SYSTEMATIC REVIEW OPEN

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Is cardiac autonomic control affected in major depressive disorder? A systematic review of heart rate variability studies

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INTRODUCTION: Major depressive disorder (MDD) is a heterogeneous psychiatric disorder that is a risk factor for cardiovascular diseases. Autonomic dysregulation, estimated as an important correlated pathophysiological cause, was investigated in many studies mainly through a quantitative evaluation of the heart rate variability (HRV).
AIM: The objective of this review was to provide any reproducible insights on autonomic regulation characteristics of MDD through the selection, revision, and joint interpretation of a restricted sample of studies based on systematic criteria.
METHODS: The literature research resulted in thirty eligible articles that reported the comparison of short-term resting-state HRV measures between drug-free MDD patients and healthy controls, excluding subjects affected by cardiovascular diseases.
RESULTS: Most of the reviewed studies reported significant differences between MDD patients and controls in the investigated HRV measures, especially for those that mainly reflect vagal activity. Nonlinear measures, although computed by fewer studies, seem to be more sensitive in detecting autonomic changes in MDD.
CONCLUSIONS: Our findings can be considered as evidence that the intrinsic autonomic state of MDD is characterized by decreased parasympathetic tone, which, interpreted in the context of the polyvagal theory, might be associated with impaired emotion regulation and flexible adjustment in MDD.

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INTRODUCTION

Major depressive disorder (MDD) is a heterogeneous psychiatric disorder causing severe symptoms that affect feelings, thinking, and handling of daily activities. It is the most common mental disorder in human beings, with an estimated 3.8% of the population affected [1], and its multiple clinical characteristics can be determined by a variety of causes, including genetic, biological, environmental, and psychological factors.

Besides psychopathological symptoms, the link between MDD and autonomic dysfunction has attracted more attention since epidemiological studies revealed that depressed patients have an augmented risk of cardiovascular morbidity and mortality [2]. Also, psychiatric illnesses, like depression [3], schizophrenia, and bipolar disorder [4, 5], are risk factors for the development of metabolic syndrome [3, 6].

In general, the relationship between psychiatric illnesses and cardiovascular diseases is likely driven by a complex interplay of behavioral, biological, and pathophysiological mechanisms [6]. This connection can occur both directly, via biological pathways, and indirectly, through unhealthy behaviors [6, 7]. More in detail, patients with psychiatric conditions often exhibit higher rates of unhealthy behaviors and known lifestyle risk factors for cardiovascular diseases, including smoking, obesity, hypertension, physical inactivity, alcohol misuse, poor diet, and non-adherence to prescribed medication [5, 8].

In addition to the behavioral pathway, some of the biological mechanisms underlying psychopathology might also adversely impact the cardiovascular system. These include platelet reactivity, platelet aggregation, and endothelial dysfunction [9, 10], hypercortisolemia [11], which results from the overstimulation of the hypothalamic-pituitary-adrenal axis (HPA) [12], and abnormal immune system activation [6, 13, 14]. Specifically for MDD, elevated levels of proinflammatory markers and cytokines, such as IL-1, IL-6, C-reactive protein, and tumor necrosis factors, often found in patients with MDD [15], might explain the presence of high risk of cardiovascular diseases in these patients. Similarly, the chronic effect of environmental stressors, usually determinant in the depressive psychopathology [16], can suppress the hypothalamic-pituitary-gonadal (HPG) axis, which plays a crucial role not only in regulating reproductive health but also in influencing the neuroendocrine and cardiovascular systems [17]. This suppression leads to reduced levels of gonadal hormones like estrogen and testosterone, which are known to have mood-regulating and neuroprotective effects [18].

Although the exact underlying mechanisms of this relation remain unclear, autonomic imbalance has been projected as an important pathophysiological factor in developing cardiac dysregulation [19–22].

Many studies investigated the relationship between MDD and autonomic dysfunction through a quantitative evaluation of heart

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rate variability (HRV), extracted from the electrocardiogram (ECG), but even if some efforts have been made to integrate their results, a comprehensive view of the findings is still missing.

HRV features are non-invasive measures for assessing cardiac autonomic modulation, through the interplay between sympathetic and parasympathetic neural activities, that controls the physiological beat-to-beat variations of the heart frequency [23].

The sympathetic (SNS) and parasympathetic (PNS) nervous systems are the two main branches of the autonomic nervous system (ANS). The SNS prepares the body for stressful or emergency situations, whereas the PNS controls body processes mainly during ordinary situations [24, 25]. Heart rate (HR) is continuously influenced by ANS activity to maintain body homeostasis in accordance with physiological and psychological requirements. Lower HRV, interpreted as a reduced capacity of the organism to flexibly adjust itself [26], is an indicator of dysregulated cardiac autonomic function as well as a predictor of poor health status [27].

HRV assessment contains time-domain and frequency-domain methods. As regards time-domain measurements, the standard deviation of normal-to-normal intervals (SDNN) can indicate SNS and PNS activities. The root mean square of successive differences (RMSSD) and the percentage of adjacent intervals that differ more than 50 ms (pNN50) are highly specific indicators of PNS activity [28].

The analysis of HRV in the frequency domain, referred to spontaneous oscillations in HR [29], was reported as a useful tool for the detection of ANS regulation on the heart [30–34]. In 1996, its standard procedure and physiological interpretation were defined allowing this method to be valuable for the clinical use [23].

HR fluctuations oscillate at different frequencies: ultra-low (≤0.0033 Hz) and very low frequencies (VLF) (0.0033–0.04 Hz), mainly related to slow circadian rhythms, low frequency (LF) (0.04–0.15 Hz), and high frequency (HF) (0.15–0.4 Hz). LF power may contain both SNS and PNS contributions, according to different conditions and clinical protocols, while HF power is primarily mediated by PNS. On the other hand, a sympathetic activation always results in increased LF power. The LF/HF ratio is considered to assess the comparative balance of the two ANS branches [28, 32, 34, 35], even if it has been subject of critique in the last years, mainly due to the difficult interpretation of LF power [36, 37].

Low HRV is associated with an increase in cardiac sympathetic activation or a relative decrease in parasympathetic modulation, whereas high HRV is guaranteed by an efficient PSN regulation [38].

An imbalance of the ANS activities might contribute to the relation of depression with cardiac-related diseases. However, studies investigating the ANS in MDD patients have revealed conflicting results, which might be due to the heterogeneity of the disease itself [20, 39, 40], differences in age and sex distributions [19, 41, 42], physical health and psychiatric comorbidities [43], as well as differences in types and dosages of antidepressant medications [20, 41, 44]. Other possible reasons for the variety of findings could be the diversity of applied study designs [20, 39, 40], methods to investigate autonomic function [19], HRV measures [45, 46], and failure in matching the control group.

Overall, the heterogeneity of the HRV results might reflect the variety of environmental and biological factors that characterize the long disease course and possibly impact on multiple dimensions of functioning [47].

Regarding environmental factors, traumatizing experiences in childhood and adolescence are associated with chronic stress in important developmental stages and could have a lasting influence on psychological and physiological processes in adulthood, potentially via epigenetic mechanisms [48–51]. The stress role in the pathogenesis of MDD is widely discussed and changes in HPA axis activity, activation of a proinflammatory response and cytokine production, as well as changes in neuroplasticity and autonomic regulation are considered as the major factors facilitating the onset of the depressive symptomatology [52]. The accumulation of these changes over a lifetime affects the development of neural circuits involved in stress response and adaptation [53, 54].

Then, the reduced ability to flexibly adapt to external stimuli and correctly process new experiences could have a consequent effect on affective dysfunctions in MDD patients, which are usually associated with compromised regulation of emotional stimuli and biased information processing [55–57]. HRV, which has emerged as a physiological marker also for emotional regulation [58], could become an additional instrument to provide further insights on MDD psychopathology [59, 60].

Despite the hypothesized relevance of autonomic factors in the variety of symptoms characterizing MDD, a clear picture of these mechanisms is still lacking. Meta-analyses and reviews published some years ago addressed similar research questions [61–64]. All of them suggested reduced HRV in MDD than in healthy controls, strengthening evidence for lower HRV as a potential cardiovascular risk factor in these patients. However, given the impact that new evidence on this topic could apport in clinical practice, some aspects need to be improved and updated to the current research in the field. Sgoifo et al. [63] and Stapelberg et al. [64] proposed a purely narrative review of autonomic dysfunction in MDD and its clinical implications, whereas a systematic comparison of HRV measures between MDD patients and HC was not performed. Few years ago, Koch et al. [62] provided a meta-analysis on resting-state HRV measures between unmedicated adults with MDD and controls, including both time-domain and frequency-domain metrics; however, nonlinear measures, which are demonstrating potential in discriminating psychiatric diseases, were not considered in this work. In this respect, the meta-analysis by Kemp et al. [61] had already hinted that nonlinear HRV measures could provide increased sensitivity of change in HRV. However, this study included few studies and did not consider the published work in the last 15 years, suggesting the necessity to update and integrate the new available findings.

Within this context, considering the limitations of previously published similar works, the objective of this review is to provide further insights into cardiac autonomic regulation in individuals affected by MDD to better characterize this chronic disabling disorder considering its multidimensional symptoms, highlighting the need to clarify the available results also with respect to non-standard metrics. Given the heterogeneity of the aspects that influence HRV characteristics in MDD, confounding factors were limited by the selection of a suitable restricted sample of studies that are as homogeneous as possible, in terms of both subjects' characteristics and design methods.

