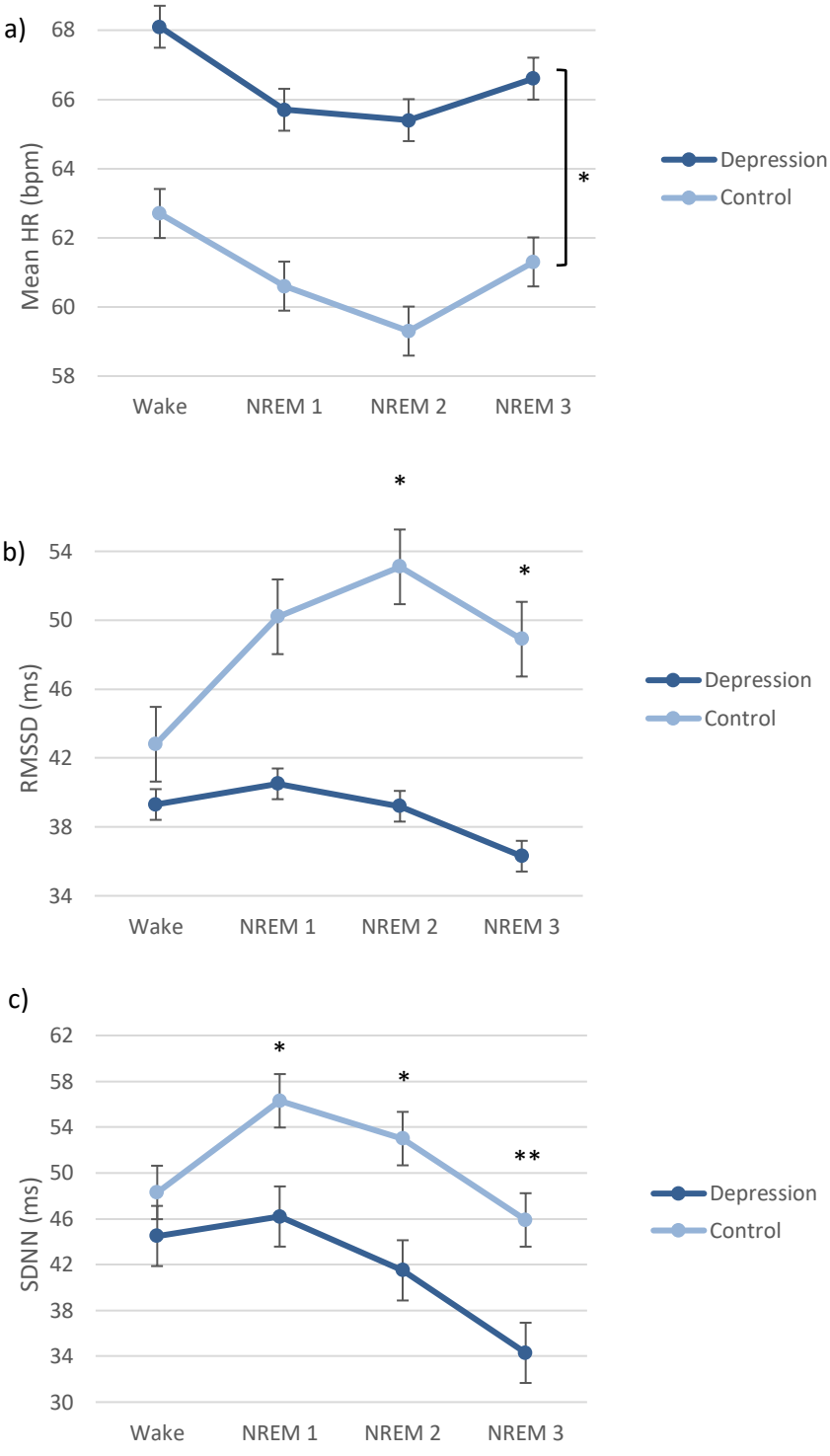
Figure 1. HR and HRV parameters across sleep states



Averaged measures of a) mean heart rate (mean HR), b) root mean squared of successive differences (RMSSD), and c) standard deviation of normal RR intervals (SDNN) across wake,

NREM and REM sleep in the depression vs. control groups. Error bars indicate the standard error of the mean. *Significant group differences at $p<.050$, $^{(*)}$Trend for group differences at $p<.055$.

Figure 2. HRV parameters across levels of sleep depth



Averaged measures of a) mean heart rate (mean HR), b) root mean squared of successive differences (RMSSD), and c) standard deviation of normal RR intervals (SDNN) across wake vs.

levels of sleep depth (NREM1, 2, and 3) in the depression vs. control groups. Error bars indicate the standard error of the mean. *p<.050, **p<.010.

Chapter 3 – Using heart rate profiles during sleep as a biomarker of depression

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Abstract

Background: Abnormalities in heart rate during sleep linked to impaired neuro-cardiac modulation may provide new information about physiological sleep signatures of depression. This study assessed the validity of an algorithm using patterns of heart rate changes during sleep to discriminate between individuals with depression and healthy controls.

Methods: A heart rate profiling algorithm was modeled using machine-learning based on 1203 polysomnograms from individuals with depression referred to a sleep clinic for the assessment of sleep abnormalities, including insomnia, excessive daytime fatigue, and sleep-related breathing disturbances (n=664) and mentally healthy controls (n=529). The final algorithm was tested on a distinct sample (n=174) to categorize each individual as depressed or not depressed. The resulting categorizations were compared to medical record diagnoses.

Results: The algorithm had an overall classification accuracy of 79.9% [sensitivity: 82.8%, 95% CI (0.73-0.89), specificity: 77.0%, 95% CI (0.67-0.85)]. The algorithm remained highly sensitive across subgroups stratified by age, sex, depression severity, comorbid psychiatric illness, cardiovascular disease, and smoking status.

Conclusions: Sleep-derived heart rate patterns could act as an objective biomarker of depression, at least when it co-occurs with sleep disturbances, and may serve as a complimentary objective diagnostic tool. These findings highlight the extent to which some autonomic functions are impaired in individuals with depression, which warrants further investigation about potential underlying mechanisms.

Keywords: Heart rate variability, autonomic nervous system, major depressive disorder

1. Introduction

The search for an objective biomarker of depression may lead to the development of complimentary clinical tools to improve diagnosis and reveal novel therapeutic targets. Changes in sleep physiology specifically linked to depressive states have been proposed as a candidate. As compared to healthy controls, people with depression have increased sleep latency, more fragmented sleep, a higher proportion of rapid eye movement (REM) sleep, decreased REM latency, and, in some cases, decreased amounts of slow-wave sleep (SWS)(84,85). However, these abnormalities in sleep architecture are not specific to depressive states(86,87,191). In parallel to efforts investigating sleep-related characteristics of depression, research focused on identifying depression biomarkers in cardiovascular functions and related inflammatory processes offers promising findings, including increased levels of peripheral vascular endothelial growth factor(192,193), interleukin-6(194), and C-reactive protein(195). Furthermore, depression is often accompanied by increased heart rate and reduced heart rate variability in both sleep and wake states(51,100). Considering the growing body of evidence suggesting that sleep disturbances may play an active role in the pathophysiology of both cardiovascular dysfunctions and depression, we propose that changes in heart rate during sleep may have potential as an objective biomarker of depression.

Approximately 80% of individuals with a current major depressive episode have co-occurring sleep difficulties(196), and sleep disruptions are known to be detrimental to cardiovascular function. Sleep loss can contribute to the emergence and/or worsening of cardiovascular ailments through changes in vascular functions(197), altered autonomic neuro-cardiac modulation(198), as well as dysregulation of the hypothalamic-pituitary axis(199). For instance, experimental studies have demonstrated that sleep deprivation actively increases heart rate and plasma levels of vascular

endothelial cell activation markers(197,200). Sleep deprivation also induces a shift in the autonomic sympathovagal balance towards increased sympathetic cardiac modulation(198), which may lead to alterations in cardiovascular regulatory processes. Thus, sleep difficulties linked to depression may influence cardiovascular functions.

The pathophysiological changes in both cardiovascular regulation and sleep patterns associated with depression are likely to interact and alter heart rate dynamics during sleep, thereby providing a relevant window to observe multi-systemic biomarkers of depression. The cardiovascular signature of depression may be more prominent during sleep since this state is shielded from several external influences such as fluctuating daytime stress, physical activity, and cognitive and emotional processing. Additionally, the reactivity of heart rate to endogenous dynamic changes across the night (e.g., progression of sleep stages, interactions between homeostatic and circadian processes, and changes in autonomic regulation) may yield more specific indices of depression. Previous findings indeed suggest that heart rate patterns across wake and sleep differ between people with depression, anxiety disorders and healthy controls(99). In a subsequent study, Iverson, Stampfer, et al. (2002) reported an inter-rater agreement of 78% between two experts who visually inspected heart rate patterns across wake and sleep to determine the likelihood that an individual has a psychiatric illness or not(201). While promising, this approach is subjective and time consuming. Furthermore, these previous studies were mostly descriptive and did not directly assess the validity of heart rate-based classifications against diagnoses determined by standard psychiatric assessment. Therefore, the current study aimed to validate the diagnostic accuracy of an automated heart rate profiling tool designed to capture changes across sleep-wake states in order to objectively classify individuals according to depression status. To assess generalizability, we also sought to compare classification performance across different subgroups based on potential confounding

factors, including age, depression severity, psychiatric comorbidity, psychoactive and cardiovascular medication use, cardiovascular disease, and smoking status.

2. Methods

An artificial intelligence based algorithm for automated heart rate profiling was developed by an industry-based team of scientists and engineers (Medibio Limited, VIC, Australia; Related patents: PCT/AU2016/050490 and PCT/AU2018/050578). This algorithm was modeled using machine-learning based on a sample of 1203 polysomnography recordings in people with clinician-based depression diagnoses and healthy controls (training sample), and then tested in a distinct sample of 174 cases (testing sample). Both the training and testing samples were collated by the authors from retrospective and secondary databases as described below. This project was approved by the Royal Ottawa Mental Health Centre (ROMHC) Group Research Ethics Board and the "Comité d'éthique de la recherche" of the Hôpital du Sacré-Cœur de Montréal. Data from all other sites was originally collected under approval from each site's respective research ethics board. Preliminary analyses were previously done by the authors and an independent biostatistician in parallel on a slightly smaller portion of this sample for the purpose of CE marking ("Conformité Européenne"; Certificate Registration Number: 532495 MR6). In the present article, a larger data sample was used.

2.3 Cases

2.3.1 Training sample

Depression group. The training sample contained 664 depression cases retrospectively collated from the ROMHC Sleep Disorders Clinic polysomnography recordings. All of these individuals were referred by physicians to the Sleep Disorders Clinic due to a sleep complaint such as

insomnia, excessive daytime fatigue, or sleep-related breathing disturbances. To be included in this sample, all individuals had a diagnosis of a depressive syndrome documented in medical records (e.g., major depression, dysthymic disorder, depressive disorder not otherwise specified), and current depressive symptoms on the Beck Depression Inventory (BDI-II $\geq$ 14)(150) at the time of polysomnography. A psychologist reviewed and classified all diagnostic information for the purpose of this study. Table 1 provides the rates of psychiatric comorbidities, but none of the individuals included in this sample had a diagnosis of bipolar disorder or psychotic disorder.

Control group. The training sample contained 529 healthy control cases. This sample was pooled from the National Sleep Research Resource (NSRR)(202–205) and the Montreal Archive of Sleep Studies (MASS)(206) databases. Control cases across both sites had no history of depression, anxiety disorder, ADHD, neurological disorders or sleep disorders. All cases from the MASS also scored asymptomatic on the BDI (BDI-II < 14 or BDI-Short Form <5).

2.3.2 Testing sample

Depression group. The depression cases used for the final testing sample comprised a total of 87 individuals. These cases were issued from the ROMHC Sleep Disorders Clinic database, but were all distinct from the cases included in the training sample. Inclusion/exclusion criteria matched those of the training sample depression group. Additionally, in order to limit the heterogeneity of the sample, none of the patients included in this sample were taking antipsychotic medications or had a diagnosis of post-traumatic stress disorder. These additional exclusion criteria were applied on the remaining sample available for the testing phase.

Control group. The control group for the testing sample consisted of a total of 87 cases, all distinct from the control training sample. This sample was collated from four sites: the MASS (51 cases),

Western University's Brain & Mind Institute Sleep Research Laboratory (BMISRL; 20 cases), the "Centre d'étude des troubles du sommeil" (CÉTS: 3 cases), and the ROMHC Sleep Disorders Clinic (13 cases). Control cases sourced from the MASS, BMISRL and CÉTS were healthy controls undergoing standard polysomnography without any active intervention, and those from ROMHC Sleep Disorders Clinic were patients referred by physicians for the assessment of sleep abnormalities, including sleep-related breathing disturbances. Control cases were selected from larger datasets collected at each site in an effort to approximate the age and sex distribution of the depression cases. Inclusion/exclusion criteria matched those of the training sample control group. In addition, individuals from the MASS, BMISRL and CÉTS were excluded if they were using any medications known to interfere with sleep, participated in regular night work, or had been on a trans-meridian trip within 3 months prior to the polysomnography recording.

2.4 Polysomnographic recordings

Polysomnography recordings were conducted with similar procedures at all sites. This included scalp electroencephalogram (EEG) channels F3 and/or Fz, C3 and/or Cz, and O1 and/or Oz, left and right electrooculogram (EOG), electrocardiogram (ECG), chin and leg electromyogram (EMG), blood oxygen saturation via an oximeter probe on the finger, and respiratory effort via a nasal thermistor, as well as thoracic and abdominal respiratory belts (MASS and ROMHC). Detailed acquisition parameters for each site are shown in Table 3. Sleep stage scoring was manually performed by qualified personnel in accordance with the clinical scoring guidelines established by the American Academy of Sleep Medicine(65). Across all sites, none of the scorers were aware of the present study aims. The ECG signal was processed to remove artefacts and extract inter-beat interval (IBI) time series. In the testing set, all ECG recordings began at least 3

minutes prior to the first 30-second epoch scored as sleep (mean recording durations before and after sleep are reported in Table 4).

2.5 Algorithm Training and Testing Procedures

Data Division. While collating the datasets, the independent research team used a random list generator to progressively select 10% of the data to put aside for the testing sample. The remainder of the data was used for algorithm training.

Features. The heart rate profiling algorithm is based on a computational model of the relationship between mental state and heart rate pattern characteristics. This integrated multiple features of ECG dynamics including heart rate and heart rate variability, as well as sleep stages scored from the EEG.

Training. The Medibio team was provided with a sample of de-identified ECG and EEG data including healthy controls and people with depression. Using this training sample, a logistic regression with lasso regularization model was employed to determine the optimal weight of each feature in order to attain the best classification of cases in the depression and control groups. To avoid over-fitting and over-optimistic results, a 10-fold cross-validation procedure was performed using the training sample.

Testing. All files from the testing sample were carefully reprocessed by the authors to ensure all formats and parameters were exactly the same across files from all sites (e.g. using the same labels and formats for derivations and sleep stage, excluding all signals except the ECG signals, down-sampling the ECG signal to the lowest acquisition rate). These files were identified by unique codes randomly allocated across the mixed sample of depression and control cases. The final algorithm was applied to this testing sample by the Medibio team under blinded conditions. The

resulting classifications were sent back to the authors, who then conducted the independent validation analyses by comparing these to actual medical record diagnoses.

2.6 Statistical analyses

All statistical analyses were carried out using the Statistical Package for the Social Sciences (SPSS, version 22.0, Armonk, NY: IBM Corp). For descriptive purposes, chi-square and Mann-Whitney U tests were performed in the final testing sample to detect any significant differences between the control and depression groups in the sex distribution, age, apnea/hypopnea index (AHI) and sleep architecture.

As part of the validation analyses, the diagnostic classification based on the heart rate profiling algorithm was compared to diagnostic information collated from medical records. This was done using a confusion matrix(207), as well as Cohen's kappa statistic to determine 'inter-rater agreement' between the two sets of classifications.

