Journal of Affective Disorders 376 (2025) 139–148

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Review article

Exploring the dynamic relationships between nocturnal heart rate, sleep disruptions, anxiety levels, and depression severity over time in recurrent major depressive disorder

Elena Condominas [a,b], Albert Sanchez-Niubo [c,d], Joan Domènech-Abella [a,d], Josep Maria Haro [a,d,e], Raquel Bailon [f,g], Iago Giné-Vázquez [a,d], Gemma Riquelme [a], Faith Matcham [h,i], Femke Lamers [j,k], Spyridon Kontaxis [f], Estela Laporta [f], Esther Garcia [g,l], Maria Teresa Peñarrubia Maria [m], Katie M. White [h], Carolin Oetzmann [h], Peter Annas [n], Matthew Hotopf [h], Brenda W.J.H. Penninx [j,k], Vaibhav A. Narayan [o], Amos Folarin [h], Daniel Leightley [p], Nicholas Cummins [h], Yathart Ranjan [h], Giovanni de Girolamo [q], Antonio Preti [r], Sara Simblett [h], Til Wykes [h,s], Inez Myin-Germeys [t], Richard Dobson [h], Sara Siddi [a,d,e,*], RADAR-CNS consortium

[a] Impact and Prevention of Mental Disorders Research Group, Sant Joan de Déu Research Institut, Esplugues de Llobregat, Spain
[b] Universitat Politécnica de Catalunya, Barcelona, Spain
[c] Department of Social Psychology and Quantitative Psychology, University Barcelona, Barcelona, Spain
[d] Biomedical Research Networking Center for Mental Health Network (CIBERSAM), Madrid, Spain
[e] Parc Sanitari Sant Joan de Déu, Sant Boi de Llobregat, Spain
[f] Aragón Institute of Engineering Research (I3A), University of Zaragoza, Zaragoza, Spain
[g] Centros de investigación biomédica en red en el área de bioingeniería, biomateriales y nanomedicina (CIBER-BBN), Madrid, Spain
[h] King's College London, Institute of Psychiatry, Psychology and Neuroscience, London, UK
[i] School of Psychology, University of Sussex, Falmer, UK
[j] Department of Psychiatry, Amsterdam UMC, Vrije Universiteit, Amsterdam, the Netherlands
[k] Amsterdam Public Health Research Institute, Amsterdam, the Netherlands
[l] Microelectrónica y Sistemas Electrónicos, Universidad Autónoma de Barcelona, CIBER, Spain
[m] Catalan Institute of Health, Primary Care Research Institute (IDIAP Jordi Gol), CIBERESP, BBN, Barcelona, Spain
[n] H. Lundbeck A/S, Valby, Denmark
[o] Davos Alzheimer's collaborative, Geneva, Switzerland
[p] Academic Department of Military Mental Health, King's College London, London, UK
[q] IRCCS Instituto Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy
[r] Dipartimento di Neuroscienze, Università degli Studi di Torino, 10126 Torino, Italy
[s] South London and Maudsley NHS Foundation Trust, London, UK
[t] Department for Neurosciences, Center for Contextual Psychiatry, Katholieke Universiteit Leuven, Leuven, Belgium

ARTICLE INFO

Keywords:
Depression
Mobile health (mHealth)
Real-world monitoring
Night resting heart rate

ABSTRACT

Background: Elevated night resting heart rate (HR) has been associated with increased depression severity, yet the underlying mechanisms remain elusive. This study aimed to investigate the mediating role of sleep disturbance and the influence of anxiety on the relationship between night resting HR and depression severity.
Methods: This is a secondary data analysis of data collected in the Remote Assessment of Disease and Relapse (RADAR) Major Depressive Disorder (MDD) longitudinal mobile health study, encompassing 461 participants

Abbreviations: ANS, Autonomous nervous system; aRMT, Active remote measurement technology; CIBER, Centro de Investigación Biomédica en Red; HR, Heart rate; GAD, Generalised Anxiety Disorder; IDS-SR, Inventory of Depressive Symptomatology – Self Report; KCL, King's College London; MDD, Major depressive disorder; mHR, mean HR; PPG, photoplethysmography; pRMT, passive remote measurement technology; RADAR-CNS, Remote assessment of disease and relapse - central nervous system; RADAR-MDD, Remote assessment of disease and relapse - major depressive disorder; RMT, remote monitoring technology; stdHR, Standard deviation Heart Rate; VUmc, Vrije Universiteit Medisch Centrum.