METHODS

The layout of the following systematic review was planned according to the Joanna Briggs Institute guidance for the conduct of scoping reviews [65]. We decided to adopt the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guidelines [66]. The PRISMA-ScR Checklist is reported in the Supplementary Materials.

Search strategy

A systematic literature search was conducted on PubMed, Scopus, and ScienceDirect databases. Literature search was performed starting from January 1990 up to December 2024. Extensive search strategy and the strings used for each database are reported in Supplementary Material.

Inclusion criteria

The inclusion criteria for the studies were the following: (i) original research articles, (ii) English language, (iii) inclusion of subjects

clinically diagnosed with MDD, (iv) presence of a healthy control (HC) group, (v) studies that computed and reported HRV metric results, (vi) studies that included adult subjects with age between 18 and 65 years, (vii) MDD patients and HC not affected by other cardiovascular diseases (CVD).

We excluded reviews, meta-analyses, clinical trials, and publications different from original research articles (e.g., book chapters, comments, conference abstracts, symposia).

We excluded the studies that considered only female or male participants. Previous studies showed that sex differences seem to exist both in healthy HRV [67] as well in the relationship between MDD and HRV [68]; however, most of the studies on HRV did not consider the effect of sex. Therefore, we decided to review only the studies that included both males and females, mainly balanced within the MDD and HC groups, to have a general conclusion on the available findings at net of sex effect.

Considering patients' medications, we excluded all the studies that included medicated patients, and we considered participants who were drug-free, drug-naïve or who had stopped the medications at least two weeks before the ECG acquisition.

As regards data acquisition, we included only the studies with short-term ECG recordings acquired during resting state with duration shorter than 30 min. HRV measures extracted from long-term recordings were excluded due to their specific contributors, such as circadian rhythms, which make them non-comparable with HRV measures from short-term recordings [12].

Study selection

The database literature search resulted in 984 articles, with 312 resulting from PubMed, 488 from Scopus, and 184 from ScienceDirect. After duplicate removal, we obtained 565 articles that were subsequently screened for eligibility by reading the abstract or the full text. Of these, 30 studies met our inclusion criteria (Fig. 1).

Data extraction

Several variables of interest were retrieved from the full text of the eligible studies. General information, such as authors and year of publication, were extracted, along with the sample characteristics (demographic, numerosity, and clinical data). ECG acquisition setup was reported, followed by time-domain, frequency-domain and non-linear HRV metrics that were computed in the studies, as well as the relationships between HRV metrics and clinical scales.

RESULTS

In this section, the results of the 30 reviewed studies are reported. After the summary of demographic and clinical sample characteristics and the acquisition protocols of the included studies, the results of the HRV metrics are described in the following order: time-domain, frequency-domain, and nonlinear measures. Finally, the relationships between HRV metrics and clinical scales are presented. The effect sizes for the most relevant results, reported by the authors or newly computed when unavailable, are provided.

The results are reported in Table 1, in narrative form in the main text, and graphically in Fig. 2.

Demographics and clinical information

All studies included individuals clinically diagnosed with MDD and individuals without psychiatric diagnoses for comparison with comparable sex and age distributions. All participants were physically healthy and were not affected by cardiovascular or respiratory diseases, which enabled the exclusion of potential biases in the HRV evaluation. In most of the studies, the patients were diagnosed considering the Diagnostic and Statistical Manual (DSM) of mental disorders (III IV or V edition) [69–73] criteria for MDD, assessed by the Structured Clinical Interview for DSM. In other studies, MDD was diagnosed according to ICD-10 (International Classification of Diseases-10) guidelines [22] or through the Mini-International Neuropsychiatric Interview [74, 75].

All subjects were free of any medications at the time of the study, allowing to capture autonomic dysregulations derived from the pathology itself, at net of any drug effects. Some studies compared HRV before and after medication administration, but only the results reported for the baseline condition were considered.

Study protocol and design

In most studies, the cardiac electrical activity was registered through ECG, only two studies derived cardiac cycle information from photoplethysmography [58] and magnetoencephalography [76]. The datasets analyzed lasted a maximum of 30 min and were acquired from participants in seated or supine position during resting state, after a period of relaxed adaptation in the same position. Heart activity acquisition in resting state allowed to investigate intrinsic cardiac variability without confounding effects that could come from autonomic-eliciting tasks. Finally, although some studies included a task-based ECG acquisition following the resting-state one, for these studies we only considered the HRV results that were reported for the baseline condition.

Time-domain measures

Time-domain indices of HRV quantify the amount of variability in measurements of the inter-beat intervals (IBI), which is the time between successive heartbeats. The main time-domain measures that were computed in the selected studies are mean HR, mean IBI, variance, coefficient variation (CV), SDNN, RMSSD, and pNN50.

HR was computed in seventeen studies, of which nine reported a significantly higher mean HR in MDD patients than in HC, suggesting an increased sympathetic modulation [4, 23, 26, 37, 62, 66–69]. The same tendency, but only at trend levels, was reported in other two studies [19, 77], while the remaining ones reported that the HR was comparable in the two groups [41, 58, 78–81].

Other studies computed the mean IBI, a metric directly comparable with the previous one. Group comparisons showed significant differences in IBI in half of the studies (5 out of 10) that computed this metric [43, 45, 46, 47, 52]. The authors found that the IBI had a lower mean value in the MDD patients with respect to the control group, coupled with faster HR, as mentioned above. Notably, Chang et al. [43] (reported Cohen's $d = 0.40$, medium effect) and Chang et al. [47] (calculated Cohen's $d = 0.33$, small-medium effect), are two of the works with the highest number of participants.

The same studies, plus another one, calculated the total variance of HRV, and they all reported that it was significantly reduced in MDD patients with respect to HC [27, 29–31, 70]. Chen et al. [30] reported lower values for both IBI and variance for the MDD group compared to HC, and significantly lower values in MDD patients affected also by anxiety or panic disorders compared to HC. Of note, the studies with significant results for variance are the studies with the larger sample size. Specifically, Chang et al. [43] had 152 MDD and 472 HC (reported Cohen's $d = 0.25$, small effect), Chang et al. [47] had 498 MDD and 462 HC (computed Cohen's $d = 0.3$, small-medium effect), and Yeh et al. [82] had 618 MDD and 506 HC (reported Cohen's $d = 0.17$, small effect).

SDNN was computed by nine studies. Even if most of them reported no significant differences between MDD and HC groups [22, 24, 40, 75, 81, 83], the overall trend was of lower SDNN values in MDD patients than in controls. This tendency was confirmed with statistical significance in two studies [52] (computed Cohen's $d = 1.02$, large effect) [76], and at trend-level in [74].

Among the eighteen works that computed RMSSD, six studies found that MDD patients were characterized by significantly lower

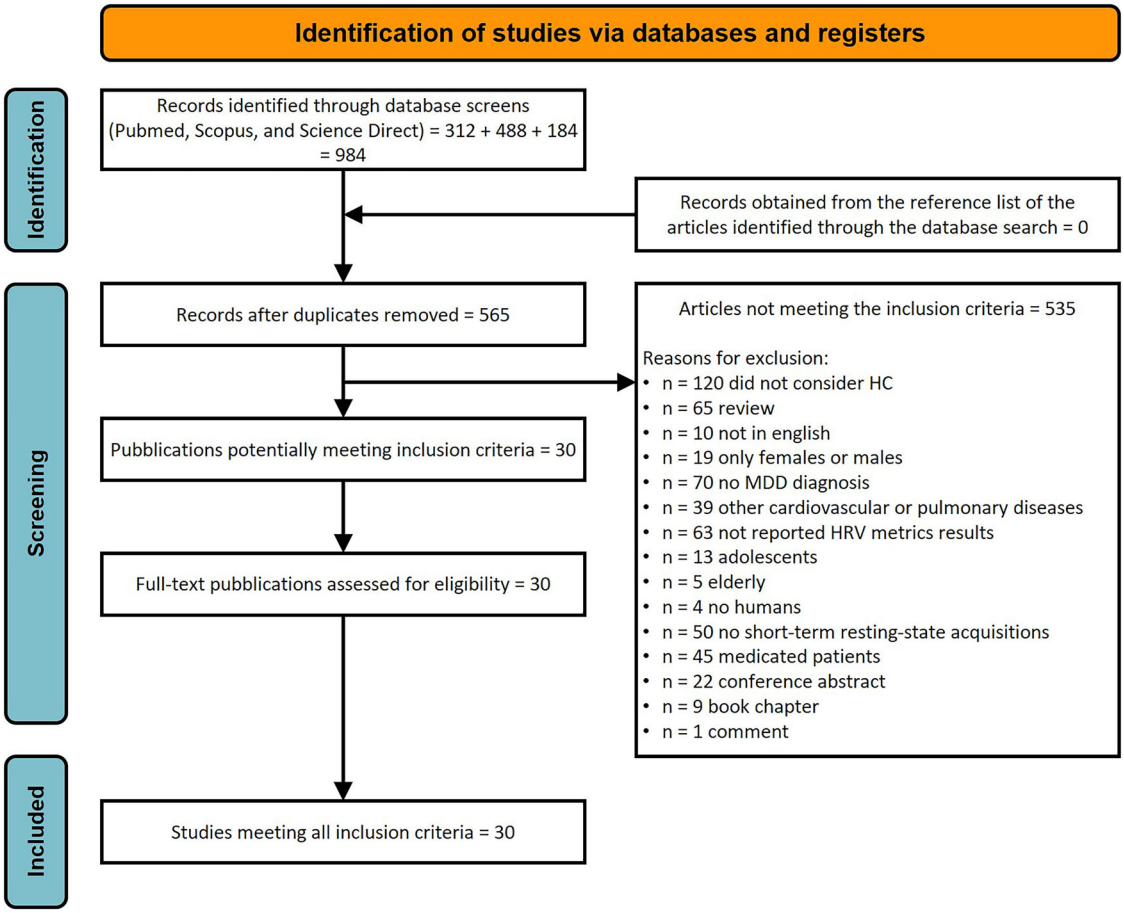

Fig. 1 PRISMA Flow Diagram.