To evaluate how potential confounders may affect the algorithm's performance, the entire sample was stratified by age and sex to compare kappa statistics across subgroups. The depression group was further stratified according to Body Mass Index [Underweight (<18.5 kg/m^2), Normal (18.5 to 24.99 kg/m^2), Overweight (25.0 to 29.99 kg/m^2), and Obese (≥30 kg/m^2)(208), psychotropic medication use, depression severity [Mild Depression (BDI- II: 14-19), Moderate Depression (BDI- II: 20-28), Severe Depression (BDI- II: 29-63)], the presence of psychiatric comorbidities, the presence of cardiovascular diseases or related risk factors, current smoking status and polysomnographic variables found to differ between the control and depression group (median split). The algorithm's sensitivity was computed for each stratified subgroup.

Sleep architecture variables were compared for individuals who were incorrectly classified by the

algorithm (i.e. false positives and false negatives) with age and sex-matched subsets of correctly classified individuals (i.e. true negatives and true positives). Furthermore, false positive rates were compared across all control sites in order to determine whether the use of different ECG systems had an impact on the algorithm's performance.

3. Results

3.1 Descriptive group characteristics

The training sample depression group was comprised of 72.9% females (mean age = 45.0 ± 15.7 years; age range 14 to 85 years). Of the overall training sample depression group, 81.6% was taking psychotropic medication (see Table 2 for details). The sex distribution of the training sample control group was 55% female (mean age = 41.3 ± 18.5 years; age range 14 to 81 years). In the testing sample, the depression group was comprised of 59% females (mean age = 43.6 ± 10.5 years; age range = 20 to 71 years), and the control group was comprised of 55% females (mean age = 43.3 ± 11.3 years; age range = 20 to 65 years). Further descriptive information for both groups of the final testing sample is outlined in Table 4**.** There were no significant age or sex differences between the depression and control group. On average, total sleep time was 30.6 minutes shorter in the depression group than in the control group. Compared to the control group, the depression group also had significantly longer sleep onset latency and REM onset latency, as well as a lower amount of REM sleep, both in absolute time and as a percentage of total sleep time. Although the AHI remained below the clinical threshold for both groups, the depression group had a slightly but significantly higher AHI than the control group.

3.2 Validation of the heart rate profiling algorithm

The classification matrix is shown in Table 5**.** Overall, the heart rate profiling algorithm had a classification accuracy of 79.9% [sensitivity: 82.8%, 95% CI (0.73 to 0.89), specificity: 77.0%, 95% CI (0.67 to 0.85)]. There was a moderate level of agreement with diagnoses derived from medical records [$\kappa = 0.60$, 95% CI (0.48 to 0.72), $p<.001$]. The degree of concordance between heart rate-based classifications and diagnoses documented from medical records stratified by age and sex subgroups is shown in Table 6. Cohen's kappa reached at least the moderate level in all subgroups, with similar concordance for males and females, and a higher concordance for the 36-50 year old subgroup.

3.3 Sensitivity stratifications

Table 7 lists the algorithm's sensitivity across subgroups of the depression sample stratified by potential confounding factors. There was no significant difference in the algorithm's sensitivity across subgroups based on psychiatric comorbidities, smoking status, the presence of cardiovascular disease and/or related risk factor, or the use of cardiovascular medication. Conversely, the algorithm demonstrated significant differences in sensitivity across subgroups stratified by psychotropic medication use ($\chi^2(1) = 4.1$, $p<.050$) and body mass index ($\chi^2(2) = 10.5$, $p=.005$), with the highest sensitivities in the subgroup taking psychotropic medication, and the subgroup with a BMI in the obese range.

3.4 False positives/false negatives

Fifteen of the 87 individuals with depression were incorrectly classified as controls (i.e. false negative: 60% female, mean age ± SD = 43.2 ± 14.3 years; age range = 20 to 68 years). Compared to age and sex-matched depression cases who were correctly classified, the false negative group had significantly lower amounts of N1 sleep in absolute time ($t(28) = -4.4$, $p<.001$), with an

average of 30.1 (± 13.7) minutes of N1 sleep, as compared to 60.4 (± 22.8) minutes of N1 sleep in the true positive group. There was no significant difference in AHI between false negatives (median=0.6) and true positives (median=2.7), U=67.5, p=.061, nor between false positives (median=0.7) and true negatives (median=0.5), U=186.0, p=.703.

Twenty of the 87 healthy controls were incorrectly classified as depressed (i.e. false positive: 55% female, mean age ± SD= 44.3 ± 12.1 years; age range = 20 to 63 years). Compared to age and sex-matched controls who were correctly classified, these false positives had significantly higher amounts of N1 (t (38) = 3.5, p=.001) and REM (t (38) = -2.1, p<.05) sleep, in absolute time. The false positive group had an average of 45.6 (± 16.9) minutes of N1 sleep, and 65.4 (± 26.0) minutes of REM sleep, whereas the true negative group had an average of 27.0 (± 17.0) minutes of N1 sleep, and 81.5 (± 22.5) minutes of REM sleep. There were no significant differences in the rates of false positives across the BMISRL, CÉTS, MASS, and ROMHC sites (x^2 (3) = 6.8, p=.080).

4. Discussion

This study demonstrates, for the first time, that changes in heart rate across sleep-wake states may be valid physiological markers for the identification of depression in a sample of people with sleep complaints. The heart rate profiling algorithm classified individuals with an accuracy of 79.9%. Specifically, the algorithm was able to detect 82.8% of the depression cases, and rule out 77.0% of healthy controls (these results are in line with the preliminary analyses conducted for CE marking). In comparison, the detection rate of depression amongst primary care practitioners is thought to be approximately 47%(122). Considering that the algorithm performed substantially well in comparison to standard diagnostic procedures, this tool may serve as an objective, adjunctive measure to assist in depression diagnosis and monitoring. Subsequent studies should evaluate whether currently accessible ambulatory ECG devices could be used to track sleep-

derived profiles indicative of depression. From this perspective, the algorithm could potentially serve as a non-invasive and low-cost tool. The combined use of a classification instrument with clinician-based diagnosis may improve diagnostic accuracy and means of patient monitoring.

Depressive disorders are associated with sympathetic hyperactivity and reduced cardiac vagal control, which increases the risk of cardiovascular disease. Considering the associations between depression and inflammation(194,195), as well as the role of the vagus nerve in mediating the cholinergic anti-inflammatory pathway(209,210), it has been suggested that this autonomic imbalance may occur via the effects of pro-inflammatory cytokines on the central autonomic network(173). The accuracy of this sleep ECG tool in detecting depression simply based on heart rate profiles during sleep highlights the extent to which autonomic neuro-cardiac regulation is dysfunctional in individuals with depression and sleep complaints. Further investigation is warranted to identify the specific physiological mechanisms of depression, alone or in combination with sleep disturbances, that underlie the abnormal profiles of heart rate dynamics during sleep. Given the increased risk of cardiac morbidity and mortality in these individuals, and the fact that increased heart rate and reduced heart rate variability are known to increase the risk of cardiac morbidity and mortality(211–213), this also emphasizes the need to assess whether chronic autonomic dysfunctions during sleep may, over time, contribute to poor health outcomes in people with depression. Prospective work is required to clarify how heart rate changes during sleep may relate to cardiovascular events and related risks factors in people with depression.

Trait versus state marker

Preliminary studies of heart rate recordings during wake have shown that deviant heart rate patterns progressively normalize with effective antidepressant medication treatment of

depression(214), and electroconvulsive therapy(215). This reinforces the notion that the observed atypical heart rate patterns are manifestations of the physiological changes associated with depressive states resulting from autonomic nervous system dysfunction(132). Whether heart rate profiles during sleep may be sensitive to changes in depressive states remains to be more thoroughly investigated. If further studies are able to establish that heart rate profiles during sleep normalize following successful treatment, the heart rate profiling algorithm used in this study may provide a helpful tool to objectively monitor treatment effectiveness over time.

Sensitivity Stratifications

The algorithm performed well across subgroups stratified based on sex, age, depression severity, comorbid psychiatric illness, comorbid cardiovascular disease and related risk factors, and smoking status. This suggests that the algorithm's sensitivity to depression is generalizable across individuals with several potential confounding factors.

The algorithm had a significantly higher sensitivity in individuals with a BMI in the obese range and in those with elevated AHI, two factors often interconnected(216) and known to interact with cardiovascular functions. One the one hand, obesity is linked to a clear autonomic imbalance, with elevated sympathetic activity and lower vagal activity(217–219). On the other hand, sleep-related breathing disorders are associated with a hyperactivation of the sympathetic nervous system due to intermittent hypoxia and sleep fragmentation(220). Overall, cardiovascular alterations resulting from obesity and/or sleep-related breathing disturbances may have led to a higher likelihood of detection by the algorithm. Nevertheless, the algorithm's sensitivity remained above 61% and 83% in people with a BMI within the normal and overweight ranges respectively, and remained above 79% in those with an AHI below 5. Even if the depression group had, on average, higher

BMI and AHI than the control group, the ability of the algorithm to efficiently detect depression cases amongst individuals with low BMI and AHI suggests that the algorithm's sensitivity to depression was not solely based on indirect effects of elevated BMI or AHI on the ECG.

The depression subgroup with psychotropic medication use also had a higher rate of correct detection based on the heart rate profiling algorithm. This could be simply due to differences in statistical power, as only 20.7% of the depression group was free of psychotropic medication use at the time of polysomnography. However, the use of antidepressants is associated with reductions in heart rate variability, and prospective studies are required to determine if these medications could possibly lead to better detection by the algorithm. Statistical power issues may also apply for the high detection rate in the 36-50 year age group, since this age bracket was over-represented. As such, the sensitivity of the algorithm should be further investigated in individuals who do not use psychotropic drugs, as well as across varying age groups. Various profiles of sleep disturbances have been found in individuals with depression, such as shortened REM onset latency, increased amounts of REM sleep as a percentage of total sleep time, increased REM density, and lengthened sleep onset latency(85,87). However, these abnormalities in REM sleep were not observed in our sample, possibly due to the use of antidepressant medication. However, in subgroups of patients with different sleep patterns, namely those with longer or shorter sleep, and longer or shorter REM onset latencies, the algorithm's sensitivity remained consistent. Of note, the algorithm had a higher sensitivity in individuals with a lower proportion of REM sleep. Considering the higher classification sensitivity observed in those taking antidepressant medications, which are known to actively suppress REM sleep, this is likely to be related to the higher sensitivity found in the subgroup of medicated individuals. Interestingly, while the overall depression group had significantly higher amounts of N1 sleep on average than the controls, the

subgroup of controls incorrectly classified as depression cases (i.e. false positives) also had high N1 amounts, and the depression cases incorrectly classified as controls (i.e. false negatives) had low N1 amounts. From this perspective, heart rate changes during shallow sleep may be an especially important feature used by the algorithm for the identification of depression.

Overall, the new biomarker developed herein persisted at a high level, independently of global differences in sleep architecture. Considering that abnormalities in standard EEG-based sleep measures are known to be poorly specific to depressive states(86,87,191), this multi-systemic biomarker tapping on dynamic changes in both brain and heart activity, may be more promising to distinguish between different mental illnesses.

5. Limitations

We acknowledge several limitations in this study. Due to intellectual property rights, the specific content of the algorithm cannot be disclosed. The control group data was obtained from four different sites with slightly differing EEG and ECG acquisition parameters, while the depression group data was sourced from one site. However, the sourcing of data from multiple sites allowed testing the algorithm on a larger and more diverse sample, which highlights its robustness and generalizability. Also, there were no significant differences in the false positive rate across different sites. The depression group consisted of individuals with sleep complaints who were referred to a specialized sleep disorders clinic, but only a portion of the control group had sleep complaints and was referred to a sleep clinic. As such, the large majority of depression cases had significant sleep problems, including sleep-related breathing disorders, which may influence heart rate patterns. However, the average AHI amongst both testing groups were below the clinical cut-offs for sleep apnea. Although sleep disturbances often co-occur with depression, the sample used in the present study may not be representative of the general depression population. Further work

is required to decipher the relative contribution of depression and sleep abnormalities, including breathing disturbances, to the abnormal heart profiles detected by the algorithm. Importantly, working with this sample allowed us to establish that the algorithm classification remained accurate across a wide range of sleep profiles. Moreover, due to the effects of psychotropic medication on cardiac activity, the use of psychotropic medication in the majority of our sample could possibly have facilitated better detection of depression by the algorithm. Therefore, the algorithm's performance must be investigated in a larger sample of individuals free of psychotropic medication use. Due to the retrospective nature of this study, it was not possible to ascertain whether individuals from the depression group and part of the control group had traveled across time zones or worked night shifts close to the time of the sleep recordings.

6. Conclusions

The current study validated a novel diagnostic classification tool based on an objective, multi-systemic biomarker of depression in a clinical sample of individuals with depression and sleep complaints. This tool, based on heart rate changes under the influence of autonomic regulation during sleep, was found to be highly generalizable across several potential confounding variables, as well as across differing ECG/EEG acquisition systems. In addition to providing an improved biological underpinning for the diagnosis of depression, this could possibly offer supplemental information to psychiatric clinical assessment, and objective measures for early screening. Moreover, the use of distinct physiological variables as biomarkers of depression may help emphasize the interactions between mental and physical health. This may contribute to reducing the stigma associated with depression, lifting some social barriers to accessing psychiatric treatment, and allowing for more holistic patient care.

Table 1. Psychiatric comorbidities in the depression training and testing samples

	Training Sample ***n*** **(%)**	**Testing Sample** ***n*** **(%)**
Any psychiatric comorbidity	240 (36.1)	29 (33.3)
Anxiety disorder	175 (26.4)	21 (24.1)
Post-traumatic stress disorder	3 (0.5)	0 (0.0)
Obsessive compulsive disorder	15 (2.3)	4 (4.6)
Personality disorder	31 (4.7)	4 (4.6)
Substance abuse disorder	54 (8.1)	8 (9.2)
Intermittent explosive disorder	0 (0.0)	1 (1.1)
Adjustment disorder	5 (0.8)	0 (0.0)
Eating disorder	13 (2.0)	0 (0.0)
Developmental disorder	33 (5.0)	5 (5.7)
Neurocognitive disorder	5 (0.8)	0 (0.0)

Table 2. Psychotropic medications in the depression training and testing samples

	Training sample *n* (%)	Testing sample *n* (%)
Any psychotropic medication	542 (81.6)	69 (79.3)
SSRI	239 (36.0)	28 (32.2)
SNRI	190 (28.6)	19 (21.8)
TCA	39 (5.9)	6 (6.9)
NaSSA	43 (6.5)	2 (2.3)
MAOI	4 (0.6)	1 (1.1)
NRI/NARI	5 (0.8)	1 (1.1)
SARI	119 (17.9)	25 (28.7)
NDRI	89 (13.4)	12 (13.8)
RIMA	6 (0.9)	1 (1.1)
Other antidepressant	0 (0.0)	0 (0.0)
Antipsychotic	126 (19.0)	0 (0.0)
Mood stabilizer	71 (10.7)	8 (9.2)
Lithium	17 (2.6)	3 (3.4)
Melatonin agent	15 (2.3)	1 (1.1)
Benzodiazepine	96 (14.5)	8 (9.2)
Hypnotic/Sedative/Anxiolytic	123 (18.5)	2 (2.3)
Stimulant	38 (5.7)	4 (4.6)
Dopamine agonist	1 (0.2)	3 (3.4)
NMDA receptor antagonist	0 (0.0)	1 (1.1)
Acetylcholinesterase inhibitor	1 (0.2)	0 (0.0)

SSRI: Selective Serotonin Reuptake Inhibitor, SNRI: Serotonin-Norepinephrine Reuptake Inhibitor, TCA: Tricyclic Antidepressant, NaSSA: Noradrenergic/Specific Serotonergic Antidepressant, MAOI: Monoamine Oxidase Inhibitor, NRI/NARI: Noradrenergic Reuptake Inhibitor, SARI: Serotonin Antagonist and Reuptake Inhibitor, NDRI: Norepinephrine-Dopamine Reuptake Inhibitor, RIMA: Reversible Monoamine Oxidase Inhibitor

Table 3. EEG and ECG Acquisition Parameters

Site	Hardware (Software)	Sampling Rate (Filters) [Hz]	Timing of lights on/off	ECG Location
ROMHC	Sandman SD32 (Sandman 10.1; Natus Medical Incorporated, San Carlos, CA, USA)	256 (none)	Mean habitual bedtime and wake time (up to 6:15-6:30AM)	Top of shoulders
NSRR	Edentrace I or II; Edentec, Eden Prairie, MN, USA)	128 (0.15)	Habitual sleep schedule	1) Below the midpoint of the right clavicle 2) Below the left breast crease, in line with the midpoint of the left clavicle (or below the midpoint of the left clavicle)
MASS	Grass 15A54 (Harmonie Stellate System; Natus Medical Incorporated, San Carlos, CA, USA)	256 or 512 (0.3-100)	Mean habitual bedtime and wake time	Left and right arms
BMISRL	Embla Titanium (RemLogic; Natus Medical Incorporated, San Carlos, CA, USA)	512 (0.1-220)	Mean habitual bedtime and wake time	Below each clavicle
CÉTS	Grass Model 12 (Harmonie Stellate System; Natus Medical Incorporated, San Carlos, CA, USA)	256 (0.01-100)	Mean habitual bedtime and wake time	Below each clavicle

ROMHC: Royal Ottawa Mental Health Centre, NSRR: National Sleep Research Resource, MASS: Montreal Archive of Sleep Studies, BMISRL: Western University's Brain & Mind Institute Sleep Research Laboratory, CÉTS: Centre d'étude des troubles du sommeil

Table 4. Sleep architecture and descriptive information for the testing sample

Variable	Control [$\bar{x}$ ± SD][b]	MDD [$\bar{x}$ ± SD][b]	U/χ^2	*p*
n	87	87	-	-
Sex Distribution (%female)	55.2	58.6	.211	.646
Age (years)	43.3 ± 11.3	43.6 ± 10.5	3744.0	.903
AHI	1.7 ± 2.8	3.3 ± 5.0	2769.5	.002
BMI (kg/m^2)	-	29.6 ± 6.8	-	-
BDI II Score	-	24.6 ± 9.0	-	-
Recording Time Before Sleep (min)	21.6 ± 15.0	40.2 ± 28.3	1882.5	.000
Recording Time After Sleep (min)	9.5 ± 28.9	4.6 ± 8.2	3398.5	.295
Total Recording Duration (min)	468.4 ± 35.6	474.2 ± 55.4	3550.5	.563
Total Sleep Time [TST (min)]	386.2 ± 43.8	355.6 ± 76.4	2891.0	.007
Sleep Efficiency (%)	87.7 ± 7.3	82.9 ± 14.3	3305.0	.149
Sleep Onset Latency (min)	13.6 ± 13.0	20.3 ± 18.7	2782.5	.003
REM Latency (min)[a]	98.6 ± 48.3	190.9 ±106.6	1363.5	<.001
WASO (min)	55.1 ± 32.4	72.9 ± 62.2	3451.5	.316
N1 (min)	32.8 ± 18.8	66.4 ± 37.4	1617.5	<.001
N2 (min)	223.1 ± 47.9	207.3 ± 63.4	3151.0	.057
N3 (min)	54.7 ± 39.1	34.8 ± 33.7	2595.0	<.001
REM (min)	75.7 ± 25.5	47.1 ± 32.9	1788.0	<.001
N1 (% of TST)	8.7 ± 5.3	19.5 ± 11.5	1441.0	<.001
N2 (% of TST)	57.7 ± 10.5	58.0 ± 11.5	3760.0	.941
N3 (% of TST)	14.2 ± 10.1	9.7 ± 8.6	2758.0	.002
REM (% of TST)	19.4 ± 5.7	12.9 ± 9.0	1780.0	<.001

[a] Eight individuals from the depression group had no REM sleep
[b] Despite the use of a non-parametric test, the mean and standard deviation is reported for better clarity

AHI: Apnea-Hypopnea Index, BMI: Body Mass Index, BDI: Beck Depression Inventory, REM: Rapid eye movement, WASO: Wake after sleep-onset, N1: Non-REM 1, N2: Non-REM 2, N3: Non-REM 3

Table 5. Confusion matrix of algorithm classification vs. actual diagnosis

	Actual Diagnosis: Depression	Actual Diagnosis: Control	Total	
Algorithm				
Depression	**72**[a]	**20**[b]	87	PPV: 78.3%
Control	**15**[c]	**67**[d]	87	FOR: 18.3%
Total	82	92	174	
	Sensitivity: 82.8%	FPR: 23.0%		
	FNR: 17.2%	Specificity: 77.0%		

[a] True positives: Individuals with depression who were correctly classified
[b] False positives: Healthy controls who were incorrectly classified as depressed
[c] False negatives: Individuals with depression who were incorrectly classified as healthy controls
[d] True negatives: Healthy controls who were correctly classified

PPV: Positive Predictive Value, FOR: False Omission Rate, FNR: False Negative Rate, False Positive Rate

Table 6. Classification agreement across age and sex groups in the testing sample

	Group	Cohen's kappa (κ)[a]	*n*	95% CI	*p*
Sex	Female	0.60	99	0.44 to 0.75	<.001
	Male	0.60	75	0.42 to 0.78	<.001
Age Group	18-35	0.56	47	0.32 to 0.80	<.001
	36-50	0.72	71	0.54 to 0.89	<.001
	51-71	0.41	56	0.17 to 0.65	.002

[a] Concordance between heart rate-based classification and diagnoses documented from medical records

Table 7. Algorithm sensitivity across the testing sample depression group stratified by potential confounding factors

	Stratification	Sensitivity (%)[a]	*n*	χ^2(df)	*p*
Body Mass Index	Normal	61.9	21	10.5 (2)	.005
	Overweight	83.3	36		
	Obese	96.7	30		
Psychotropic Medication Use	Yes	87.0	69	4.1 (1)	<.050
	No	66.7	18		
Depression Severity	Mild	83.9	31	0.2 (2)	.927
	Moderate	80.6	31		
	Severe	84.0	25		
Psychiatric Comorbidity	Yes	75.9	29	1.5 (1)	.229
	No	86.2	58		
Cardiovascular Disease or Related Risk Factor	Yes	83.9	31	0.0 (1)	.838
	No	82.1	56		
Cardiovascular Medication Use	Yes	82.6	23	0.0 (1)	.982
	No	82.8	64		
Smoking Status	Non-Smoker	82.5	63	0.0 (1)	.930
	Current Smoker	83.3	24		
AHI	< 5	79.7	69	2.2 (1)	.141
	≥ 5	94.4	18		
Sleep Onset Latency (min)	≤ 15	82.2	45	0.0 (1)	.891
	> 15	83.3	42		
REM Onset Latency (min)	≤ 164	80.0	40	0.7 (1)	.390
	> 164	87.2	39		

%REM	≤ 13	90.9	44	4.1 (1)	<.050
	> 13	74.4	43		

[a] The algorithm's ability to accurately detect cases of depression (i.e. true positive rate)

AHI: Apnea-Hypopnea Index, REM: Rapid eye movement

Chapter 4 – Selective Serotonin Reuptake Inhibitor use is associated with worse sleep-related breathing disturbances in individuals with depressive disorders and sleep complaints; A retrospective study

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results interpretation and manuscript preparation. All authors read, critically revised, and approved the final manuscript. *RR is the corresponding author. † Shared first-authorship.

Abstract

Background: The effects of serotoninergic agents on respiration neuromodulation may vary according to differences in the serotonin system, such as those linked to depression. This study investigated how sleep-related respiratory disturbances relate to depression and the use of medications commonly prescribed for depression.

Methods: Retrospective polysomnography data was collated for 365 individuals referred to a sleep clinic between 2006 and 2016. The apnea-hypopnea index (AHI) and oxygen saturation nadir ($minSpO_2$) during REM and NREM sleep were compared across 3 main groups: medicated individuals with depressive disorders (Antidepressant group; subdivided into selective serotonin reuptake inhibitors (SSRIs) and Norepinephrine/Norepinephrine-Dopamine Reuptake Inhibitor (NRI/NDRI) subgroups), non-medicated individuals with depressive disorders (Non-Medicated group), and mentally healthy controls (Control group).

Results: The Antidepressant and Non-Medicated groups had significantly higher AHIs compared to the Control group ($F(2, 350)=8.0$, $p<.001$). The Antidepressant group also had a lower NREM $minSpO_2$ than the Control and Non-Medicated groups ($F(2, 350)=3.6$, $p=.028$). Independently of depression severity, the SSRI group had a higher AHI ($F(2, 203)=4.2$, $p=.017$) and lower $minSpO_2$ ($F(2, 203)=5.0$, $p=.008$) during NREM sleep than the Non-Medicated and NRI/NDRI groups (all $p<.050$).

Limitations: Information about medication dosage and intake duration was unavailable. This study being cross-sectional, causation cannot be inferred. All participants were referred to a single sleep clinic, which may limit generalizability.

Conclusion: While further investigations with prospective studies are required, these findings suggest that the use of SSRIs may be associated with impaired breathing and worse blood oxygen saturation during sleep in individuals with depressive disorders and sleep complaints.

1. Introduction

Medications commonly prescribed for mood disorders, such as selective serotonin reuptake inhibitors (SSRIs), are known to markedly impact sleep(221). In fact, sleep disturbances are one of the most common adverse drug reactions reported by SSRI users(222). In addition to inducing alterations in sleep architecture, SSRIs have been shown to modulate breathing patterns during sleep in animal models and humans with sleep-related breathing disorders(223–225). Yet, surprisingly little information is available on the effects of serotoninergic agents on respiratory functions in depressed individuals. Considering the high comorbidity between depressive disorders and sleep-related breathing disorders (SRBD), such as obstructive sleep apnea (OSA)(102), there is a need to better understand how SSRIs may interact with respiratory functions in the context of depression.

Depression is accompanied by dysfunctions in the serotonin (5-HT) neurotransmitter system, both centrally and peripherally. For instance, individuals with depression have decreased plasma levels of tryptophan, a 5-HT pre-cursor(112,113), and reduced levels of 5-HT metabolites in the cerebrospinal fluid. Depression has also been linked to lower 5-HT1A receptor binding(114–116), and low availability of 5-HT reuptake sites in the brainstem(226). These 5-HT abnormalities could possibly interfere with respiratory functions, especially during sleep. Most 5-HT neurons are located in the raphe nuclei, a structure heavily involved in respiratory control and sleep regulation(227). Furthermore, the serotonergic input to motor neurons regulating upper-airway muscles is known to decrease during sleep(228,229). This sleep-related decrease in serotonergic input is thought to play a key role in upper airway obstruction at the source of OSA(230).

Beyond the possible effects of depression pathophysiology on sleep-related breathing disturbances, active pharmacological manipulations of the serotonergic system may also impact

respiratory functions. Early animal work demonstrated that intravenous injection of 5-HT triggers acute apneas(110). Subsequent studies have shown that exogenous 5-HT increases the occurrence of breathing disruptions during sleep in a dose-dependent manner(96,231), while 5-HT antagonists actively reduce sleep apneic events(97). Although some animal studies found opposite effects(225,232), overall, these findings suggest that increased levels of 5-HT may contribute to the generation of breathing disturbances during sleep(98). Findings in humans are limited. Small (n = 8 to 17) trials have attempted to use SSRIs to improve breathing in people with OSA(223,233,234). However, these studies yielded conflicting results; some reporting a reduced AHI in a subset (i.e. 33 to 65%) of their sample(223,233) and some reporting an overall slight (non-significant) increase in AHI following SSRI intake(234).

These inconsistencies may notably result from individual differences in the vulnerability to serotonergic agents. For instance, recent work suggests that the direction of serotonergic effects on respiratory functions may vary with the expression of 5-HT receptors(60,61). It has been proposed that 5-HT3 receptors may have inhibitory effects on upper airway dilators, thereby reducing patency and airflow on respiratory centers(97,111), while 5-HT1A may have excitatory effects on respiratory centers(235,236). From this perspective, considering the dysregulation of 5-HT receptors expression and binding in depression, depression may shape the response of the respiratory system to serotonergic agents. For instance, there are some indications that depressive states may be linked to increased 5-HT3 receptors activity(237), a factor which may potentiate the inhibition of respiratory muscles. In addition, depression-related impairments in 5-HT1A binding may diminish the excitatory effects of serotonergic agents on the respiratory system.

To the best of our knowledge, there is currently no empirical study reporting on the effects of serotonergic agents on respiratory functions in people with depression. Based on a retrospective

cross-sectional chart review, the present study assessed how sleep-related respiratory function relate to depression and the use of medications prescribed for depression in individuals referred to a sleep clinic. The relative influence of serotonergic and non-serotonergic medication use was also evaluated. Based on previous observations suggesting a dysregulation of 5–HT receptors in depression that inhibits respiratory functions in sleep, it was anticipated that people with depression who take antidepressants, and more specifically SSRIs, would have a higher apnea hypopnea index (AHI) and lower blood oxygen saturation compared to those taking non-serotonergic medication (i.e. norepinephrine or norepinephrine-dopamine inhibitor (NRI/NDRI)) and those not taking any psychotropic medication.

2. Methods

2.1 Patients

Data were retrospectively collated for all patients who underwent diagnostic overnight Level 1 polysomnography at the Royal Ottawa Mental Health Centre (ROMHC) Sleep Disorders Clinic between 2006 and 2016 who met the selection criteria listed below.

2.1.1 Depression group

Individuals included in the depression group had a documented history of a unipolar depressive syndrome (e.g., major depression, dysthymic disorder, depressive disorder not otherwise specified) from medical charts, and current depressive symptoms of at least mild severity [Beck Depression Inventory-II (BDI) $\geq$ 14] at the time of the sleep assessment. Patients were systematically excluded if they had co-morbid bipolar disorder, psychotic disorder, post-traumatic stress disorder, or neurocognitive disorder documented from medical records. A psychologist reviewed and classified all diagnostic information.

The depression group was first split into two mutually exclusive groups based on the use of psychotropic medications at the time of polysomnography: the Antidepressant group (individuals who reported taking at least one antidepressant medication and no other psychotropic medication on the night of the sleep study), and the Non-Medicated group (individuals who were free of any psychotropic medication use on the night of the sleep study). The Antidepressant group was subsequently split into 2 subgroups based on the class of antidepressant used: the SSRI group, and the NRI/NDRI group. Individuals taking any other psychotropic drug were systematically excluded. Additionally, participants were free of other serotonergic drugs including triptans, 5HT-3 receptor antagonists such as ondansetron, and muscle relaxants such as cyclobenzaprine.

2.1.2 Control group

Individuals included in the control group had no history of mood disorders, anxiety disorders, psychotic disorders, post-traumatic stress disorder, or neurocognitive disorders as documented from medical records. Participants had to score in the asymptomatic range on the Beck Depression Inventory-II (BDI < 14) and not use any psychotropic medication.

Descriptive information for each group and specific medication subtypes are reported in Table 1. This retrospective study was approved by the Human Research Ethics Board of the Royal Ottawa Health Care Group.

2.2 Procedures

All patients underwent height and weight measurement to determine body mass index (BMI), rated the severity of their depressive symptoms on the Beck Depression Inventory-II (BDI-II), and underwent level 1 polysomnography at the ROMHC Sleep Clinic. Polysomnography was recorded with the Sandman SD32 acquisition software (Sandman 10.1; Natus Medical Incorporated, San

Carlos, USA) using 3 electroencephalogram (EEG) channels (F3, C3, and O1), left and right electrooculogram (EOG), chin and leg electromyogram (EMG), as well as 2 electrocardiogram (ECG) channels. Respiration was monitored with an airflow cannula (pressure transducer), nasal-oral thermistor, chest and abdomen plethysmography. Pulse oximetry data was used to calculate the minimum oxygen saturation percentage reached during sleep ($minSpO_2$).

Sleep stages, apneas/hypopneas and arousals were visually scored by registered sleep technologists according to guidelines established by the American Academy of Sleep Medicine(65). This enabled the quantification of two types of breathing events: apneas ($\geq$10-second pause in breathing with at least a 90% drop in baseline breathing amplitude for 90% of the event), and hypopneas (at least 10 seconds of a >30% reduction in air flow, with a $\geq$3% drop in oxygen saturation from pre-event baseline, with 90% of the event's duration meeting the amplitude reduction criteria). The following indices of respiratory function were computed: Apnea-Hypopnea Index (AHI; number of apneas and hypopneas per hour), Oxygen Desaturation Index (number of blood oxygen desaturations $\geq$3% per hour), and $minSpO_2$ (lowest blood oxygen saturation percentage) across total sleep time, as well as during REM and NREM sleep.

2.3 Statistical analysis

For descriptive purposes, chi-square and independent t-tests were used to identify significant differences in sex distribution, age, BMI, and sleep architecture across all groups. Additionally, BDI-II scores were compared across the 3 depression groups.