values with respect to HC [39, 50, 74–76, 84]. Specifically, Kemp et al. [74] (Cohen's $d = 0.48$, medium effect) and Koschke et al. [39] are two of the studies with the highest number of participants. Other four studies reported the same tendency at trend-levels [20, 24, 77, 85], while the remaining studies showed that RMSSD values were comparable between the two groups [19, 22, 40, 41, 58, 80, 81, 83].

Only negative results were reported for CV and pNN50 by the few studies that evaluated these measures. The three studies that computed CV [19, 80, 84] and pNN50 [24, 40, 41] did not report significantly different values between MDD and HC groups.

Frequency-domain measures

Frequency-domain analysis of HRV is a tool for the detection of cardiac autonomic regulation that can complement information on quantification over time-domain HRV analysis.

All the studies that computed the VLF power of HRV reported that VLF values were comparable between MDD and control subjects [19, 43, 53, 82], except for one work where absolute VLF power was significantly lower in the patient groups [52].

Most of the studies calculating the absolute LF power of HRV (16 out of 23) reported no significant differences between MDD patients and HC [19, 41, 43, 50, 53, 58, 74, 75, 78–81, 83–86]. However, five works showed significant differences in LF power of HRV between patients and controls, with the former group showing lower values [24, 47, 52, 82, 87]. Specifically, among them, Chang et al. [47] and Yeh et al. [82] are two of the studies with the largest sample size among the included studies; however, even if they reported statistically significant results regarding LF power, the effect size associated with their statistics had a small effect [47] (computed Cohen's $d = 0.11$, small effect), [82] (reported Cohen's $d = 0.19$ small effect). Two studies reported that MDD patients with generalized anxiety disorder comorbidity (GAD) demonstrated significantly lower values of LF power compared to controls [45, 46].

In the same line, considering the normalized LF power, three studies found no differences between MDD patients and HC [40, 47, 52], while one study showed significantly higher values in MDD patients [22].

Among the twenty-six studies that computed both absolute and normalized HF power of HRV, more than half (N = 14) reported significant group differences. Of note, no significant differences in absolute HF power were found in some of the studies that reported negative findings also for the LF power measure plus another one [19, 41, 53, 58, 78–81, 83, 87]. Instead, eleven works demonstrated significantly lower absolute HF values in MDD patients, even in those with melancholic type [75] and with comorbid GAD [46], compared to HC [24, 43, 46, 47, 52, 74, 82, 84, 86]. Notably, the studies with significant results on HF power are the ones with the largest sample size among the included studies and the corresponding Cohen's *d* values showed a mean medium effect size ([43] reported Cohen's $d = 0.48$, medium effect; [47] computed Cohen's $d = 0.32$, small-medium effect; [46] computed Cohen's $d = 0.64$, medium-large effect; [74] reported Cohen's $d = 0.46$, medium effect; [82] reported Cohen's $d = 0.27$, small-medium effect). Three studies showed the same tendency with trend-level significance [42, 50, 85].

Accordingly, three out of four works that computed the normalized version of HF power reported significant lower values in MDD patients than in HC [22, 47, 52], whereas Schulz et al. [40] found no differences between the two groups.

Finally, twenty-two studies assessed possible dysfunctions in the autonomic sympathovagal balance, computing the ratio

Table 1. Summary of sociodemographic, clinical characteristics, and HRV metrics results of the reviewed studies.

Reference	Title	Sample (M/F) Age (years) mean ± SD	Medications	Depression severity	Acquisition protocol	Time-domain metrics	Frequency-domain metrics	Non-linear metrics	Relationship HRV-parameters and depression severity	Main results
Bar et al., [19]	The influence of major depression and its treatment on heart rate variability and pupillary light reflex parameters	18 MDD (6/12) 43.2 ± 14.3 18 HC (6/12) 41.8 ± 11.9	Not taken antidepressants for at least 8 weeks prior to the investigations.	HAM-D 28.9 ± 6.1 BDI MDD: 23.11 ± 4.5 HC: 4.1 ± 1.7	ECG recording resting-state supine position – 5 min	HR CV RMSSD	VLF LF HF LF/HF	–	–	Acutely depressed patients did not different significantly in the parameters of HRV.
Berger et al., [20]	Autonomic modulation in healthy first-degree relatives of patients with major depressive disorder	30 MDD (12/18) 33.1 ± 10.6 30 HC (12/18) 34.4 ± 12.8	Stopped psychotropic medication before admission to hospital or never taken any psychotropic medication.	HAM-D 20.03 ± 7.51 BDI 23.60 ± 9.42	ECG recording in resting-state – 30 min	HR[a] RMSSD	LF/HF	CompEn	In patients, we did not find significant correlations between BDI or HAM-D scores and autonomic parameters.	Significant difference between groups for the mean HR and lnRMSSD.
Berger et al., [85]	Cardio-respiratory coupling in untreated patients with major depression	18 MDD (6/12) 43.8 ± 14.02 18 HC (7/11) 42.2 ± 14.6	Stopped medication 4 weeks before admission or never taken any psychotropic medication.	HAM-D 26.78 ± 7.23 BDI 28.06 ± 12.77	ECG recording in resting-state – 20 min	HR[a] RMSSD	LF HF LF/HF[a]	ApEn[a]	We did not find significant correlations between BDI or HAM-D scores with any autonomic parameter.	Significant differences for HR, lnLF/HF, lnApEn.
Chang CC et al., [43]	Effects of depression and melatonergic antidepressant treatment alone and in combination with sedative-hypnotics on heart rate variability: Implications for cardiovascular risk	152 MDD (86/66) 34.1 ± 12.5 472 HC (241/231) 35.3 ± 12.4	Medication-naïve or medication-free.	HAM-D 29.70 ± 9.46 HAM-A 14.20 ± 6.87	ECG recording in resting state supine position – 5 min	RR[a] Var[a]	VLF LF HF[a] LF/HF[a]	–	–	Compared with the controls, the patients with MDD displayed significant reductions in mean IBI, HF and Var, as well as a significant increase in LF/HF ratio.
Chang HA et al., [47]	Major depression is associated with cardiac autonomic dysregulation	498 MDD (249/249) 39.1 ± 14.1 462 HC (238/224) 40.7 ± 14.9	Not taken medication for the last two weeks.	HAM-D MDD: 27.65 ± 9.93 HC: 4.46 ± 2.54 BDI MDD: 32.85 ± 13.16 HC: 5.6 ± 3.33	ECG recording in resting state supine position – 5 min	RR[a] Var[a]	LF[a] HF[a] LF/HF LF nu HF nu[a]	–	HAM-D scores were inversely associated with RR, Var, LF, HF and HF nu.	MDD patients had lower HRV compared with HC. Significant differences were found in RR, Var, LF, HF and HF nu between MDD and HC groups.