To address the main objectives, mixed ANCOVAs were used to compare the AHI, Oxygen Desaturation Index and $minSpO_2$. These ANCOVAs had one within-subjects factor (sleep stages: REM vs. NREM) and one between-subjects factor (either 1) main groups: Antidepressant vs. Non-

Medicated vs. Control groups, or 2) depression subgroups: the SSRI vs. NRI/NDRI vs. Non-Medicated groups). When found to differ significantly across groups in descriptive analyses, sex, age, and BMI were integrated as covariates.

To improve normality, BMI, sleep onset latency, and the Oxygen Desaturation Index were log-transformed, and the AHI and BDI-II were transformed with square-root. All statistical analyses were carried out using the Statistical Package for the Social Sciences (SPSS, version 22.0, Armonk, NY: IBM Corp).

3. Results

3.1 Sample characteristics

Sample characteristics and sleep architecture for the main groups, as well as the SSRI and NDRI/NRI subgroups are reported in Tables 1 and 2, respectively.

3.1.1 Age, Sex and Body Mass Index

The Control group consisted of 148 individuals (45.9% female) with a mean age of 52.8±15.2 years, and BMI of 28.2±5.5 kg/m^2. The Non-Medicated group consisted of 117 individuals (67.5% female), with a mean age of 43.7±13.7 years, and BMI of 28.9±6.5 kg/m^2. The Antidepressant group included 100 individuals (65.0% female) with a mean age of 43.6±14.9 years, and BMI of 29.6±6.6 kg/m^2. Across the main groups, there were significant differences in age ($F(2, 364)=17.2$, $p<.001$) and sex distributions ($x^2(2)=15.2$, $p=.001$), but there was no difference in BMI ($p=.311$). Specifically, compared to the control group, the Antidepressant and Non-Medicated groups were significantly older (both $p<.001$), and had significantly lower proportions of females (both $p\leq.003$). Across the depression subgroups, there was a significant difference in BMI ($F(2, 216)=1.3$, $p=.024$) wherein the SSRI group had a significantly higher BMI compared to the

NRI/NDRI group (p=.009), but there were no significant differences in sex distributions, age, or BDI-II (all p>.050).

3.1.2 Sleep architecture

Significant differences between the main groups were found for sleep efficiency (F(2, 364)=5.6, p=.004), REM latency (F(2, 354)=24.8, p<.001), sleep onset latency (F(2, 364)=7.7, p=.001), and the percentages of NREM (F(2, 364)=9.4, p<.001) and REM (F(2, 364)=9.4, P<.001) sleep. The Antidepressant group had significantly higher sleep efficiency compared to the Control group (p=.006), but not the Non-Medicated group (p=.998). The Antidepressant group also had significantly longer sleep and REM onset latencies compared to both the Non-Medicated (p=.011 and p<.001, respectively) and Control groups (both p<.001). Moreover, the Antidepressant group had a lower percentage of REM sleep and a higher percentage of NREM sleep compared to the Non-Medicated group (both p<.001).

Amongst the depression subgroups, significant differences were found for sleep onset latency (F(2, 216)=3.4, p=.035), REM latency (F(2, 206)=39.0, p<.001), the percentage of REM sleep (F(2, 216)=10.7, p<.001) and the percentage of NREM sleep (F(2, 216)=10.7, p<.001). Compared to the Non-Medicated group, the SSRI group had significantly longer sleep onset latency (p=.011). The SSRI group also had longer REM latency, lower percentage of REM sleep, and higher percentage of NREM sleep than both the NRI/NDRI and Non-Medicated groups (all p<.050).

3.2 Comparison of respiratory measures across groups and sleep stages

3.2.1 Main groups analyses

Figure 1 depicts respiratory measures for the Antidepressant, Non-Medicated, and Control groups. Detailed respiratory data is reported in Table 3. All main group analyses were conducted while controlling for age and sex.

There was no significant group*sleep stage interaction or main effect of sleep for the AHI. A significant main effect of group ($F(2, 350)=8.0$, $p<.001$) showed that the AHI was significantly higher in the Antidepressant ($p<.001$) and the Non-Medicated ($p=.002$) groups compared to the Control group. While the Antidepressant group had a higher AHI than the Non-Medicated group, this difference was not statistically significant ($p=.395$).

For the $minSpO_2$, there was a group*sleep stage interaction ($F(2, 350)=3.6$, $p=.028$) driven by a significant group difference emerging only during NREM sleep. Specifically, during NREM sleep, the Antidepressant group had significantly lower $minSpO_2$ than both the Control ($p=.002$) and Non-Medicated ($p=.006$) groups. There was no significant difference in NREM $minSpO_2$ between the Non-Medicated and Control groups ($p=.753$). There was no significant group difference in the $minSpO_2$ during REM sleep.

A trend for a group*sleep stage interaction for the Oxygen Desaturation Index ($F(2, 350)=2.6$, $p=.074$) suggested that during NREM sleep, the Antidepressant group had a higher Oxygen Desaturation Index compared to both the Control ($p<.001$) and Non-Medicated ($p<.001$) groups. No significant difference in the NREM Oxygen Desaturation Index was observed between the Non-Medicated and Control groups ($p=.979$). There was no significant group difference in the Oxygen Desaturation Index during REM sleep.

3.2.2 Antidepressant subtypes

Figure 2 depicts respiratory measures for the SSRI, NRI/NDRI, and Non-Medicated groups. Detailed respiratory data is reported in Table 4. All analyses focused on subtypes of antidepressant medications included BMI as a covariate.

There was a significant antidepressant subtypes*sleep stage interaction for the AHI ($F(2, 203)=4.2$, $p=.017$). During NREM sleep, the SSRI group had a significantly higher AHI compared to both the Non-Medicated ($p=.021$) and NRI/NDRI ($p=.043$) groups. The NREM AHI did not differ significantly between the NRI/NDRI and Non-Medicated groups. There were no significant group differences in AHI during REM sleep.

There was also a significant antidepressant subtypes*sleep stage interaction for the minSpO_2 ($F(2, 203)=5.0$, $p=.008$). During NREM sleep, the SSRI group had significantly lower minSpO_2 compared to both the Non-Medicated ($p=.001$) and NRI/NDRI ($p=.032$) groups. There was no significant difference in NREM minSpO_2 between the NRI/NDRI and Non-Medicated groups ($p=.798$). There were no significant group differences in minSpO_2 during REM sleep.

A significant interaction ($F(2, 203)=6.9$, $p=.001$) showed that the SSRI group had a significantly higher Oxygen Desaturation Index during NREM sleep compared to both the Non-Medicated ($p<.001$) and NRI/NDRI ($p=.026$) groups, whereas there were no differences between the NRI/NDRI and Non-Medicated groups. There were no significant group differences in the Oxygen Desaturation Index during REM sleep.

4. Discussion

In this sample of patients referred to a sleep clinic, individuals with depression had significantly more frequent sleep-related breathing disruptions compared to non-depressed individuals. In those individuals with depression who were taking antidepressant medications, the effects of these

breathing disruptions on blood oxygen saturation during NREM sleep were worse than in non-medicated individuals with depression. More detailed analyses highlighted more pronounced breathing dysfunctions in people taking serotonergic versus non-serotonergic medications despite similar depressive symptoms severity.

Individuals using SSRIs, the most common medication prescribed for depression(238–240) had significantly more frequent apneas and hypopneas, lower blood oxygen saturation and more frequent desaturations during NREM sleep, compared to non-medicated individuals with depression or those using non-serotonergic antidepressants (i.e. NRI/NDRIs). These differences were not trivial, with the overall rates of apnea and hypopnea being 1.5 to 2.3 times higher in the SSRI group than in the other groups. Although this needs to be further investigated with prospective studies, this is the first empirical evidence in humans suggesting that the use of SSRIs in the context of depression and sleep complaints, may be associated with worse sleep-related breathing disturbances. The hypothesis that this may operate via alterations in serotonin-mediated respiratory functions is reinforced by the observation that breathing disturbances were not significantly elevated in people taking non-serotonergic antidepressant (i.e. NRI/NDRIs).

Previous studies yielded inconsistent findings concerning the role of serotonin on respiratory function during sleep in individuals without depression. While some clinical studies are investigating the use of SSRIs to treat OSA(223,233,234), others suggested that serotonin agents may play a role in the development or worsening of sleep apnea(98,241). Since the expression of 5-HT receptors may influence the nature of serotonergic effects on respiratory functions(60,61), we focused on people with depression to assess potential interactions between the pharmacological effects of SSRIs and 5-HT receptors abnormalities linked to depression.

Previous work indicates that, in the central nervous system, the excitatory effects of 5-HT on respiration centers are mostly mediated by 5-HT1A, 5-HT2A and 5-HT2C receptors(242). For instance, serotonin in the brainstem increases activation of upper airway dilators, notably via excitatory input to the hypoglossal motor nuclei(235,236), which facilitates respiration. Conversely, in the periphery, serotonin has mostly inhibitory effects on respiration which are mediated by 5-HT2A, 5-HT2C and 5-HT3 receptors. Hence, while the stimulation of 5-HT2A and 5-HT2C receptors may have opposite effects on respiration in different parts of the nervous system, 5-HT1A and 5-HT3 receptors may induce more consistent excitatory and inhibitory modulation, respectively. While this remains to be formally investigated, depression-related reduction in 5-HT1A receptors activity(243,244) and potential increases in 5-HT3 receptors activity(237), may worsen individual vulnerability to the suppressing effects of SSRIs on respiration.

It may also be relevant to assess if distinct OSA phenotypes mediate the sensitivity of the respiratory system to 5-HT agents in people with depression. For instance, some OSA phenotypes are associated with an intensification of the magnitude and/or time course of the chemoreflex feedback loop regulating ventilatory responses to breathing challenges (i.e. high loop gain)(245), and a recent animal study suggests that the duration of the laryngeal chemoreflex is modulated by 5-HT3 receptors(246). Another OSA phenotype is linked to low arousal threshold, which may interact with depression and/or SSRI-related sleep fragmentation. From this perspective, the combination of the phenotypic traits leading to oversensitive ventilatory control or low arousal threshold with potential 5-HT receptors or sleep abnormalities linked to depression may have additive or interactive effects on the vulnerability of the respiratory system to SSRIs.

In line with the well-known REM suppressing effects of SSRIs, the SSRI group was found to have significantly reduced amounts of REM sleep and increased REM onset latency compared to the

non-medicated and NRI/NDRI groups. Considering that there is an increased risk for upper airway collapse during REM sleep, it has previously been suggested that antidepressant medications may reduce sleep apneas by way of the suppression of REM sleep(247). However, in the present study, significant differences in AHI and blood-oxygen desaturation persisted despite the reduction in REM sleep, and occurred most prominently during NREM sleep. This suggests that the effects of SSRIs on respiratory function in people with depression are not solely due to changes in sleep architecture.

These findings have important clinical implications considering the potential for sleep-related breathing disturbances to worsen depression. In addition to the high comorbidity between depression and sleep-related breathing disorders(103,248–250), epidemiological studies have reported an increased risk of developing depression following the onset or worsening of OSA(251). Also, residual depressive symptoms persisting after multiple unsuccessful antidepressants trials in adolescents with depression have been found to correlate with worse respiratory disturbances during sleep(252). The adverse effects of sleep-related breathing disturbances on mood are notably thought to occur via the effects of chronic hypoxia and excessive daytime sleepiness resulting from sleep fragmentation(253,254). For example, the degree of hypoxia arising from OSA correlates with hypoperfusion in the prefrontal cortex and the insula, two brain regions that are highly involved in emotional regulation and have been implicated in depression pathophysiology. If, as the current findings suggest, SSRIs use worsens not only sleep apneas/hypopneas but also oxygen desaturation in some people with depression, in the long term, this may lead to adverse depression outcomes. Of note, these potential sleep-related respiratory disturbances, and the resulting sleep fragmentation, are also likely to add to other SSRI-driven alterations in sleep architecture, such as reduced sleep consolidation(94,255,256).

5. Limitations

This study has several limitations. Since this was based on retrospective data, we were unable to control for factors such as medication dosage and duration of treatment. Due to the cross-sectional nature of this study, causation cannot be inferred, and prospective studies are needed to confirm whether the use of SSRIs actively induces and/or worsens sleep-related breathing disturbances in individuals with depression. Since the sample included individuals referred to a sleep clinic, the findings may not generalize to people with depression without marked sleep problems. Generalizability is further limited by the fact that all cases included were issued from the same sleep clinic. Also, the sample size of the group taking NRI/NDRI medication was fairly small and prevented comparisons across men and women. Further comparative work is required to investigate the specificity of the effects of different serotonergic agents on respiratory functions during sleep, and to determine if they may be modulated by sex.

6. Conclusion

Based on a retrospective clinical sample, the current study suggests that individuals with depressive disorders have worse sleep-related breathing disturbances than mentally healthy individuals, and that this may be worse in those taking medications typically prescribed for depression. Detailed analyses suggest that, independently of depression severity, sleep-related respiratory disturbances during NREM sleep are more prominent in people using SSRIs, as opposed to NRI/NDRIs. This could possibly result from interactions between depression neuropathophysiology and the effects of exogenous serotonin manipulation on the respiratory system. Prospective investigations are required to determine whether serotonergic agents may actively exacerbate sleep-related breathing disorders in individuals with depression, and whether this may be modulated by 5-HT receptors expression and/or binding. Such findings may unveil a

new unsuspected side effect to one of the most heavily prescribed classes of psychotropic medication. This would have serious implications for the clinical management of depression, not only to limit the adverse impacts of sleep-related breathing disorders on physical health, but also to identify potential factors that may worsen depression pathophysiology and symptomatology over time.

Table 1. Sleep architecture and descriptive information across main groups

Variable	Antidepressant	Non-Medicated	Control	F/χ^2	p
N	100	117	148	-	-
Sex Distribution (%female)	65.0	67.5	45.9	15.2	.001
Age (years)	43.6 ± 14.9	43.7 ± 13.7	52.8 ± 15.2	17.2	<.001
BMI (kg/m^2)	29.6 ± 6.6	28.9 ± 6.5	28.2 ± 5.5	1.2	.311
Sleep Architecture ($\overline{x}$ ± SD)					
Sleep Efficiency (%)	84.0 ± 11.0	84.0 ± 11.9	79.8 ± 12.2	5.6	.004
Total Sleep Time [TST (min)]	356.8 ± 61.1	357.8 ± 75.0	341.9 ± 63.0	2.1	.126
Sleep Onset Latency (min)	24.8 ± 24.7	17.7 ± 19.1	14.7 ± 15.4	7.7	.001
REM Latency (min)*	207.6 ± 104.1	130.2 ± 74.6	136.0 ± 81.5	24.8	<.001
NREM (%)	86.9 ± 7.6	83.2 ± 5.8	85.5 ± 8.0	9.4	<.001
REM (%)	13.1 ± 7.6	16.8 ± 5.8	14.5 ± 6.0	9.4	<.001

BMI: Body Mass Index, TST: Total sleep time, REM: Rapid eye movement, WASO: Wake after sleep-onset, N1: Non-REM 1, N2: Non-REM 2, N3: Non-REM 3. F/χ^2 and p-values reflect global omnibus statistics (statistics for paired-comparisons are reported in the text).

*1 individual from the Non-Medicated group and 9 from the Antidepressant group had no REM sleep.

Table 2. Sleep architecture and descriptive information across depression subgroups

Variable	Non-Medicated	NRI/NDRI	SSRI	F/χ^2	p
N	117	20	80	-	-
Sex Distribution (%female)	67.5	55.0	67.5	1.3	.529
Age (years)	43.7 ± 13.7	38.9 ± 15.8	44.7 ± 14.5	1.3	.263
Comorbid Anxiety [n (%)]	18 (15.4)	6 (30.0)	24 (30.0)	-	-
Substance Use Disorder	5 (4.3)	4 (20.0)	4 (5.0)	-	-
SSRI Subtypes [n (%)]					
Citalopram (Celexa)	-	-	23 (28.8)	-	-
Escitalopram (Cipralex)	-	-	24 (30.0)	-	-
Fluoxetine (Prozac)	-	-	16 (20.0)	-	-
Sertraline (Zoloft)	-	-	14 (17.5)	-	-
Fluvoxamine (Luvox)	-	-	5 (6.3)	-	-
Paroxetine (Paxil)	-	-	2 (2.5)	-	-
NRI/NDRI Subtypes [n (%)]					
Bupropion (Wellbutrin)	-	19 (95.0)	-	-	-
Atomoxetine (Strattera)	-	1 (5.0)	-	-	-
BMI (kg/m^2)	28.9 ± 6.5	26.4 ± 6.1	30.3 ± 6.5	3.8	.024
BDI-II Score	23.1 ± 8.6	27.4 ± 10.2	24.1 ± 7.9	2.2	.107
Sleep Architecture ($\bar{x}$ ± SD)					
Sleep Efficiency (%)	84.0 ± 11.9	86.2 ± 11.8	83.5 ± 10.8	0.5	.633
Total Sleep Time [TST (min)]	357.8 ± 75.0	360.2 ± 65.9	355.9 ± 60.3	0.04	.964
Sleep Onset Latency (min)	17.7 ± 19.1	19.1 ± 16.9	26.3 ± 26.2	3.4	.035
REM Latency (min)*	130.2 ± 74.6	111.6 ± 58.3	231.3 ± 99.3	39.0	<.001
NREM (%)	83.2 ± 5.8	84.1 ± 8.4	87.6 ± 7.3	10.7	<.001
REM (%)	16.8 ± 5.8	15.9 ± 8.4	12.4 ± 7.3	10.7	<.001

SSRI: selective serotonin reuptake inhibitor, NRI/NDRI: norepinephrine or norepinephrine–dopamine reuptake inhibitor, BMI: Body Mass Index, BDI-II: Beck Depression Inventory-II, TST: Total sleep time, REM: Rapid eye movement. F/χ^2 and p-values reflect global omnibus statistics (statistics for paired-comparisons are reported in the text).

* 1 individual from the non-medicated group, 2 from the NRI/NDRI and 7 from the SSRI groups had no REM sleep.

Table 3. Respiratory data across main groups.

	Control $\bar{x} \pm SD$	Non-Medicated $\bar{x} \pm SD$	Antidepressant $\bar{x} \pm SD$	Statistics (F)		
				Group	Sleep	Interaction
AHI (events/hr)				8.0**	1.8	2.5
NREM	10.9 ± 16.7	9.8 ± 13.0	13.6 ± 16.8			
REM	17.9 ± 20.2	20.2 ± 20.3	20.3 ± 22.3			
$MinSpO_2$ (%)				3.1*	1.6	3.6*
NREM	89.6 ± 5.2	91.0 ± 3.5	89.4 ± 4.4			
REM	90.0 ± 5.3	90.9 ± 3.7	90.4 ± 4.6			
ODI (events/hr)				4.1*	.003	$2.6^{(*)}$
NREM	7.0 ± 12.7	3.6 ± 5.6	8.4 ± 14.3			
REM	13.7 ± 17.9	9.9 ± 11.7	13.0 ± 18.8			

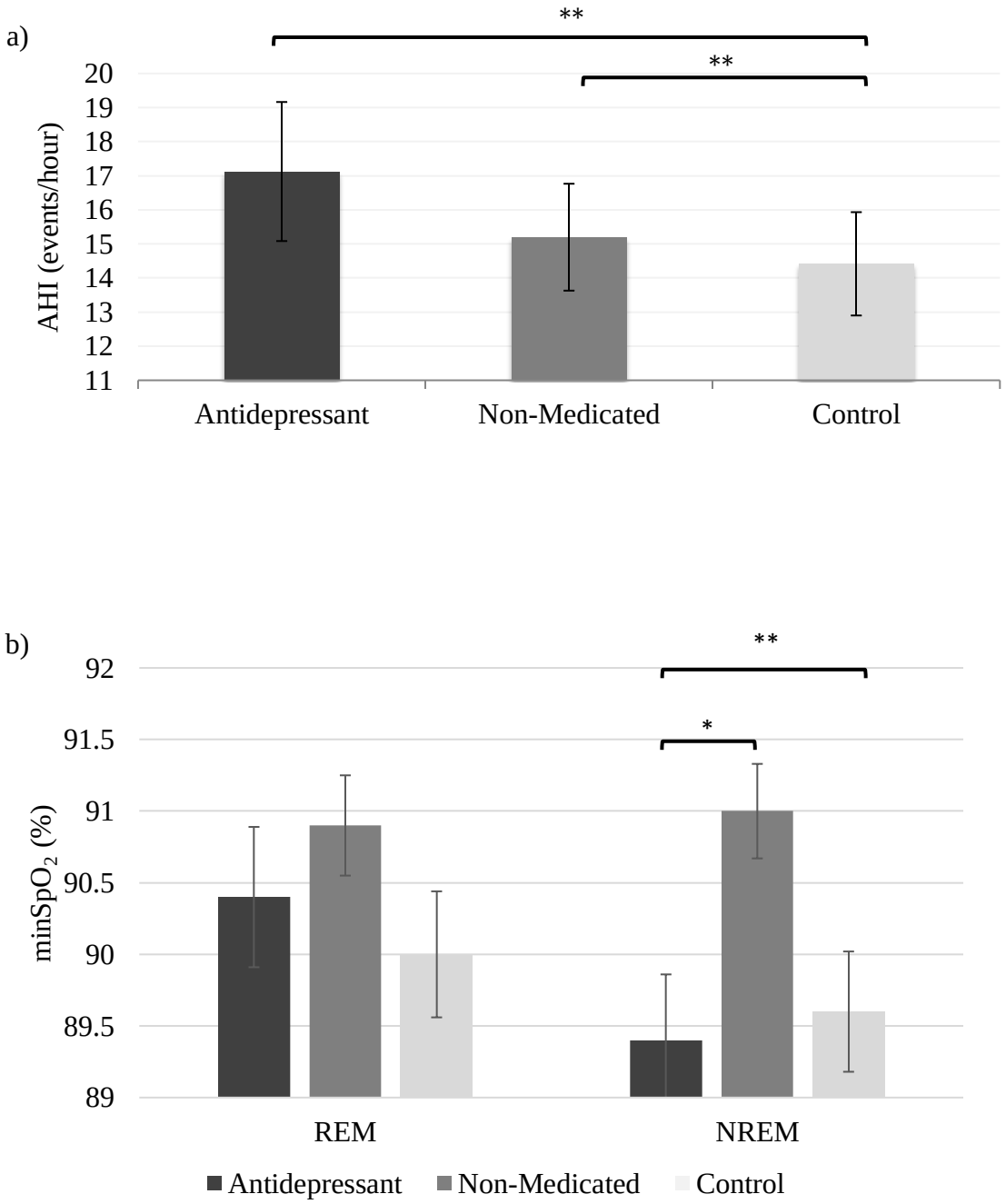
AHI: Apnea-Hypopnea Index, $MinSpO_2$: minimum blood-oxygen saturation level, ODI: Oxygen Desaturation Index. F values are reported for main group effects (differences between mentally healthy controls, Non-Medicated people with depression and Medicated people with depression), main effects of sleep stages (NREM and REM sleep), and interactions between main groups and sleep stages . *p<.050, **p<.001, $^{(*)}$ p<.075 (i.e. trends). 9 individuals in the Antidepressant group, 1 in the Non-Medicated group had no REM sleep.

Table 4. Respiratory data across depression subgroups.

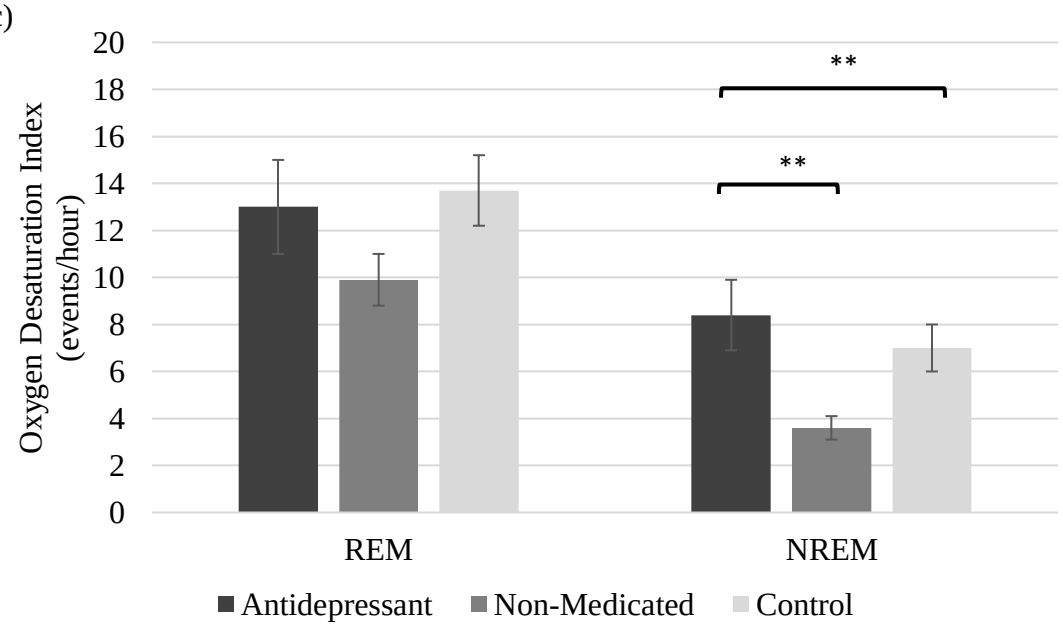
	Non-Medicated $\bar{x} \pm SD$	NRI/NDRI $\bar{x} \pm SD$	SSRI $\bar{x} \pm SD$	Statistics (F)		
				Group	Sleep	Interaction
AHI (events/hr)				0.4	1.4	4.2*
NREM	9.8 ± 13.0	7.3 ± 11.0	15.2 ± 17.6			
REM	20.2 ± 20.3	17.4 ± 26.2	21.1 ± 21.4			
$MinSpO_2$ (%)				2.5	0.5	5.0**
NREM	91.0 ± 3.5	91.7 ± 2.3	88.9 ± 4.6			
REM	90.9 ± 3.7	91.7 ± 3.8	90.1 ± 4.8			
ODI (events/hr)				2.2	9.6**	6.9***
NREM	3.6 ± 5.6	2.7 ± 2.3	9.8 ± 15.6			
REM	9.9 ± 11.7	12.0 ± 20.9	13.3 ± 18.3			

AHI: Apnea-Hypopnea Index, $MinSpO_2$: minimum blood-oxygen saturation level, ODI: Oxygen Desaturation Index, NRI/NDRI: norepinephrine or norepinephrine-dopamine reuptake inhibitor, SSRI: selective serotonin reuptake inhibitor. F values are reported for main group effects (differences between people with depression taking SSRIs, NRI/NDRIs, and Non-Medicated people with depression), main effects of sleep stages (NREM and REM sleep), and interactions between main groups and sleep stages . *p<.050, **p<.010, ***p<.001. 1 individual in the Non-Medicated group, 2 in the NRI/NDRI group, and 7 in the SSRI group had no REM sleep.

Figure 1. Distribution of respiratory parameters in the main groups.

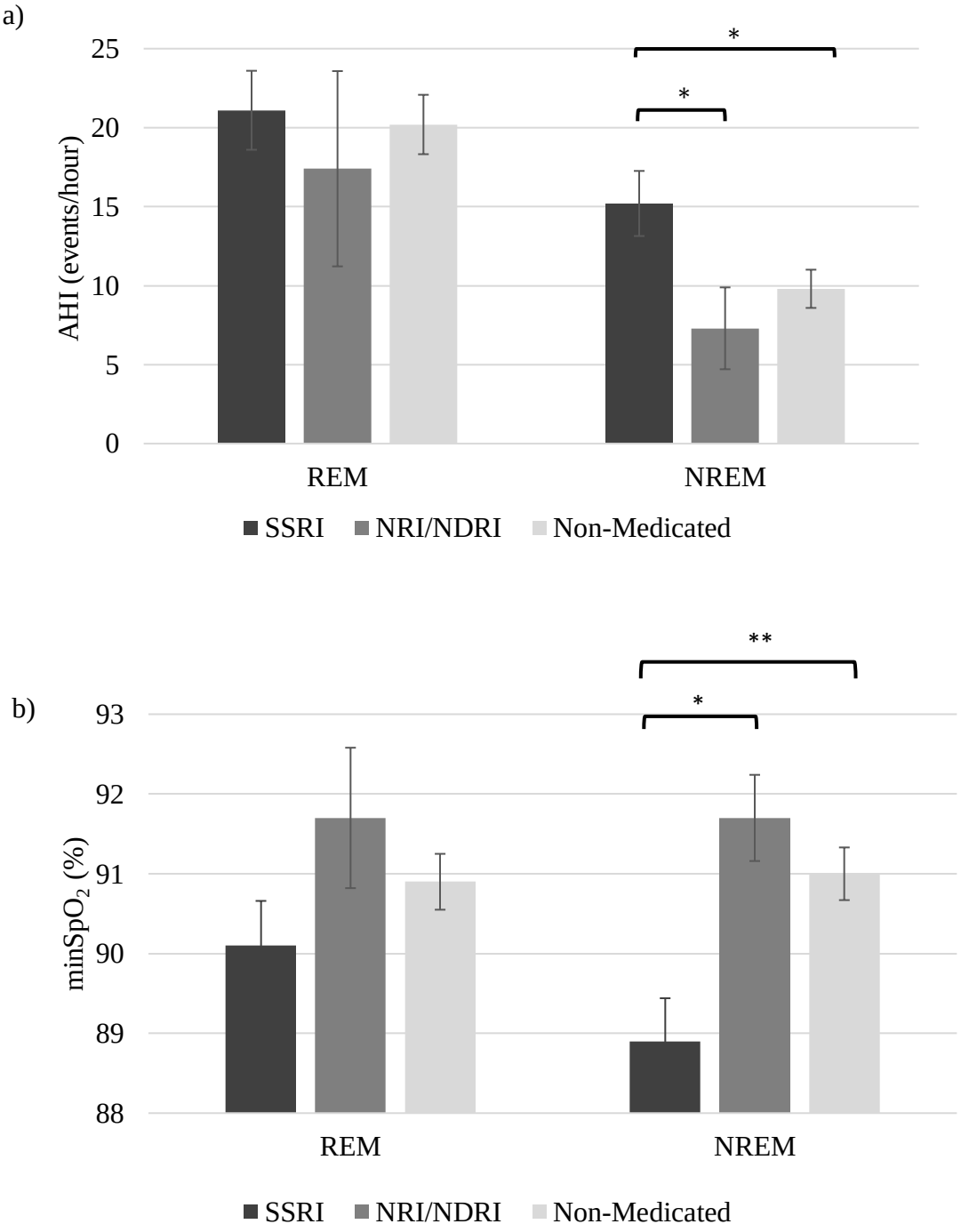


c)

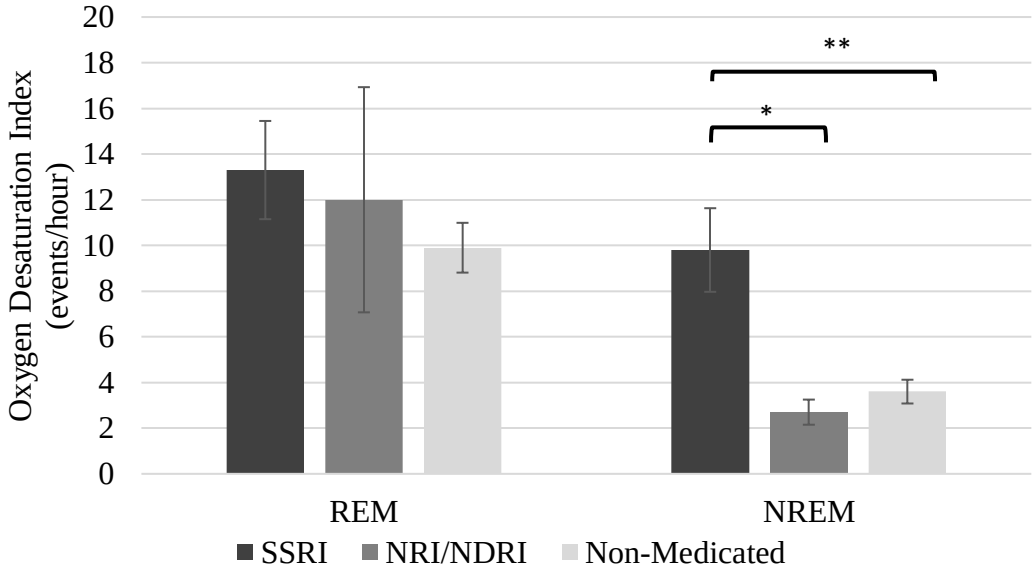


Distribution of respiratory parameters across the main groups: a) AHI (REM and NREM combined), and b) minSpO_2, and c) Oxygen Desaturation Index across REM and NREM sleep. Bars indicate unadjusted mean and error bars indicate the standard errors of the mean. AHI = Apnea-Hypopnea Index (events per hour). MinSpO_2 = Minimum blood oxygen saturation, %. ** $p<0.005$, * $p<.010$.