Table 1. continued

Reference	Title	Sample (M/F) Age (years) mean ± SD	Medications	Depression severity	Acquisition protocol	Time-domain metrics	Frequency-domain metrics	Non-linear metrics	Relationship HRV-parameters and depression severity	Main results
Chang HA et al., [45]	Generalized anxiety disorder, comorbid major depression and heart rate variability: a case-control study in Taiwan	40 MDD (8/32) 45.9 ± 5.4 60 HC (12/48) 47.5 ± 7.2	Stopped medications at least two weeks before evaluation.	HAM-A 7.6 ± 1.75 BAI 10.66 ± 2.45 HAM-D 36.4 ± 6.16 BDI 42.98 ± 6.48	ECG recording in resting-state – 5 min	RR[a] Var[a]	LF[a] HF[a] LF/HF	–	Greater scores of HAM-A/HAM-D had significantly faster HR. Either HAM-A or HAM-D scores were inversely associated with variance, LF and HF.	Group comparisons showed significant differences in mean RR intervals, Var, LF and HF.
Chen et al., [46]	Depression, anxiety and heart rate variability: A case-control study in Taiwan	49 MDD (10/39) 44.1 ± 4.8 81 HC (15/66) 42.9 ± 8.4	Not taken medication for the last two weeks.	HAM-D MDD: 28.71 ± 10.77 HC: 4.49 ± 2.37 BDI MDD: 32.22 ± 10.98 HC 6–77 ± 2.57	ECG recording in resting state supine position - 5 min	RR[a] (with GAD) Var[a] (with GAD)	LF[a] (with GAD) HF[a] LF/HF[a] (with GAD)	–	Subjects with higher scores of HAM-D/HAM-A had significantly faster HR. Both the HAM-D and HAM-A scores were inversely associated with variance, LF and HF.	MDD patients had lower HF than controls.
Chen et al., [24]	Heart rate variability in patients with major depression disorder during a clinical autonomic test	40 MDD (15/25) 40 HC (15/25)	Free of any medication.	–	ECG recording in resting-state supine position – 4 min	RR SDNN RMSSD pNN50	LF[a] HF[a] LF/HF	SD1 SD2 MultEn[a]	–	MultEn, LF, and HF of MDD patients were lower than those of the control group.
Dawood et al., [79]	Specific serotonin reuptake inhibition in major depressive disorder adversely affects novel markers of cardiac risk	24 MDD (10/14) 45 ± 11 15 HC (9/6) 40 ± 11	None of the patients or controls were on any form of medication.	HAM-D 26 ± 3 BDI 29 ± 7	ECG recording in resting- state supine position – 20 min	HR	LF HF	–	–	HRV measures were similar in patients with untreated MDD and HC.
Deuter et al., [50]	Yohimbine-induced reactivity of heart rate variability in unmedicated depressed patients with and without adverse childhood experience	24 MDD (11/13) 38.4 ± 10.9 48 HC (22/26) 35.5 ± 10.3	Unmedicated participants.	–	ECG recording in resting-state seated position – 5 min	RMSSD[a]	LF HF	SD1[a] SD2[a]	–	Patients with MDD had lower values in the parameters HF-HRV (trend level) and RMSSD, SD1 and SD2.

Table 1. continued

Reference	Title	Sample (M/F) Age (years) mean ± SD	Medications	Depression severity	Acquisition protocol	Time-domain metrics	Frequency-domain metrics	Non-linear metrics	Relationship HRV-parameters and depression severity	Main results
Druzhkova et al., [52]	Acute stress response to a cognitive task in patients with major depressive disorder: potential metabolic and proinflammatory biomarkers	33 MDD (14/19) 32.9 ± 7.8 43 HC (19/24) 30.5 ± 5.5	No use of antidepressants within a year prior to inclusion into the study.	HAM-D 20.12 ± 4.13 BDI MDD: 24.42 ± 8.01 HC: 4.15 ± 4.19	ECG recording in resting-state seated position – 5 min	RR[a] SDNN[a]	VLF[a] LF[a] HF[a] VLF nu LF nu HF nu	–	–	Baseline HRV parameters were decreased in the MDD group with the mean RR and SDNN. Analysis of spectral components demonstrated significantly lower absolute powers of VLF, LF and HF in MDD patients compared to control.
Garcia et al., [41]	Sex differences in cardiac autonomic function of depressed young adults	50 MDD (16/34) 22.6 ± 4.6 50 HC (16/34) 23.4 ± 4.8	Treatment-naïve.	–	ECG recording in resting-state supine position – 5 min	HR RMSSD pNN50	LF HF LF/HF	–	–	No significant differences were observed in the time- or frequency-domain variables of HRV between MDD patients and HC.
Jangpangi et al., [22]	Alteration of Heart Rate Variability in Patients of Depression	30 MDD (14/16) 30.3 ± 1.3 30 HC (14/16) 29.8 ± 1.1	Drug naïve.	–	ECG recording in resting-state supine position – 5 min	SDNN RMSSD	LF nu[a] HF nu[a] LF/HF[a]	–	–	Values of LF (nu), LF/HF were significantly higher, and HF (nu) parameter was significantly lower in MDD group compared to HC.
Kemp et al., [74]	Depression, comorbid anxiety disorders, and heart rate variability in physically healthy, unmedicated patients: implications for cardiovascular risk	24 MDD (14/10) 36.4 ± 10.6 94 HC (44/50) 35.7 ± 11.2	All participants were free from anti-depressant medication for at least five half-lives.	HAM-D 18.5 ± 5.3 DASS-42 Depression: 27.5 ± 8.9 Anxiety: 6.6 ± 6.1 Stress: 18.3 ± 9 .8	ECG recording in resting-state seated position – 2 min	SDNN RMSSD[a]	LF HF[a] LF/HF[a]	SD1[a] DFA[a]	–	The MDD group displayed reductions in RMSSD and SDNN (at trend levels). The groups differed on HF and LF/HF ratio. The groups differed on SD1 and DFA.

Table 1. continued

Reference	Title	Sample (M/F) Age (years) mean ± SD	Medications	Depression severity	Acquisition protocol	Time-domain metrics	Frequency-domain metrics	Non-linear metrics	Relationship HRV-parameters and depression severity	Main results
Kemp et al., [75]	Major depressive disorder with melancholia displays robust alterations in resting state heart rate and its variability: implications for future morbidity and mortality	72 MDD 94 HC	All participants were medication free for at least five half-lives	HAM-D NMEL: 18.78 ± 0.68 MEL: 21.50 ± 0.69	ECG recording in resting-state seated position – 2 min	HR[a] SDNN RMSSD[a]	LF HF	SD1[a]	–	Groups differed significantly on heart rate, RMSSD, HF (at trend levels), and SD1.
Kikuchi et al., [87]	Heart rate variability in drug-naïve patients with panic disorder and major depressive disorder	15 MDD (9/6) 33.7 ± 10.4 15 HC (8/6) 29.9 ± 10.5	None of the patients had ever received medication that acts upon the central or autonomic nervous system.	HAM-D 20.9 ± 5.3	ECG recording in resting-state supine position – 5/10 min	RR	LF[a] HF LF/HF	–	Correlation tests did not reveal any significant correlations between HRV variables and HAM-D total score in MDD patients.	Significant lower LF power in the MDD group as compared to the control.
Koschke et al., [39]	Autonomy of autonomic dysfunction in major depression	75 MDD (21/54) 33 ± 13 75 HC (23/52) 31 ± 11	Not taken antidepressants for at least 8 weeks before hospital admission	HAM-D 21 (6–45) BDI 21 (4–44)	ECG recording in resting-state – 30 min	HR[a] RMSSD[a]	LF/HF	CompEn[a]	Correlation analyses between the HRV measures and HAM-D and BDI revealed any significant association.	Significant difference between patients and controls for HR, RMSSD and CompEn.
Lim et al., [58]	Sex-Specific Differences in Severity of Depressive Symptoms, Heart Rate Variability, and Neurocognitive Profiles of Depressed Young Adults: Exploring Characteristics for Mild Depression	32 MDD (13/19) F: 24.3 ± 4.0 M: 24.5 ± 3.0 44 HC (17/27) F: 24.2 ± 3.8 M: 24.7 ± 2.7	Not used psychotropic medication within the 8 weeks prior to enrolment.	-	PPG recording in resting-state seated position – 6 min	HR RR RMSSD	LF HF LF/HF[a]	–	The only HRV measure included in the correlation analyses was the LF/HF ratio, which showed no significant correlations with any measure.	There was a significant main effect for group in the LF/HF ratio.

Table 1. continued

Reference	Title	Sample (M/F) Age (years) mean ± SD	Medications	Depression severity	Acquisition protocol	Time-domain metrics	Frequency-domain metrics	Non-linear metrics	Relationship HRV-parameters and depression severity	Main results
Moser et al., [42]	Increased heart rate in depressed subjects in spite of unchanged autonomic balance?	26 MDD (7/19) 33.7 ± 11.1 26 HC (7/19) 34.1 ± 10.5	Medication free for at least 3 months before the investigation.	BDI 23.5 ± 9.6	ECG recording in resting-state supine position –10 min	HR[a]	HF	–	–	HR was significantly higher in patients. MDD patients showed slightly lower mean vagal tone, regardless of the method used, although this difference was not significant.
Pradeep et al., [78]	Heart rate variability responses to standing are attenuated in drug naive depressed patients	46 subjects 36 ± 10	Drug naive.	HAM-D 22.77 ± 4.9	ECG recording in resting-state supine position –10 min	HR	LF HF LF/HF	–	–	There was no significant difference between the groups for any of the HRV parameters.
Rechlin et al., [80]	Are affective disorders associated with alterations of heart rate variability?	16 MDD 16 HC	The patients with major depression had not been treated at least during the preceding 14 days.	–	ECG recording in resting state supine position – 5 min	HR[a] CV RMSSD[a]	LF HF[a]	–	–	MDD patients had a significantly higher HR, a significantly lower RMSSD and a significantly lower HF as compared with the HC.
Rechlin et al., [84]	Heart rate variability in depressed patients and differential effects of paroxetine and amitriptyline on cardiovascular autonomic functions	24 MDD (8/16) 43.4 (range 20–72) 24 HC (8/16) 43.0 (range 21–68)	The patients had not been treated with any antidepressants or neuroleptic drugs in the preceding four weeks.	–	ECG recording in resting state supine position – 5 min	HR CV RMSSD	LF HF	–	–	Unmedicated MDD patients showed no significant abnormities as compared to HC.