Figure 2. Distribution of respiratory parameters in the depression subgroups.



c)



Distribution of respiratory parameters during REM and NREM sleep across the depression subgroups: a) AHI, b) minSpO_2, and c) Oxygen Desaturation Index. Bars indicate unadjusted mean and error bars indicate the standard errors of the mean. AHI = Apnea-Hypopnea Index (events per hour). SpO2 = Minimum blood oxygen saturation, %. SSRI = Selective Serotonin Reuptake Inhibitor. NRI/NDRI = Norepinephrine or Norepinephrine-Dopamine Reuptake Inhibitor. .** $p<0.005$, * $p<.050$.

Chapter 5 – Discussion

5.1 Result summary and implications

There is a strong link between depression and cardiovascular disease, and sleep plays a crucial role in the pathophysiology of both types of disorders. Altogether, the present work contributed to a better understanding of the potential factors underlying the complex relationship between depression, cardiovascular disease, and sleep. Considering the reciprocal links between these factors, this work also examined a novel biomarker at the intersection that may yield promising results for the diagnosis of depression. The three main goals of this thesis were: 1) to examine the autonomic modulation of cardiac activity, indexed by HRV, across sleep states and levels of sleep depth in individuals with depression compared to healthy controls, 2) to assess the validity of a novel physiological biomarker of depression based on autonomic cardiac regulation during sleep, and 3) to examine sleep-related breathing disturbances related to depression and antidepressant medication use.

5.1.1 Chapter 2

In the first article (Chapter 2), we compared time-domain HRV parameters across sleep states and all levels of sleep depth. The key finding of this study was that the abnormalities in autonomic cardiac modulation related to depression are more prominent during sleep, specifically NREM sleep, than during wake. This suggests that depression is associated with aberrant parasympathetic modulation of the cardiac sinoatrial node, reflecting an inability to rapidly adjust heart rate in response to external influences as well as internal physiological processes. This reduction in physiological flexibility may contribute to the increased risk of cardiovascular disease amongst this population.

Findings from animal studies suggest a role for serotonin in the autonomic dysregulation associated with depression. Preganglionic neurons in the nucleus ambiguus and dorsal vagal motor nucleus modulate parasympathetic outflow to the heart, and serotonin influences autonomic outflow at these sites(257). In fact, the administration of a 5-HT1A receptor agonist potentiates vagally-mediated reductions in HR in animals(258). Moreover, both baroreflex sensitivity and HF HRV have been found to be reduced in a genetic rat model of depression, compared to control strains(259). The administration of a 5-HT1A receptor agonist resulted in HR reductions and enhanced baroreflex sensitivity in the control strain of rats, but these effects were not observed in the rat model of depression(260). Combined with the known impairments in 5-HT1A binding associated with depression(115), these findings support the notion of abnormal serotonergic control of vagal cardiac modulation.

Furthermore, considering that our results point to abnormalities in vagal modulation specifically, the inflammation associated with depression may also represent a plausible pathway(173). Importantly, the autonomic nervous system plays a role in regulating the inflammatory response via signalling mediated by the vagus nerve. This results in the release of acetylcholine leading to the inhibition of pro-inflammatory cytokine synthesis(209,210). On the other hand, increased inflammation is associated with reductions in vagal activity. Accordingly, studies have found an inverse relationship between inflammatory markers and HRV measures of vagal activity(178,210,261). A prospective study also found negative correlations between HRV and inflammatory markers including CRP and IL-6 in depressed individuals, which both contributed to an increased risk of cardiovascular mortality compared to non-depressed individuals after a median follow-up period of 13.3 years(262). Therefore, inflammatory processes associated with

depression may result in vagal impairments, which may represent an important pathway for the development of cardiovascular disease in individuals with depression.

Moreover, there is constant two-way communication between the heart and the brain. Ascending cardiovascular signaling influences the autonomic control of the heart through higher order feedback loops. Afferent signals from the heart modulate autonomic neuro-cardiac control via several regions in the forebrain, including the insular cortex, cingulate gyrus, and basal ganglia. These forebrain regions, which have been implicated in depression pathophysiology, control top-down regulation of autonomic output that influences cardiovascular function(263,264). As such, aberrant cardiac signaling/information processing could be one of the factors underlying autonomic dysfunction in depression. Heartbeat-evoked potentials (HEPs) in the EEG represent an objective measure of the cortical processing of afferent signals originating in the heart, as well as a psychophysiological correlate of interoception, or bodily awareness(265). Unlike event-related potentials, which are evoked by external stimuli (e.g. auditory), heartbeat-evoked potentials quantify the neural response to a visceral stimulus. One study found that individuals with depression had reduced cardiac interoceptive awareness during the wake state, demonstrated by impaired heartbeat perception accuracy on the Mental Tracking Task, as well as lower amplitudes of heartbeat-evoked potentials, as compared to healthy controls(266). Furthermore, a study examining the link between sleep quality and cardiac interoception found that poor sleep quality predicted a greater reduction in interoceptive accuracy on a heartbeat discrimination task in individuals with depression. This suggests that the sleep difficulties associated with depressive disorders may enhance the disruption of viscerosensory information processing(267). Considering the present study findings of sleep-related impairments in autonomic modulation, future studies must assess HEPs in individuals with depression

specifically during sleep, and examine their relation to sleep HRV. This could point to abnormalities in neuro-cardiac communication underlying autonomic dysregulation in depression.

Although this is the first study assessing HRV across levels of sleep depth in individuals with depression, there has been prior investigation into the effects of acute psychophysiological stress on HRV across sleep stages. Hall et al. (2004) reported decreased levels of vagal modulation, indexed by HF HRV, during NREM and REM sleep, in healthy individuals exposed to a pre-sleep stress condition, compared to controls. They also observed that increases in vagal modulation across successive NREM cycles were blunted in the stress group, compared to controls(268). As such, the assessment of sleep stage-specific HRV across different sleep cycles throughout the night may reveal further autonomic impairments in individuals with depression.

5.1.2 Chapter 3

In the second article (Chapter 3), we found a 79.9% classification accuracy of depression status based solely on the analysis of heart rate patterns across sleep stages. The algorithm maintained a high sensitivity across depression subgroups stratified by depression severity, psychiatric comorbidity, history of cardiovascular disease, and cardiovascular medication use. Thus, nocturnal heart rate profiling may be a generalizable, accurate, and objective adjunct diagnostic tool for depression. The relative ease, inexpensiveness, and non-invasive nature of this tool are promising factors for the use of heart rate profiling in clinical settings. The accuracy by which the algorithm was able to diagnose depression based solely on measures of autonomic function highlight the extent to which this process is impaired amongst this population, strengthening the link between depression and cardiovascular disorders. Although the exact features used by the algorithm are

under patent protection, findings from our first study (Chapter 2) suggest that differences in HRV (i.e. SDNN and RMSSD) across depression and control groups are most pronounced during NREM sleep. Moreover, our preliminary findings (Appendix A) suggest that there are significant differences in the temporal dynamics of heart rate across the night in individuals with depression vs. controls. Specifically, we plotted heart rate against time during the sleep period, beginning at sleep onset, and found that depression was associated with a steeper slope of heart rate across the night, and increased heart rate at the time of sleep onset (i.e. higher y-intercept), compared to non-depressed controls. We also found that heart rate fluctuated within a narrower range (i.e. reduced confidence interval) in individuals with depression, compared to controls. As such, specific heart rate pattern metrics (e.g. the slope of the heart rate profile across the night) and various HRV parameters during distinct sleep states (e.g. NREM-specific SDNN) may be key features enabling the differentiation of individuals with and without depression.

Other proposed physiological biomarkers of depression such as sleep architecture characteristics, inflammatory markers, and neurotrophic factors lack the required specificity to serve as a diagnostic tool for depression. For instance, blood levels of brain-derived neurotrophic factor (BDNF) are reduced in individuals with depression, and normalize following antidepressant treatment(269–271). However, reduced levels of BDNF have also been found in schizophrenia(272), and eating disorders(273). Conversely, HRV is an index at the intersection of autonomic, cardiovascular, sleep, and emotional regulation, and may therefore be a more promising biomarker when assessed across sleep stages. Although similar abnormalities in autonomic cardiac regulation have been noted in other psychiatric disorders(274), the interactions between depression-related sleep neurophysiology and autonomic function may result in a distinct depression biomarker. In fact, one study found that various psychiatric disorders including

depression, panic disorder, and generalized anxiety disorder were associated with distinct patterns of heart rate across sleep-wake transitions(99). Future studies must compare sleep stage-specific HRV and heart rate patterns across various psychiatric conditions in order to evaluate the specificity of this biomarker for depression.

The use of an objective physiological measure of depression alongside traditional diagnostic tools may reduce the likelihood of diagnostic error. Moreover, if deviant heart rate patterns are found to normalize following the treatment of depression, this biomarker could be used as an indicator of treatment outcomes in clinical and research settings. Heart rate recordings using ambulatory monitoring tools may be transmitted to clinicians and researchers electronically, which would ease the monitoring of depressive symptoms over time. Finally, the stigma associated with mental illness may lead to reluctance to seek psychiatric care. The use of an easily measurable physiological marker to diagnose depression may aid in reducing the stigma barriers to accessing mental health care.

5.1.3 Chapter 4

In the third article (Chapter 4), we compared indices of sleep-related respiratory disturbances amongst a group of non-medicated individuals with depression, a depression group using antidepressants, and a non-medicated non-depressed control group. These respiratory disturbance indices were then compared across the non-medicated depression group, as well as two depression subgroups using SSRIs or NRI/NDRIs. There were several key results in this study: firstly, the use of antidepressants in the context of depression was associated with worse sleep-related breathing disturbances compared to mentally healthy individuals and even non-medicated individuals with depression. Importantly, non-medicated individuals with depression also had more frequent

respiratory disturbances than controls, suggesting that depression may have an independent effect on sleep-related respiratory function. Moreover, our findings amongst medicated individuals were driven by the use of serotonergic antidepressants specifically, as opposed to antidepressants acting on the noradrenergic/dopaminergic systems. The use of SSRIs was associated with more frequent sleep-related breathing disruptions, lower blood oxygen saturation, and more frequent blood oxygen desaturations, compared to the use of NRI/NDRIs.

This is the first study to present evidence suggestive of antidepressants worsening respiratory function during sleep in individuals with depression. These findings have great implications for the clinical management of depression, considering that SSRIs are the first-line treatment. Moreover, repeated periods of hypoxia, as well as daytime fatigue associated with chronic sleep fragmentation may exacerbate the depressive disorder through adverse effects on mood. In fact, chronic hypoxia due to sleep apnea is associated with hypoperfusion in the prefrontal cortex and insula, which may impact emotional regulation. Conversely, the successful treatment of sleep apnea is associated with a reduction in depressive symptoms.

Furthermore, chronic respiratory disturbances associated with SSRI use may be an important factor underlying the increased risk of cardiovascular disease amongst depressed individuals. The cardiovascular consequences of sleep-related breathing disorders occur via several pathways. Recurrent respiratory obstruction leads to chronic hypoxemia which causes vascular endothelial dysfunction as well as oxidative stress due to free radical production(275,276). Sudden arousals following apneic events alter autonomic nervous system activity, namely causing an increase in sympathetic activity, which leads to increases in blood pressure and heart rate that persist after awakening(220,277,278). Studies assessing HRV in OSA also suggest an increase in sympathetic tone during sleep(279,280). Over time, this can lead to the development of hypertension,

atherosclerosis, myocardial ischemia, and coronary artery disease(281). In fact, it has been reported that approximately 50% of individuals with OSA are hypertensive(282), while the prevalence of sleep-related breathing disorders is two times higher in individuals with CAD, as compared to those without CAD(283). In addition to these cardiovascular implications, OSA is known to contribute to cognitive deficits in attention and memory, and is a risk factor for dementia(284–287). Reductions in hippocampal gray matter volume due to hypoxia may underlie these deficits, as the successful treatment of OSA is associated with a subsequent increase in grey matter volume and corresponding improvement in cognitive function(288). Moreover, a longitudinal study found a dose-response relationship between sleep apnea severity, indexed by AHI, and the risk of cancer mortality after a 22-year follow-up period(289), which may be due to hypoxia-mediated tumor angiogenesis and cell proliferation(290–292). Other implications of OSA include an increased risk of motor vehicle accidents, increased health-care expenditures, and an increased risk of all-cause mortality compared to those without OSA(254,293–295). Prospective studies are required to ascertain the effects of OSA on cardiovascular health, specifically in individuals with depression and in those using SSRIs.

Although our first study (Chapter 2) focused on HRV in non-medicated individuals, there are reasons to postulate that there may be a causal link between the use of SSRIs, sleep-related breathing disturbances, and HRV. Sleep-disordered breathing is known to induce changes in HR and HRV. An abrupt increase in HR occurs following apneic and hypopneic events during subsequent arousal(296). This also has chronic effects on daytime autonomic function, specifically reduced HF HRV, reflecting blunted efferent vagal tone(297). Intermittent oxyhemoglobin desaturation due to respiratory disturbances also leads to sympathetic hyperactivity, which may alter HR dynamics during sleep(298), and has been found to persist during wake(220). Moreover,

studies assessing the effects of antidepressants on HRV during wake have found that depressed individuals using SSRIs have reduced HRV compared to non-medicated individuals with depression and healthy controls(135,299). Considering the present study findings, sleep-related breathing disturbances associated with SSRI use may potentially mediate the relationship between SSRI use and reduced HRV in individuals with depression. On the other hand, serotonin is known to play a role in cardiovascular regulation. Specifically, central 5-HT1A and 5-HT3 receptors alter parasympathetic outflow to the heart(300), which modulates HRV, while 5-HT2A receptors in the nucleus of the solitary tract facilitate the baroreceptor reflex(301). Therefore, the use of SSRIs may alter cardiovascular function through direct actions on the heart or indirectly via respiratory disturbances during sleep.

While the effects of antidepressants on HRV remain to be investigated during sleep, it is likely that the pathophysiology of depression and antidepressant use interact to alter both cardiovascular and respiratory function during sleep. Further research is required to compare the effects of various classes of antidepressants on nocturnal cardiac rhythms.

Moreover, in terms of autonomic cardiac regulation, it is important to consider the effects of comorbid sleep abnormalities(302). Although our first study (Chapter 2) ruled out sleep-related breathing disturbances, the sample consisted of individuals referred to a specialized sleep clinic due to sleep complaints. Other sleep disorders, such as insomnia and periodic limb movement disorder, may also impact HRV. Bonnet and colleagues (1998) found that the SDNN was reduced in individuals with insomnia compared to healthy controls during all stages of sleep(303). However, other studies have found no significant differences in HRV during sleep(304) and the resting state(305) in individuals with insomnia vs. healthy controls. These discrepancies may be due to differing diagnostic methods across study populations, as well as methodological

differences in the measurement and assessment of HRV, including different types of HRV analysis (e.g. time vs. frequency-domain) (306). Several studies have also found that periodic limb movements during sleep are associated with increased sympathetic activity, resulting in significant increases in heart rate and LF HRV(307,308). Moreover, HRV may be directly related to sleep quality. Both the RMSSD and RSA were found to be positively correlated with average sleep efficiency over a one week period in healthy individuals, which may suggest an important role for vagal activity in the maintenance of sleep(309). Thus, our results in terms of the effects of depression on autonomic cardiac regulation must be interpreted in the context of individuals with varying sleep complaints, which does reflect the general depression population. However, there is a need to disentangle the effects of depression vs. sleep complaints on nocturnal heart rate variability.

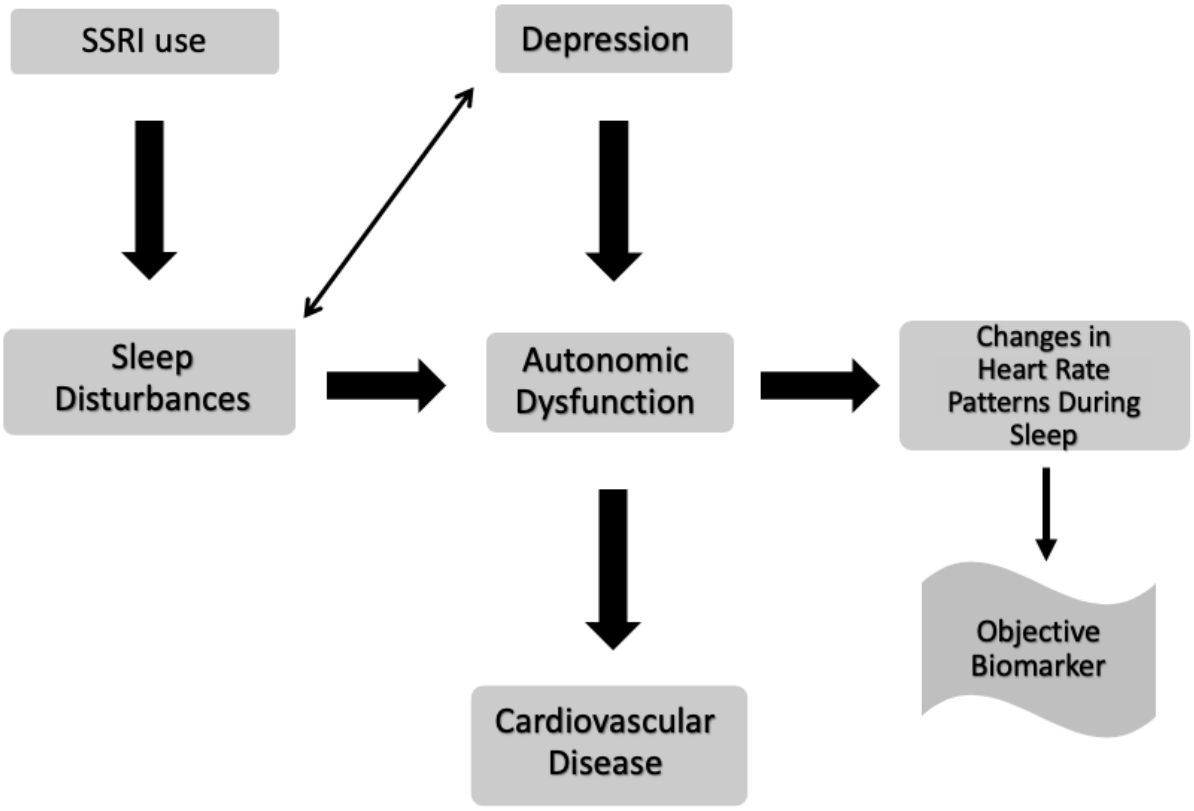


Figure 1. Links between depression, antidepressant medication use, autonomic dysfunction and cardiovascular disease. Depression is associated with abnormalities in the autonomic regulation of cardiac modulation, which results in changes in heart rate patterns during sleep (Chapter 2). Distinct nocturnal heart rate profiles may represent an objective physiological biomarker of depression that could be used as an adjunct diagnostic tool (Chapter 3). The use of the most commonly prescribed antidepressant medication is associated with sleep-related breathing disturbances (Chapter 4), which may exacerbate depressive disorders and also contribute to imbalances in the autonomic regulation of heart rate. Chronic autonomic disturbances due to depression and antidepressant use may contribute to the development or worsening of cardiovascular disease.

5.2 Future research

Further research must be conducted to determine the longitudinal effects of depression and antidepressant medication use on cardiorespiratory function during sleep. Firstly, prospective studies must determine whether the abnormalities in cardiac autonomic regulation observed during sleep subside following the treatment of depressive symptoms. If these autonomic irregularities are reversed following the successful treatment of depression, we must determine whether the heart rate profiling algorithm is capable of detecting intra-individual changes in clinical state, in order to validate it as a useful tool for monitoring treatment response and the long-term course of depressive disorders. Finally, prospective studies must be conducted to determine whether the introduction of an SSRI in depressed individuals leads to the development or worsening of sleep-related breathing disturbances, as well as abnormalities in cardiac activity during sleep.

5.3 Concluding remarks

In conclusion, depression is associated with impairments in the autonomic modulation of cardiac rhythms during sleep, particularly during NREM sleep, which may reflect vagal abnormalities. Moreover, the use of SSRIs, the most commonly prescribed antidepressant medication, is associated with sleep-related breathing disturbances in individuals with depression. These findings are interconnected such that SSRI-related breathing disturbances may also contribute to

autonomic dysfunction. This complex interaction between depression, antidepressant medication use, and cardiorespiratory function during sleep may have an impact on long-term cardiovascular health, as well as on the course of the depressive disorder. The effects of depression on the autonomic nervous system, the serotonergic system, and sleep neurophysiology interact in a synergistic manner to induce alterations in respiratory and cardiac activity during sleep, which can be used as a novel diagnostic biomarker of depression.

Appendix A – Supplementary Information

A.1 SI for *Using heart rate profiles during sleep as a biomarker of depression*

Table 1. Cardiovascular medication use

	Training Sample		Testing Sample	
	Depression *n* (%)	**Control *n* (%)**	**Depression *n* (%)**	**Control *n* (%)**
Any Cardiovascular	204 (30.7)	69 (13.0)	23 (26.4)	5 (5.7)
Anticoagulants	10 (1.5)	4 (0.8)	0 (0.0)	0 (0.0)
Antiplatelet Agents	65 (9.8)	24 (4.5)	9 (10.3)	0 (0.0)
ACE Inhibitors	36 (5.4)	26 (4.9)	9 (10.3)	2 (2.3)
ARBs	24 (3.6)	0 (0.0)	2 (2.3)	1 (1.1)
Beta Blockers	21 (3.2)	13 (2.5)	1 (1.1)	1 (1.1)
Calcium Channel Blockers	32 (4.8)	14 (2.6)	5 (5.7)	0 (0.0)
Cholesterol Lowering	106 (16.0)	21 (4.0)	8 (9.2)	1 (1.1)
Diuretics	32 (4.8)	25 (4.7)	5 (5.7)	3 (3.4)
Digitalis glycosides	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Vasodilators	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nitrates	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Anti-diabetics	54 (8.1)	18 (3.4)	6 (6.9)	1 (1.1)
Other anti-hypertensives	0 (0.0)	6 (1.1)	0 (0.0)	0 (0.0)
Other anti-arrhythmic	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)

ACE: Angiotensin converting enzyme, ARBs: Angiotensin II receptor blockers

Table 2. Comorbid medical disorders

	Training Sample		Testing Sample	
	Depression ***n*** **(%)**	**Control** ***n*** **(%)**	**Depression** ***n*** **(%)**	**Control** ***n*** **(%)**
Any cardiovascular disorder	**202 (38.0)[a]**	**81 (15.3)**	**31 (35.6)**	**3 (3.4)**
Hypotension	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Orthostatic hypotension	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Hypertension	108 (20.3)	50 (9.5)	10 (11.5)	3 (3.4)
Prehypertension	1 (0.2)	0 (0.0)	1 (1.1)	0 (0.0)
Obesity	55 (10.4)	0 (0.0)	6 (6.9)	0 (0.0)
Hypercholesterolemia	46 (8.7)	36 (6.8)	3 (3.4)	1 (1.1)
Type I diabetes	5 (0.9)	0 (0.0)	2 (2.3)	0 (0.0)
Type II diabetes	50 (9.4)	0 (0.0)	6 (6.9)	1 (1.1)
Gestational diabetes	2 (0.4)	0 (0.0)	1 (1.1)	0 (0.0)
Diabetes (unknown type)	0 (0.0)	23 (4.3)	0 (0.0)	0 (0.0)
Angina	8 (1.5)	4 (0.8)	1 (1.1)	0 (0.0)
Myocardial infarction	15 (2.8)	1 (0.2)	1 (1.1)	0 (0.0)
Stroke	7 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)
Transient ischemic attack	2 (0.4)	0 (0.0)	1 (1.1)	0 (0.0)
Coronary artery disease	25 (4.7)	0 (0.0)	1 (1.1)	0 (0.0)
Congestive heart failure	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
Arrhythmia	9 (1.7)	13 (2.5)	1 (1.1)	0 (0.0)
Congenital heart defect	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)
Cardiomyopathy	3 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Left ventricular hypertrophy	2 (0.4)	0 (0.0)	1 (1.1)	0 (0.0)
Cardiac surgery	13 (2.4)	3 (0.6)	3 (3.4)	0 (0.0)
Any sleep-related breathing disorder	**558 (86.9)[b]**	**0 (0.0)**	**72 (86.7)[c]**	**10 (11.8)[d]**
Obstructive sleep apnea	315 (49.0)	0 (0.0)	26 (31.3)	6 (7.1)
Upper airway resistance syndrome	184 (28.7)	0 (0.0)	34 (41.0)	2 (2.4)
OSA & UARS	59 (9.2)	0 (0.0)	12 (14.5)	2 (2.4)

[a] Cardiovascular Disorder data is missing for 133 participants in the Training Sample depression group

[b] Sleep-Related Breathing Disorder data is missing for 22 participants in the Training Sample depression group

[c] Sleep-Related Breathing Disorder data is missing for 4 participants in the Testing Sample depression group
[d] Sleep-Related Breathing Disorder data is missing for 2 participants in the Testing Sample control group

A.2 Temporal dynamics of heart rate during sleep in individuals with depression

A.2.1 Methods

The temporal dynamics of heart rate during the sleep period were assessed in individuals with depression compared to non-depressed controls. This retrospective study was comprised of individuals who underwent Level 1 polysomnography at the Royal Ottawa Hospital's Sleep Disorders clinic, and included 502 individuals with a history of depression and significant depressive symptoms (Beck Depression Inventory score ≥ 14) at the time of polysomnography, as well as 487 non-depressed controls.

ECG signals were extracted from polysomnographic recordings using Polyman. The inter-beat interval data was then extracted using Kubios HRV Premium. Custom MATLAB scripts were then used to model the temporal course of heart rate during sleep using a linear function to generate three cardiac variables for each participant: 1) the slope (reflecting the level of inclination of the heart rate profile throughout the entire sleep period), 2) the y-intercept (i.e. heart rate at sleep onset) and 3) the confidence interval of the heart rate profile (CI; the amplitude associated with heart rate fluctuations during sleep). This model was based on a linear regression curve of best fit using the linear least squares fitting technique. Thus, for each subject *j*, the heart rate HR_j is modeled as a linear function of time *t* according to the following equation:

$$HR_j(t) = a_j t + b_j$$

where a_j is the slope, and b_j is the y-intercept of the linear model. An error estimate was then computed using the model coefficients and heart rate against time 2-D sample points. Using the error estimate, a 95% confidence interval was generated. The average slope, y-intercept, and CI of the heart rate profile during sleep were then compared across the depression and control

groups using analyses of covariance, while controlling for age and sex differences. Furthermore, partial correlations were run to examine the associations between the cardiac variables and depressive symptom severity, as well as sleep architecture and physiological variables, while controlling for age and sex differences.

A.2.2 Preliminary Results

There were significant differences between the depression and control group in terms of the cardiac variables assessed across the night (Table 1). An example of the heart rate profile observed in each group is shown in Figure 1. Overall, the depression group's heart rate profile had a significantly steeper slope [($F(1, 984)=15.6$, $p<.001$), Figure 2], and fluctuated within a narrower range throughout the night [($F(1, 984)=207.9$, $p<.001$), Figure 3], as compared to the control group. The depression group also had significantly increased HR at sleep onset compared to the control group [($F(1, 984)=53.0$, $p<.001$), Figure 4].

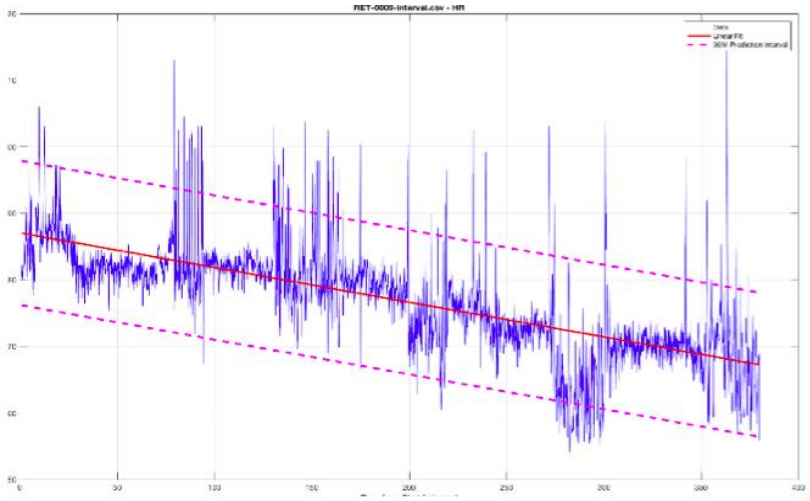
Moreover, there were significant correlations between depressive symptom severity and the slope [($r^2(497)=-.108$, $p=.016$), Figure 5], as well as the Y-Intercept [($r^2(497)=.111$, $p=.013$), Figure 6]. There was no significant correlation between depressive symptom severity and the CI ($r^2(497)=.002$, $p=.971$). The slope of the heart rate profile was also negatively correlated with BMI ($r^2(488)=-.193$, $p<.001$), while the CI was positively correlated with BMI ($r^2(488)=.179$, $p<.001$). The CI was also significantly correlated with sleep efficiency ($r^2(488)=-.137$, $p=.002$), total sleep time ($r^2(488)=-.147$, $p=.001$), and the AHI ($r^2(488)=.140$, $p=.002$). Correlations between cardiac variables and sleep architecture/physiological variables are shown in Table 2.

Table 1. Heart rate dynamics across depression and control groups

Cardiac variables	Depression mean ± SD	Control mean ± SD	F	p
Slope	-.02 ±.02	-.01 ± .01	15.6	< .001
Y-Intercept	73.0 ±10.7	67.5 ± 10.3	53.0	< .001
CI	4.4 ± 1.4	5.9 ± 1.7	207.9	< .001

SD = Standard Deviation, CI = Confidence Interval.

a)



b)

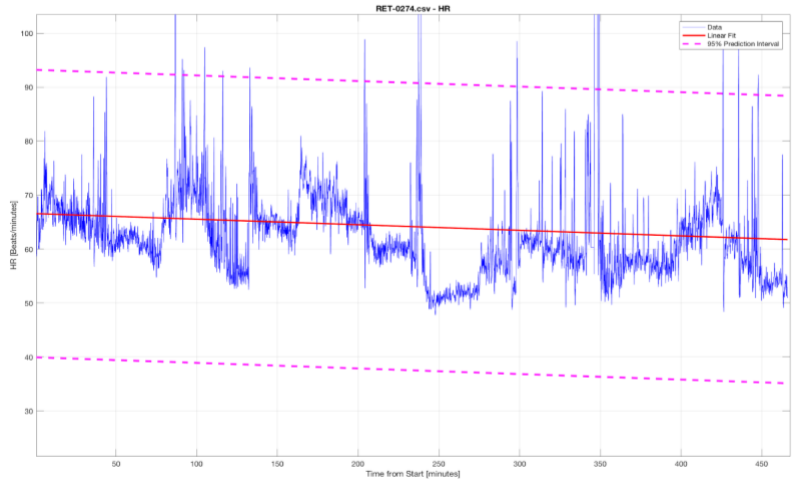


Figure 1. Example of temporal heart rate profile during sleep in a) an individual with depression and b) a non-depressed control. The x-axis represents heart rate in beats per minute and the y-axis represents the time in minutes beginning at sleep onset. The y-intercept represents heart rate (BPM) at sleep onset. The slope is represented by the solid red line and the confidence interval is defined by the dotted pink lines.