Table 1. continued

Reference	Title	Sample (M/F) Age (years) mean ± SD	Medications	Depression severity	Acquisition protocol	Time-domain metrics	Frequency-domain metrics	Non-linear metrics	Relationship HRV-parameters and depression severity	Main results
Schulz et al., [40]	The altered complexity of cardiovascular regulation in depressed patients	57 MDD (18/39) 30 ± 9 57 HC (18/39) 29 ± 8	Not taken antidepressants for at least 8 weeks prior to the investigations.	HAM-D 20 ± 8 BDI 22 ± 10	ECG recording in resting-state supine position −30 min	RR SDNN RMSSD pNN50	LF nu HF nu LF/HF	CompEn[a] SD1 SD2 DFA[a] MultEn[a]	–	HRV parameters revealed no significant differences between MDD patients and HC. CompEn was significantly reduced in MDD group. MultEn method demonstrated decreased values in MDD group. From DFA short-term scaling exponents α were significantly increased in MDD.
Schumann et al., [83]	Differences of sympathetic and parasympathetic modulation in major depression	29 MDD (8/21) 37.8 ± 12.2 29 HC (8/21) 36.9 ± 12.5	Not taken antidepressant for at least 8 weeks before hospital admission.	HAMD 24.5 ± 6.4 BDI MDD: 23.2 ± 8.9 HC: 4.0 ± 3.9	ECG recording in resting-state supine position −15 min	HR[a] SDNN RMSSD	LF HF LF/HF	–	–	We observed an elevated mean heart rate by almost 10 beats per minute in patients when compared to controls.
Shinba et al., [86]	Major depressive disorder and generalized anxiety disorder show different autonomic dysregulations revealed by heart-rate variability analysis in first-onset drug-naïve patients without comorbidity	14 MDD 38.5 ± 10 41 HC	Drug naive.	SDS 53.2 ± 7.4	ECG recording in resting-state seated position −100 s	HR[a]	LF HF[a] LF/HF[a]	–	–	HF in MDD was lower than in HC. LF/HF ratios for MDD were higher than in HC. HR for MDD was higher than in HC.

Table 1. continued

Reference	Title	Sample (M/F) Age (years) mean ± SD	Medications	Depression severity	Acquisition protocol	Time-domain metrics	Frequency-domain metrics	Non-linear metrics	Relationship HRV-parameters and depression severity	Main results
Udupa et al., [81]	Alteration of cardiac autonomic functions in patients with major depression: a study using heart rate variability measures	40 MDD (26/14) 30.6 ± 7.4 40 HC (26/14) 30.7 ± 7.1	Drug naive.	HAM-D > 16	ECG recording in resting-state supine position –15 min	HR RR SDNN RMSSD	LF HF LF/HF[a]	–	There was no significant correlation between severity of depression and autonomic parameters.	Sympatho-vagal balance was significantly more in MDD group than in HC.
Voss et al., [77]	Gender-dependent impact of major depression on autonomic cardiovascular modulation	36 MDD (18/18) F: 30 ± 5 M: 34 ± 7 36 HC (18/18) F: 31 ± 6 M: 35 ± 8	Not taken antidepressants for at least 8 weeks prior to hospital admission.	HAM-D F: 23 (11–33) M: 20 (6–44) BDI F: 25 (12–41) M: 22 (4–31)	ECG recording in resting-state supine position –30 min	HR RMSSD	LF/HF	CompEn[a]	No correlations were observed between measures of disease severity and HRV parameters.	Significant differences for CompEn were shown between MDD and HC groups.
Yeh et al., [82]	Heart rate variability in major depressive disorder and after antidepressant treatment with agomelatine and paroxetine: Findings from the Taiwan Study of Depression and Anxiety (TAISDA)	618 MDD (283/335) 41.4 ± 13.9 506 HC (231/275) 42.4 ± 13.7	Drug-naïve or not used psychotropic medications for at least one month.	HAM-D 27.45 ± 9.86 BDI MDD: 31.34 ± 12.38 HC: 5.67 ± 3.62	ECG recording in resting-state supine position – 5 min	RR[a] Var[a]	VLF LF[a] HF[a] LF/HF[a]	-	For patients with MDD, HAM-D scores correlated with reduced variance, VLF, LF, and HF, independently of covariates.	Compared with controls, the patients with MDD displayed significant reductions in Var, LF and HF and a significant increase in their LF/HF ratio.
Yeragani et al., [53]	Diminished chaos of heart time series in patients with major depression	14 MDD (11/3) 34.7 ± 7.1 18 HC (10/8) 35.4 ± 6.2	Not taken any medication for at least 2 weeks before the studies.	HAM-D MDD: 20.6 ± 3.2 HC: 0.27 ± 0.90	ECG recording in resting state supine position – 5 min	HR[a]	VLF LF HF LF/HF	LLE[a]	There were no significant correlations between HAM-D scores and any HRV variables of interest.	We found significantly lower LLE of the unfiltered series and HF series in MDD patients. LF/UF and LF/HF (LLE) were significantly higher in patients.

Table 1. continued

Reference	Title	Sample (M/F) Age (years) mean ± SD	Medications	Depression severity	Acquisition protocol	Time-domain metrics	Frequency-domain metrics	Non-linear metrics	Relationship HRV-parameters and depression severity	Main results
Zhou et al., [76]	Decreased Task-Related HRV Is Associated with Inhibitory Dysfunction Through Functional Inter-Region Connectivity of PFC in Major Depressive Disorder	20 MDD (8/12) 31.6 ± 9.8 18 HC (7/11) 30.7 ± 8.2	Not taken medication for the last two weeks.	HAM-D MDD: 24.9 ± 6.3 HC: 5.0 ± 1.4 HAM-A MDD: 7.8 ± 2.1 HC: 5.0 ± 3.3	MEG recording in resting state	SDNN[a] RMSSD[a]	–	–	–	There were significant differences in both RMSSD and SDNN values.

M male; *F* female; *SD* standard deviation; *MDD* major depressive disorder; *HC* healthy controls; *HAM-D* Hamilton depression rating scale; *HAM-A* Hamilton anxiety rating scale; *BDI* beck inventory scale; *BAI* beck anxiety inventory; *DASS-42* depression anxiety and stress scales; *NMEL* non-melancholic; *MEL* melancholic; *SDS* self-rating depression scale; *ECG* electrocardiogram; *PPG* photoplethysmography; *MEG* magnetoencephalography; *HR* heart rate; *CV* coefficient of variation; *RMSSD* root mean square of successive difference; *RR* mean RR intervals; *Var* variance; *GAD* generalized anxiety disorder; *SDNN* standard deviation of normal-to-normal intervals; *pNN50* percentage of adjacent intervals that differ more than 50 ms; *VLF* very low frequency; *LF* low frequency; *HF* high frequency; *LF/HF* ratio LF over HF; *nu* normalized units; *CompEn* compression entropy; *ApEn* approximate entropy; *SD1* standard deviation 1 (Poicarè plot width); *SD2* standard deviation 2 (Poicarè plot length); *MultEn* multiscale entropy; *DFA* detrended fluctuation analysis; *LLE* largest Lyapunov exponent.
[a]Significant difference between MDD and HC.

between LF and HF powers. Eight studies showed that this value was significantly higher in depressed patients compared to HC [22, 43, 58, 74, 81, 82, 85, 86], and two further studies found differences with trend-level significance [20, 47].

Of note, Chang et al. [43] (reported Cohen's d = 0.49, medium effect) and Yeh et al. [82] (reported Cohen's d = 0.16, small effect) are two of the studies with the highest number of participants. Chen et al. [46] reported significant differences in sympathovagal balance values only between MDD patients with GAD and HC. The remaining eleven studies did not show significant differences in the LF/HF ratio [19, 24, 39–41, 45, 53, 77, 78, 83, 87].

Non-linear measures

Non-linear HRV metrics allow to explore the complexity of the mechanisms that regulate HRV [28]. Entropy enables to quantify the regularity of a system and is proportional to the amount of HRV behavior complexity. Three different subclasses of entropy (compression, approximate, and multiscale) were proposed in the selected studies.

Among the four studies computing the compression entropy, three reported significant lower values in MDD group with respect to HC [39, 40] (computed Cohen's d = 0.66, medium-large effect); [77], whereas Berger et al. [20] reported the same tendency but only at trend-level significance.

In Berger et al. [85] (computed Cohen's d = 0.96, large effect), the approximate entropy was computed, and significantly lower values were shown in MDD patients with respect to the controls.

Passing to multiscale entropy (MSE), one study showed in third scale significant differences between MDD patients and HC, with lower values in the former group (computed Cohen's d = 0.50, medium effect) [40].

Chen et al. [24] (computed Cohen's d = 0.45, medium effect) compared three nonlinear parameters of refined composite MSE (RCMSE). The authors found that values of one of the parameters computed in MDD patients were significantly lower than those of the control group.

Five studies performed another kind of nonlinear HRV analysis based on the Poincaré plot, resulting in standard deviation (SD1 and SD2) measures, which are the ellipse's width and length, respectively, and represent the dispersion (variability) along the two principal directions of the plotted RR intervals. As regards SD1, three of them showed significantly lower values between MDD patients, also in the melancholic type [75] (reported Cohen's d = 0.56, medium effect), and HC [50, 74] (reported Cohen's d = 0.48, medium effect); another study reported significant results at trend-level [24], whereas Schulz et al. [40] showed no significant differences. Considering SD2 measure, again Deuter et al. [50] reported positive results; Schulz et al. [40] confirmed no significant difference also for SD2 between the two groups, and Chen et al. [24] was in the same direction.

Two studies applied detrended fluctuations analysis (DFA) to HRV time series, and both showed significantly different values for short-term scaling exponents (α) between MDD and HC [74] (reported Cohen's d = 0.52, medium effect), [40] (computed Cohen's d = 0.55, medium effect), being lower in the MDD group, ultimately indicating that the MDD group displays a less random signal than HC, which is consistent with a reduction in HRV.

Lastly, Yeragani et al. [53] computed the minimum embedding dimension (MED) and the largest Lyapunov exponent (LLE). Considering the unfiltered HRV time series, MED was significantly higher, and the LLE was significantly lower in patients. While no significant group differences in MED or LLE were observed for the VLF range; in LF, MED and LLE were significantly lower and higher in the patient group compared to HC, respectively. Conversely, in the patient group compared to HC, HF MED was significantly higher, and HF LLE was significantly lower.

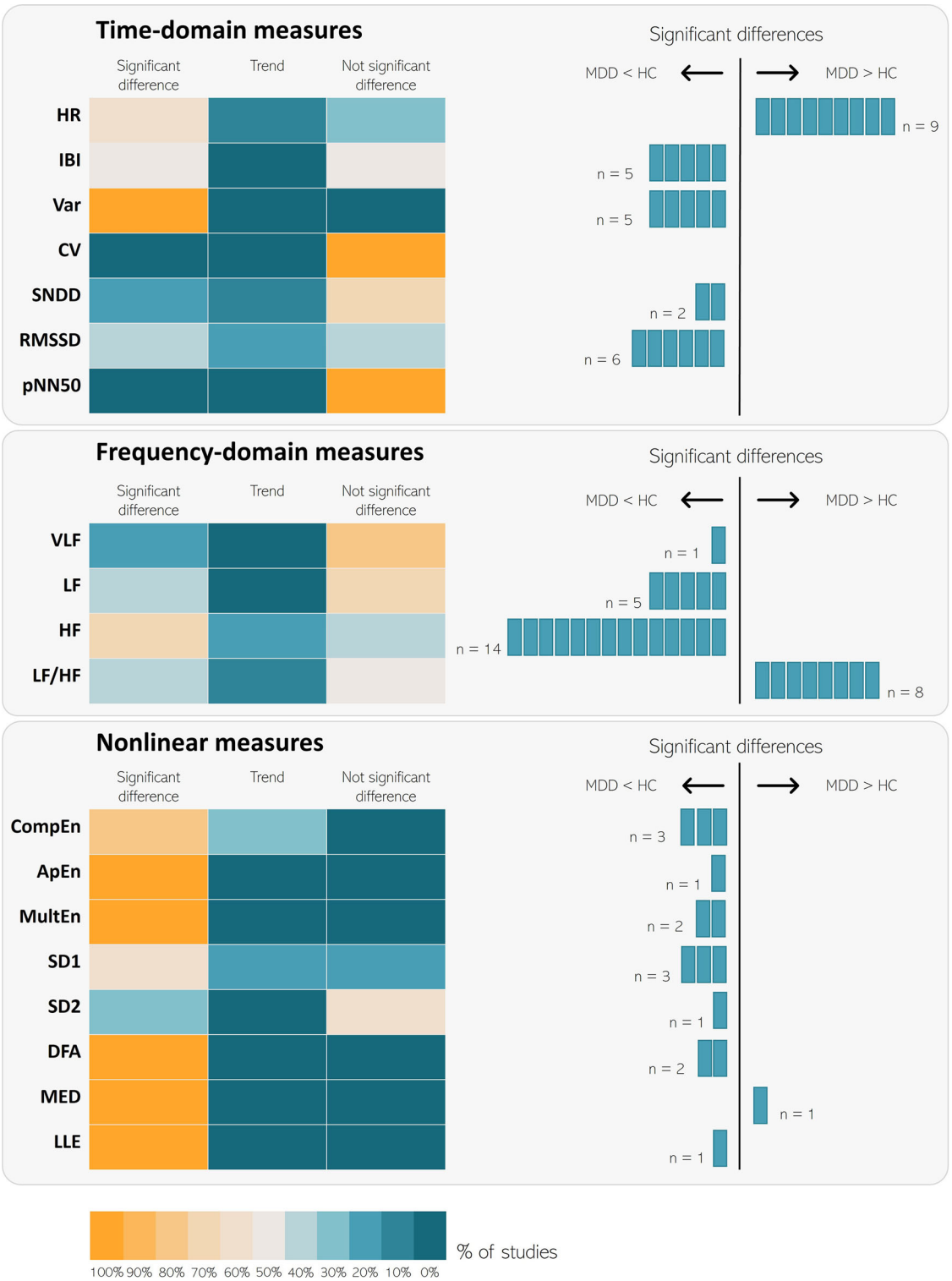

Fig. 2 Results. In the left part, the percentages of studies that reported significant results, trend-level significant results, and not significant results for each of the HRV measures considered are shown. In the right side, for each HRV measure and for the only studies that found significant results for that metric, the sign of the results is reported (if values were significantly lower or higher in MDD with respect to HC, with each bar representing a study, and n equal to the number of studies).

Relationship between HRV parameters and depression severity

Twelve studies explored the relationship between autonomic measures and depression severity by correlating ratings of psychopathological scales (BDI and HAM-D) with HRV parameter values.

In eight studies, no significant correlations between BDI or HAM-D scores and autonomic parameters were found [20, 39, 53, 58, 77, 81, 85, 87]. Instead, four studies reported significant associations between autonomic parameters and depression scores [45–47, 82].

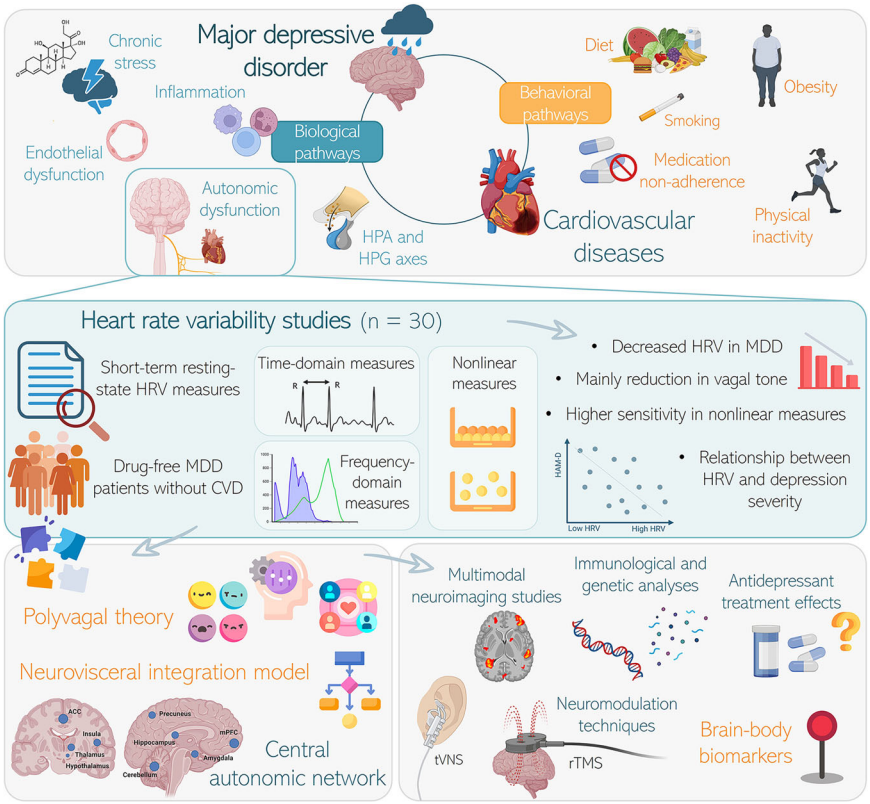

Fig. 3 Graphical summary illustrating the key concepts examined in the study on the relationship between MDD and autonomic dysfunction.

Specifically, Chang et al. [45] showed that subjects with greater scores of HAM-A/HAM-D had significantly higher HR; either HAM-A or HAM-D scores were inversely associated with variance, LF, and HF power values. However, there was no significant correlation between scores of HAM-A/HAM-D and LF/HF ratio.

Similarly, Yeh et al. [82] reported that HAM-D scores correlated with reduced variance, VLF, LF, and HF power values, independently of covariates. Also, in Chang et al. [47], HAM-D scores were inversely associated with the mean IBI, variance, LF, HF, and normalized HF.

Finally, Chen et al. [46] showed that subjects with higher scores of HAM-D/HAM-A had significantly higher HR; both the HAM-D and HAM-A scores were inversely associated with variance, LF, and HF power. HAM-A but not HAM-D scores were associated with a greater LF/HF ratio.

DISCUSSION

The main objective of this review was to explore the relationship between MDD and autonomic imbalance. Notably, although the results are far to be conclusive, a subset of the reviewed studies showed changes of HRV parameters that mainly reflect reduced vagal modulation, ultimately suggesting an autonomic dysregulation in MDD, as also reported by previous research [61–64].

The present results can be interpreted in the context of the polyvagal theory [88] that highlights the importance of the vagal pathway in attention, coordination, emotion expression, social bonding, and flexible adjustment to environmental demands [89], all of which can be altered in MDD patients [81], [90].