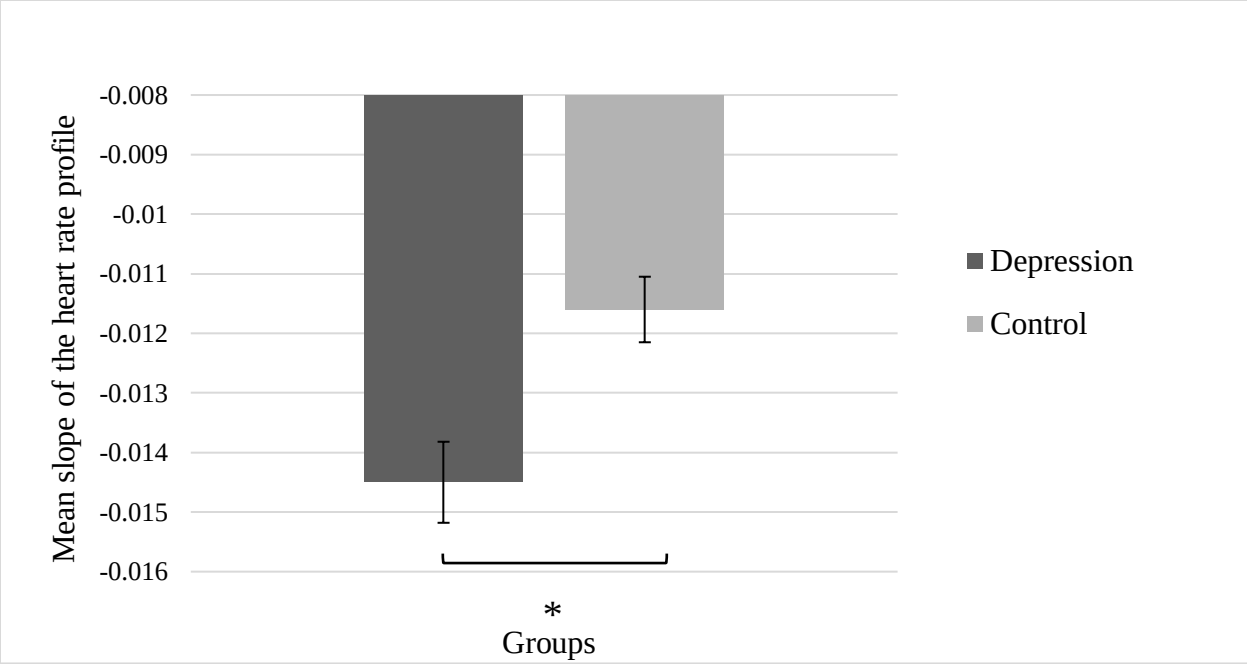


Figure 2. Mean slope of the heart rate profile during sleep in depression vs. control groups.

Error bars indicate the standard error of the mean.

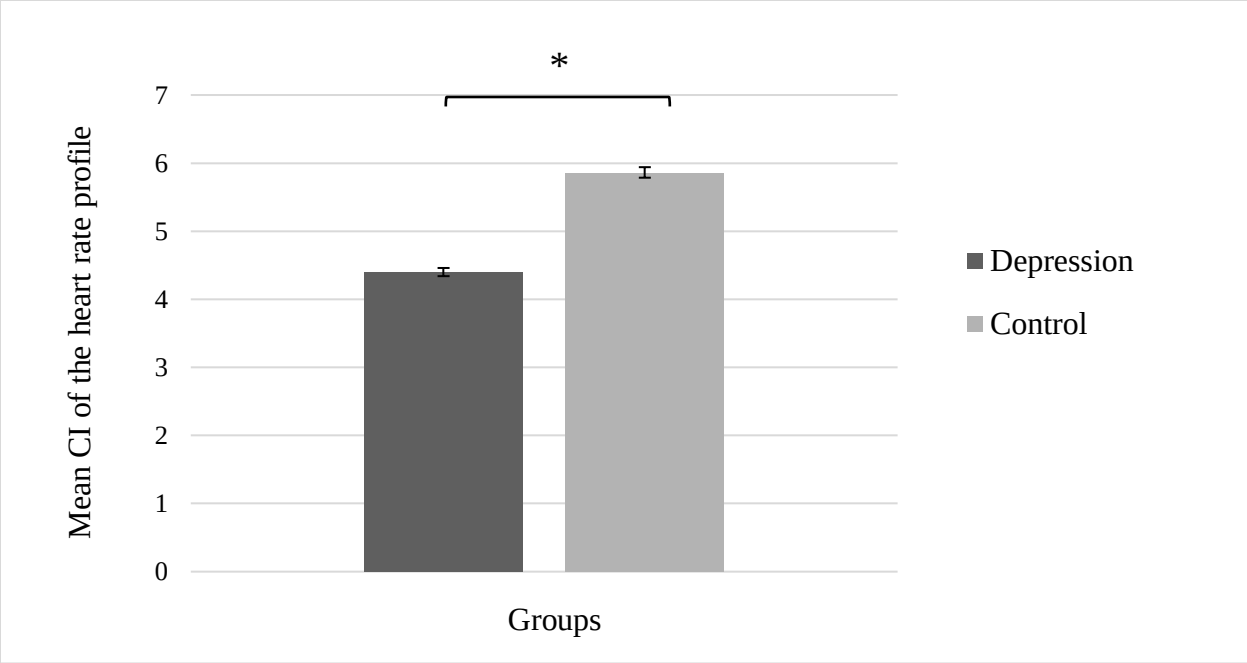


Figure 3. Mean confidence interval of the heart rate profile during sleep in depression vs. control groups. Error bars indicate the standard error of the mean.

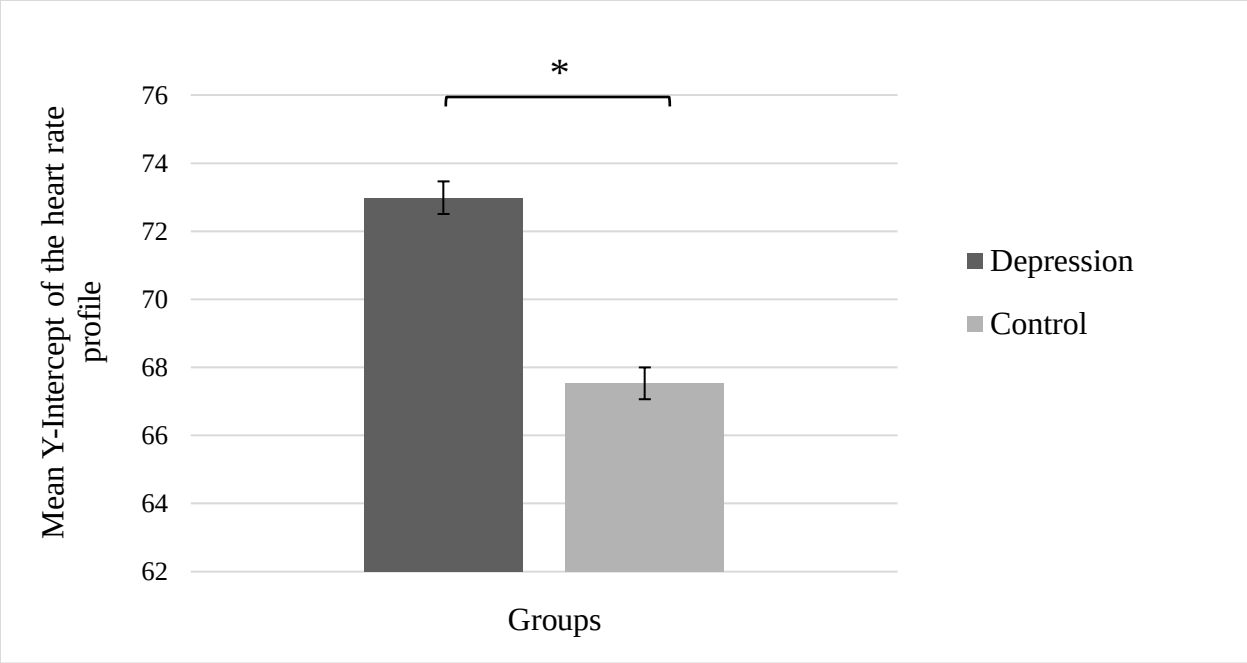


Figure 4. Mean y-intercept of the heart rate profile during sleep in depression vs. control groups. Error bars indicate the standard error of the mean.

Table 2. Partial correlations between heart rate dynamics variables and sleep architecture variables

Variables	Slope	Y-Intercept	CI
BDI-II	-.108*	.111*	.002
BMI (kg/m^2)	-.193**	.342**	.076
AHI (events/hour)	-.068	.179**	.140**
TST (min)	-.041	-.039	-.147**
SE (%)	-.044	-.048	-.188**
NREM 1 (min)	-.030	.076	-.017
NREM 2 (min)	-.074	.012	-.137**
NREM 3 (min)	.035	-.086	.090*
REM (min)	.027	-.088	.003

BMI = Body Mass Index, AHI = Apnea-Hypopnea Index, TST = Total Sleep Time, SE = Sleep Efficiency. *$p<0.05$, **$p<0.01$

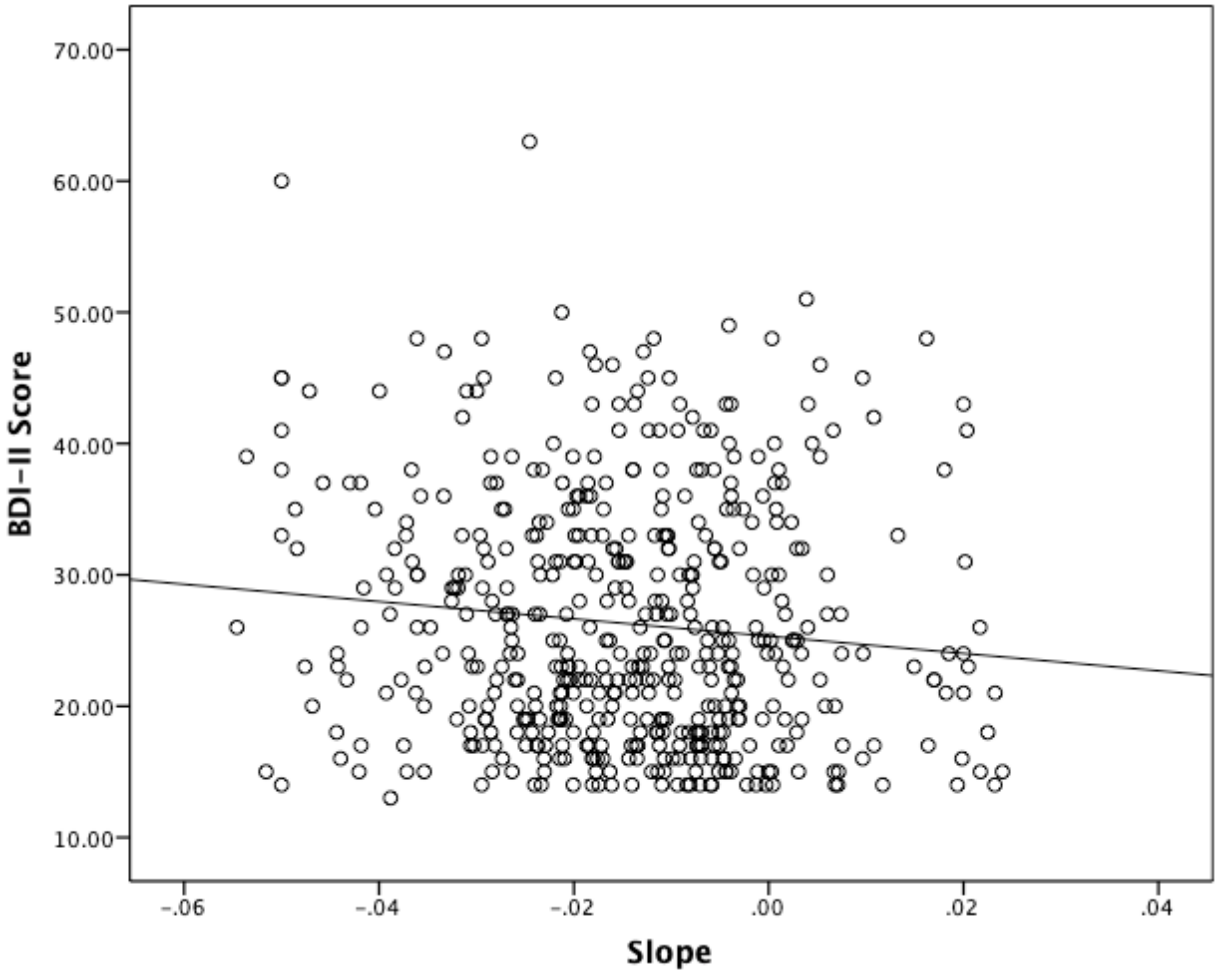


Figure 5. Partial correlation between depressive symptom severity and mean slope of the heart rate profile during sleep. Depressive symptom severity is indexed using the Beck Depression Inventory II score on the y-axis, while the slope of the heart rate is plotted on the x-axis.

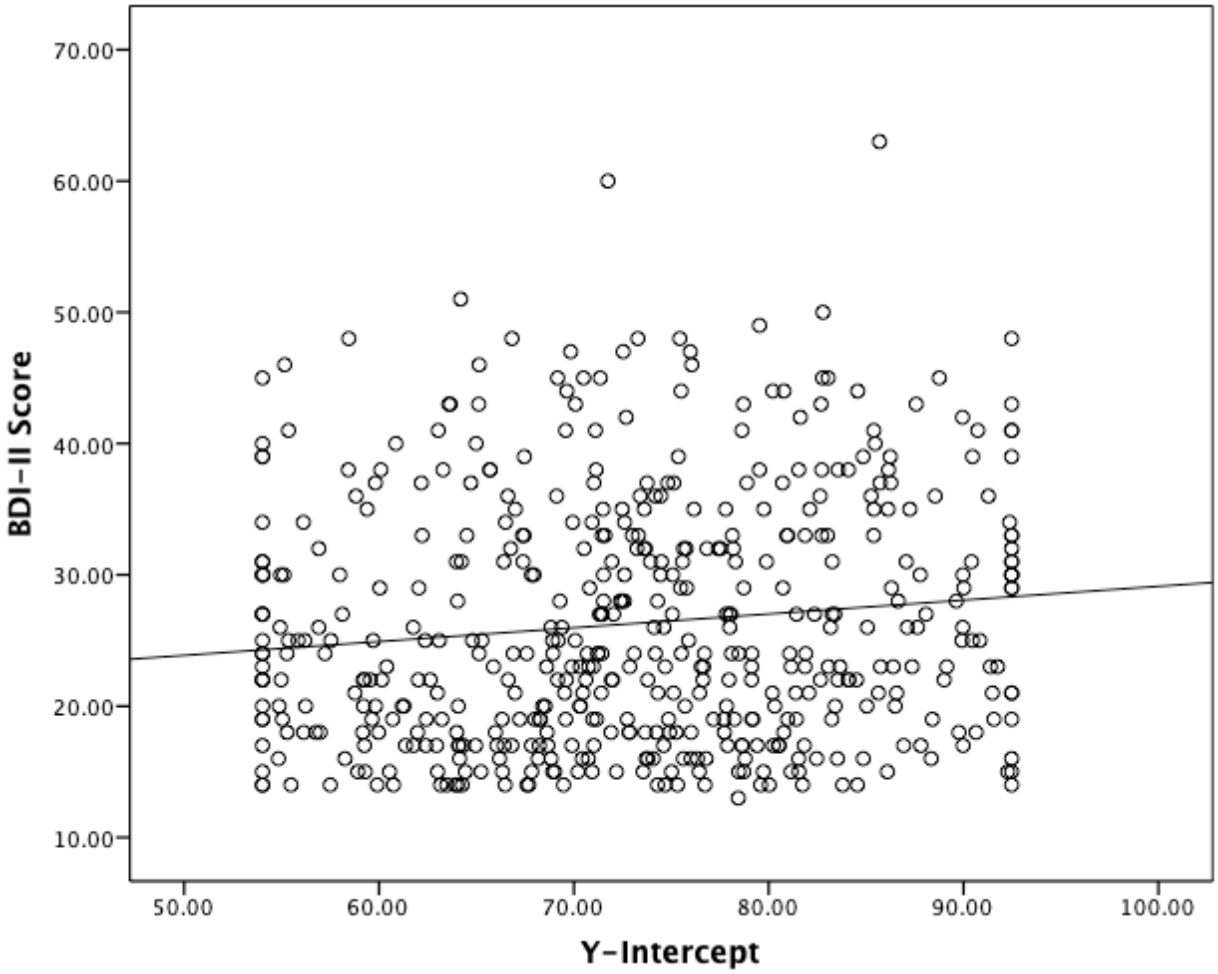


Figure 6. Partial correlation between depressive symptom severity and y-intercept of the heart rate profile during sleep. Depressive symptom severity is indexed using the Beck Depression Inventory II score on the y-axis, while the y-intercept of the heart rate is plotted on the x-axis.

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