Vagal influences on the heart serve to dampen the sympathetic reactions to stress [88] and to promote calm behavioral states and self-regulation [91]. The vagal tone exerts a protective function that prevents subjects from becoming vulnerable to anxious apprehension and worry, involving pre-attentive biases to threat information, and inflexible response patterns. Then, the inability to disengage threat detection can cause a chronic withdrawal of PNS activity and long-term reductions in HRV, which subsequently increase the risk for CVD [91]. Therefore, reduced vagal tone seems to have an important functional significance (e.g., impaired psychological flexibility [91, 92]), and over long term may lead to significant morbidity and mortality [93, 94].

The results of the present review are discussed in the next sections, and the key concepts of the whole study are graphically summarized in Fig. 3.

Main results

More in detail, considering linear metrics reflecting sympathetic activity of the ANS, some of the reviewed studies agreed on the presence of higher values of HR and reduced IBI in MDD patients with respect to HC, suggesting that the sympathetic modulation, which physiologically has an excitatory role and increases HR, is higher in the patient group. Similar results emerged in the few studies investigating SDNN, which reported significantly lower SDNN values in MDD patients than in HC, indicating a decrease in parasympathetic activity and/or an increase in sympathetic modulation.

As regards parasympathetic activity assessment via linear approaches, evidence from the reviewed studies suggests that patients affected by MDD have a reduction of vagal modulation with respect to controls. In the time domain, the variance of HRV presented a significantly lower value in MDD patients with respect to HC, ultimately suggesting that PNS activity is reduced in MDD. Similarly, RMSSD, explaining vagal activity [28], was shown to present significantly lower values in patients with respect to HC. In the frequency domain, most of the studies reported significantly decreased power in the HF band in MDD patients, confirming a reduced vagal activity. In the same line, the metrics reflecting interactions between SNS and PNS were found to be altered in MDD. The LF/HF ratio results showed a shift towards higher SNS activity and/or lower PNS control; however, a debate on the

interpretation of this metric is ongoing in the literature [36, 37]. Also, the findings on LF power, suggesting lower values in MDD with respect to HC, are of difficult interpretation. Indeed, while there is consensus that HF-HRV is controlled by vagal activity, the neurophysiological autonomic drivers influencing LF-HRV have been subject of debate [26]. Both branches of the ANS are reflected in LF power [95].

About VLF findings, suggesting no differences between MDD and HC groups, it should be noticed that the metric value highly depends on the preprocessing steps [32], thus these results should be interpreted with caution.

Although only few studies addressed HRV through nonlinear measures, they were more consistent in reporting differences between MDD and HC than studies that addressed more traditional HRV metrics. In general, these results showed less complex and repetitive HRV behavior in MDD patients compared to HC. Compression, approximate and multiscale entropies had significantly lower values in MDD patients, suggesting rhythmic and less chaotic patterns. Compression entropy, which is a nonlinear measure of complexity, was shown to be a very sensitive parameter of autonomic modulation in various psychiatric diseases [96, 97].

SD1 and SD2 measures suggested lower variability in the RR intervals in MDD patients compared to HC. SD1, which mainly correlates with HF power [28], presented significantly lower values in MDD group. SD2, which is more related to LF power and baroreflex sensitivity [28], even if it seemed to be less sensitive than SD1 in revealing differences in autonomic regulation between the two groups, in one study was reported with significantly lower values in MDD patients.

The two studies that applied DFA to HRV, used for determining its statistical self-affinity, showed significantly higher values in MDD patients compared to HC, supporting a less complex HRV behavior.

The main findings of a decrease in unfiltered LLE and HF LLE and a relative increase in the LF LLE and LF/HF LLE suggest a decrease in cardiac vagal activity and an increase in the relative sympathetic activity.

Linear vs non-linear HRV measures: which is the best?

Despite the qualitative nature of our comparison, our findings suggest that nonlinear HRV metrics seem to be more sensitive than more traditional linear HRV measures in detecting altered autonomic functioning between MDD patients and controls.

Specifically, linear time- and frequency-domain results were heterogenous, with some studies reporting significantly different values for the two groups, whereas other works showed that the MDD and HC groups were comparable. Instead, even if computed by only few studies, nonlinear measure results were more consistent.

Notably, the effect sizes related to nonlinear HRV measures were larger than the ones computed on standard HRV measures, suggesting a greater capability to separate between MDD and HC groups. In this respect, considering that not all the included studies reported significant differences in ANS regulation between MDD patients and controls, it is possible that any autonomic changes occurring in MDD are not completely detectable through linear time- and frequency-domain analysis of HRV [45]. Thus, these results underline the advantage of novel nonlinear measures and support previous concerns on the validity of time- and frequency-domain measures [98].

Since HRV modulation is one of the most complex systems in humans where various regulatory subsystems are included, resulting in a scale-invariant cardiac control across different time and frequency scales [99], it seems quite reasonable that classical linear HRV analysis methods could fail to classify this complex regulation behavior.

Notably, these nonlinear indices could be of diagnostic relevance and contribute to risk stratification. Indeed, they might be able to show new insight into HRV changes under various physiological and pathological conditions, providing additional prognostic information and complementing traditional analyses.

Autonomic dysfunctions related to MDD diagnosis appear to be better disentangled by sophisticated methods such as complex nonlinear measures than linear approaches, suggesting alterations in ANS activity more subtle in depressed patients than in other cardiovascular pathologies, in which also linear approaches robustly identified autonomic issues [100].

Relationship between HRV measures and clinical scores

The correlation analyses between autonomic measures and depression severity, carried out by some of the reviewed studies, may appear inconsistent, with a mixed picture of significant and nonsignificant relationships. Nonetheless, the results showing a significant correlation between autonomic measures and illness severity suggested heightened sympathetic activation in more depressed patients, as shown by the positive relationship between HR and depression severity [46, 47], whereas an inverse relationship emerged between variance, LF power, and HF power and depression severity [45–47, 82]. This indicates that greater reductions in HRV, indicative of diminished parasympathetic vagal tone, were associated with more severe depressive symptoms in MDD patients. Of note, the studies that showed significant associations between HRV measures and depression scores were among the most statistically powered, including the studies by Chang et al. [47] and Yeh et al. [82] with the largest sample sizes.

A key distinction between studies that found significant correlations and those that did not appear to be the statistical methods employed. Interestingly, the studies reporting significant results shared the same statistical approach to assess the present relationship, performing multiple regression analyses to evaluate the relationship between autonomic measures and depression severity, to control the effect of confounding such as sex, age, body max index (BMI), smoking, and physical activity [45–47, 82]. In contrast, non-significant findings emerged in studies that used simple correlation analyses such as Spearman rank correlation and Pearson's correlation coefficient, which did not control for potential confounders. These methods may be more prone to spurious results, particularly when sample sizes are small, as is the case in several studies that reported null findings. However, the discrepancy observed between the reviewed studies warrants further explanation. It may suggest that the relationship between HRV and MDD is not straightforward, and sample characteristics, methodological differences, variations in biological and lifestyle factors, as well as the heterogeneity of MDD itself, have crucial implications in these mechanisms. Thus, future research should account for these factors by employing larger, more homogeneous samples and using robust statistical approaches.

Clinical implications of HRV reduction in MDD patients

Our findings can be considered as evidence that the intrinsic autonomic state of MDD is characterized by decreased parasympathetic tone. Since no pure measures of sympathetic activity were used, we cannot infer whether sympathetic tone was modified.

Although pacemaker tissues play an important role in cardiac automaticity, HR largely depends on the neurotransmitters secreted by SNS and PNS. Hence HRV, which represents the rhythm of the heart, is a sensitive indicator of central-peripheral neural feedback [101].

The neurovisceral integration model further supports the idea of brain-level mechanisms involved in the control of peripheral autonomic processes, such as cardiac modulation [91]. Reductions in parasympathetic tone may be a consequence of reduced

activation within the central autonomic network (CAN), a network of brain regions that controls a variety of visceromotor, neuroendocrine, and behavioral responses critical for goal-directed and behavioral flexibility [102–104]. The neurovisceral integration model highlights the role of the prefrontal cortex in vagally mediated cardiac control. Consequently, HRV appears to index the functional integrity of the CAN and reflects self-regulation and internal and external flexibility in response to environmental demands [104].

Furthermore, in support of the autonomic dysfunctions in MDD possibly related to brain-level alterations are the unchanged values for cardio-respiratory coupling observed in MDD patients [85], which indicate that diminished vagal control of cardiac functioning is mainly related to neural-autonomic modulation. This assumption is further supported by other studies where changes were observed in the relative amplitude on the pupil's reaction to light [19, 105], electrodermal activity [106], and gastric motility [107], which are all under autonomic control.

However, studies recording single parameters derived from physiological signals can only provide limited information on hierarchically higher structures of the CAN. Therefore, the importance of carrying out brain-level investigations of these mechanisms emerges. In support of this, recent studies employing functional neuroimaging in physiology revealed that activity in limbic-related areas correlate with HF-HRV [108]. In future studies, integrated analyses of simultaneously recorded signals from different end organs innervated by the ANS and functional neuroimaging studies on the CAN in MDD might reveal more data-driven insights into the neurobiological bases of the hypothesized central autonomic imbalance in depression.

Recent work also highlighted a relationship between HRV and inflammatory markers [109, 110]. This is important because inflammation plays a role in the pathogenesis of CVD. While acetylcholine released from the vagus inhibits proinflammatory cytokine production, reduced vagal tone leads to heightened inflammatory state and development of CVD [4, 111], therefore suggesting that changes in HRV may precede the development of these other critical 'downstream' risk markers [112].

Interestingly, different neuromodulation techniques, such as vagal nerve stimulation (VNS), repetitive transcranial magnetic stimulation (rTMS) [113] and potentially deep brain stimulation, targeting key structures that are affected in depression, have proven to be successful and effective in providing clinical benefits and depressive symptom improvement [114]. Moreover, these techniques showed subsequent positive effects on cardiac measures, possibly increasing parasympathetic tone [115]. Specifically, VNS showed consistently to decelerate HR [116] and normalize HRV [117, 118].

In accordance, the results we obtained, which suggest a decrement in vagal activity, further support the use of the VNS that, by intervening in the modulation of the brain-heart pathway, could provide benefits also in autonomic regulation. The concomitant improvements in MDD both in mood and autonomic regulation suggest a possible overlap between a frontal-vagal (brain-heart) network and brain areas that are affected in MDD. These considerations also lend further support to the neurovisceral integration model [91], which proposes that decreased parasympathetic tone may be the common pathway linking negative affective states and conditions to ill health. Whether these autonomic tests could also be used as biological markers of depression and whether they would have any prognostic value are important questions that need to be answered soon.

Effect of antidepressant treatments

When assessing the relationship between depression and HRV, a first key question that arises is whether the association between MDD and CVD could be mediated by the side effects of antidepressant medications. Our study, which included only drug-naïve and drug-free MDD patients, suggests that MDD itself is an independent factor for low HRV and increased risk of developing CVD.

Consequently, a second question that emerges is whether the use of antidepressants in MDD patients without pre-existing CVD can further influence cardiac autonomic modulation, potentially even worsening HRV. While evidence indicates that antidepressant treatments can affect HRV, a clear picture of these mechanisms has yet to be defined, except for tricyclic antidepressants (TCAs) [44, 61]. Heterogeneity was observed between different types of treatment, such as TCAs, selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), mirtazapine, and nefazodone [61, 119].

Specifically, the review by Kemp et al. [61] revealed significant differences between TCAs and all other antidepression pharmacological treatments, showing that TCAs were associated with a reduction in HRV, both compared to other treatments and to baseline HRV before treatment. This reduction in HRV is consistent with anticholinergic and alpha1-adrenergic properties of this class of medication [120]. Because of their side effects, TCAs are less frequently used than SSRIs, which instead have been linked to fewer cardiovascular risks.

The most common SSRIs do not appear to significantly alter HRV, and no notable inter-treatment differences were found between paroxetine, nefazodone, mirtazapine, and other SSRIs, despite the patient response to treatment. Although SSRIs might offer cardioprotective effects, such as reducing platelet aggregation [121], these findings point towards the hypothesis that SSRIs do not significantly improve HRV, thereby conferring no HRV-mediated protective effects against CVD.

Finally, a third question that could arise is whether any antidepressants classes could also improve HRV while alleviating depressive symptoms. As is known thus far, in general pharmacological treatments seem to not improve HRV. However, no studies examined nonlinear HRV measures in MDD patients before and after treatment. Instead, for instance, research on CVD patients with comorbid MDD reported that 6 weeks of treatment with an SSRI (paroxetine) increases nonlinear heart rate complexity, suggesting a potential improvement in HRV [122]. Therefore, nonlinear measures may offer a more sensitive tool for future research on the impact of antidepressant treatments on HRV.

Interestingly, considering other treatments categories, an increase in HRV was observed after rTMS, suggesting a beneficial effect on autonomic regulation in MDD patients [113]. Brain stimulation techniques like rTMS and VNS are showing promising results, improving both depressive outcomes and autonomic modulation, offering promising alternatives to traditional pharmacological treatments.

LIMITATIONS

Although the HRV studies included in this review suggest a relationship between MDD diagnosis and cardiac autonomic dysfunction, some limitations need to be considered.

First, factors that are well known to affect the cardiovascular system, such as smoking, nutrition and physical activity, were not addressed. Moreover, given that most of the studies did not explore the effect of sex on the relationship between MDD and HRV, we did not report sex-specific conclusions on the integrated findings. In a future study, we could focus only on single-sex participants and explore more comprehensively sex effect on MDD-HRV mechanisms.

Third, the reviewed studies differed in terms of sample size, which in turn affects the statistical power of the HRV results. Although the risk of bias was not systematically estimated, the results were reported and ranked considering key aspects like sample size and effect size. Then, we weighed the discussion of the findings with respect to the corresponding statistical power.

Fourth, HRV metric extraction and statistical analysis methods were not subjected to any selection criteria (e.g., consistency in p-value corrections that were applied). Fifth, although all the ECG recordings considered were short-term acquisitions, they ranged between few minutes up to 30 min, possibly containing slightly different time- or frequency-domain information.

Moreover, spectral power analyses in the included studies were performed without evaluating respiratory sinus arrhythmia processes, that mainly represent vagal activity mechanisms in resting state and that allow to better disentangle the autonomic contributors within the LF band [54].

In addition, our review based on cross-sectional studies does not provide any causal explanation of the relationship between MDD and HRV autonomic dysfunction.

CONCLUSIONS

The aim of this review was to extensively explore the complex relationship between MDD and cardiac autonomic control, which ultimately could be associated with the increased cardiovascular risk found in MDD patients. The studies included in this systematic review were homogeneous both in terms of the methodological approach used (e.g., short-term resting-state HRV measures) and the clinical population employed that was formed by only MDD without CVD and drug-naïve or drug-free for excluding the potential effects of psychotropic medications in mediating HRV.

The overall puzzle seems to fall into place within the polyvagal theory framework, which emphasizes the importance of appropriate vagal regulation in emotion expression, social bonding, and flexible adaptation to environmental and internal demands.

Despite the variety of HRV metrics employed, most of the studies reported a significant reduction in HRV, possibly caused by a reduced parasympathetic vagal activity. Notably, the result reproducibility observed for the few studies that employed nonlinear HRV parameters suggests the latter to be more sensitive in capturing alterations in MDD patients with respect to HC. This suggests the promising direction for identifying HRV-related biomarkers of MDD through nonlinear analysis techniques, which might better capture the complexity of the underlying regulatory subsystems.

The findings observed in the reviewed studies indicate that depression is an independent risk factor for autonomic dysfunction, which seems also to be positively associated with depression severity.

However, unhealthy and CVD risk behaviors, including smoking, physical inactivity, obesity, and poor medication adherence, which have higher rates of occurrence in MDD than in the healthy population, may additionally contribute to worsening autonomic control, and are worth investigation in future studies. These lifestyle factors intersect with biological pathways linking MDD and autonomic dysregulation, such as immune system activation, inflammation, elevated cortisol levels, hormonal changes, and chronic stress and corresponding epigenetic alterations. In addition, the phenotypic heterogeneity of MDD may play a crucial role in these complex interactions.

Another key insight from our review is the plausible role of alterations in brain activity modulating ANS, aligning with the neurovisceral integration model. This suggests that neurophysiological mechanisms, rather than purely mechanical cardiovascular and respiratory processes, may underlie the relationship between MDD and autonomic dysfunction.

The integration of HRV information with other neuroimaging modalities, such as functional magnetic resonance imaging (fMRI) and electroencephalography (EEG), could be a promising direction for future research, allowing to obtain further insights into this complex relationship, especially on our understanding of the bidirectional influences between autonomic and brain functions. Since MDD is a brain disorder with heterogeneous and systemic symptomatology, HRV-fMRI and HRV-EEG multimodal approaches may offer invaluable data-driven tools for studying autonomic control in MDD at brain level.

Consistently, and given the unclear effects of psychoactive medications on HRV and that some patients do not respond to pharmacological treatments, neuromodulation techniques, targeting the fronto-vagal network, are gaining growing interest for their efficacy in improving both depressive symptoms and autonomic regulation, presenting an innovative, whole-body perspective for treating MDD. The background hypothesis is that neuroplastic changes that occur in MDD may influence autonomic regulation, therefore understanding how these interventions can promote neuroplasticity and improve both brain function and autonomic control could offer new therapeutic paths for treating MDD.

Additionally, genetic predispositions and epigenetic modifications may contribute to autonomic dysfunction in MDD, providing an additional layer of complexity to the disorder. Exploring these factors may open the door for more precise, personalized treatment approaches based on individual profiles.

In conclusion, the comprehensive study of autonomic control in MDD could lead to the identification of new clinical biomarkers for MDD stratification and to the monitoring of treatment responses, expanding the understanding about the neurobiological bases of this disabling and yet largely unknown disorder.

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AUTHOR CONTRIBUTIONS

FG: Conceptualization, Methodology, Literature search, Screening and selection, Formal analysis, Writing – original draft, Writing – review & editing. EM: Conceptualization, Methodology, Methodology review, Writing – review & editing. AMB: Methodology review, Supervision, Writing – review & editing. PB: Conceptualization, Supervision, Funding acquisition, Writing – review & editing. GD: Conceptualization, Methodology, Literature search, Screening and selection, Supervision, Writing – review & editing. All authors approved the final manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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