* Corresponding author at: Impact and Prevention of Mental Disorders Research Group, Sant Joan de Déu Research Institut, Esplugues de Llobregat, Spain.
E-mail address: sara.siddi@sjd.es (S. Siddi).

https://doi.org/10.1016/j.jad.2025.02.010
Received 29 June 2024; Received in revised form 16 January 2025; Accepted 4 February 2025
Available online 6 February 2025

Anxiety
Sleep disturbance

(1774 observations) across three national centers (Netherlands, Spain, and the UK). Depression severity, anxiety, and sleep disturbance were assessed every three months. Night resting HR parameters in the 2 weeks preceding assessments were measured using a wrist-worn Fitbit device. Linear mixed models and causal mediation analysis were employed to examine the impact of sleep disturbance and anxiety on night resting HR on depression severity. Covariates included age, sex, BMI, smoking, alcohol consumption, antidepressant use, and comorbidities with other medical conditions.

Results: Higher night resting HR was linked to subsequent depressive severity, through the mediation of sleep disturbance. Anxiety contributed to an exacerbated level of sleep disturbance, subsequently intensifying depression severity. Anxiety exhibited no direct effect on night resting HR.

Conclusions: Our findings underscore the mediating role of sleep disturbance in the effect of night resting HR on depression severity, and anxiety on depression severity. This insight has potential implications for early identification of indicators signalling worsening depression symptoms, enabling clinicians to initiate timely and responsive treatment measures.

1. Introduction

Major depressive disorder (MDD) is a common mental disorder, globally affecting approximately 265 million people of all ages internationally (James et al., 2018). The intricate relationship between psychological stress and depression is outlined by the diathesis-stress model (Monroe and Simons, 1991). As the predisposition to depression (diathesis) increases, attributed to either biological or psychological factors, individuals become psychologically more vulnerable. Consequently, the threshold of stress required to precipitate an episode of depression decreases (Kemp et al., 2010; Kontaxis et al., 2021).

The physiological response to acute stress is associated with changes in the autonomic nervous system (ANS). The ANS regulates heart rate (HR) to respond to changing circumstances (Thayer et al., 2011). During rest, sleep, or emotional tranquillity, the ANS reduces HR (typically to 60–75 bpm) (Gordan et al., 2015) and during sleep the HR may decrease to below normal from 40 to 60 bpm. The resting HR appears altered in people with depression (Carney et al., 2008; Koenig et al., 2016) indicating potential dysregulation of psychological arousal in the presence of emotional or environmental stressors (Kemp et al., 2010).

This disorder is often accompanied by physiological abnormalities, such as increased HR and reduced HR variability (Carney et al., 2008; Correll et al., 2017; Lett et al., 2004; Nabi et al., 2011), both during sleep and wake states (Pawlowski et al., 2017; Saad et al., 2019). Notably, these HR irregularities may be more pronounced during nighttime, a period shielded from external influences like daytime stressors, physical activity, and cognitive processing.

Extended periods of stress play a vital role in the development of MDD, and this may be mediated by concurrent anxiety experienced by up to 40 % of people with depression (Angermann and Ertl, 2018; Felez-Nobrega et al., 2022; Möller, 2002; Rashid et al., 2023; Tiller, 2013). Elevated anxiety levels may lead to increased release of stress hormones, such as adrenaline, heightening HR in response to everyday stressors (Kim et al., 2018; Steimer, 2002; Zou et al., 2022). Consequently, the coexistence of anxiety and depressive disorders may result in less favorable paths in the progression of depressive symptoms (Gaspersz et al., 2018).

Sleep disturbance is a core symptom of MDD (Jansson-Fröjmark and Lindblom, 2008), with a majority of individuals ($N = 3287$) (Geoffroy et al., 2018) reporting various sleep complaints, including insomnia (85.2 %) and hypersomnia symptoms (47.5 %). These disturbances manifest in different forms, such as initial, middle, terminal insomnia, or hypersomnia (Perlis and Gehrman, 2013). At the same time, pathophysiological mechanisms responsible for any of these associations between depression, HR alteration, and sleep and anxiety symptoms are poorly understood.

Moreover, individuals with comorbid MDD and heightened anxiety may particularly struggle with sleep, impacting their ability to initiate or maintain sleep (Cox and Olatunji, 2016). Elevated HR has been correlated with prolonged time to fall asleep and diminished sleep quality (Nilsson et al., 2001), with sleep disruptions linked to cardiovascular deterioration and altered autonomic neuro-cardiac modulation (Reyes del Paso et al., 2013; Sauvet et al., 2010).

A recent review (Correia et al., 2023) have highlighted limitations in existing studies, emphasizing the need for longitudinal and mediation analyses to elucidate the relationships between depression, HR alterations, sleep, and anxiety symptoms. Previous research often employed cross-sectional designs, and few studies were conducted specifically in MDD populations. Moreover, experimental circumstances, such as hospital settings using electrocardiography (ECG) (Eddie et al., 2020; Ottaviani et al., 2015; Saad et al., 2019; Yang et al., 2011) and short follow-up periods (< of 1 month) (Leistedt et al., 2011), further limit the understanding of these associations. Recording the ECG during daily life and long periods has several limitations most seriously participant acceptability. Wrist-worn devices that are available today facilitate the measurement of HR, derived from pulse photoplethsymography (PPG), in naturalistic conditions. These technologies have several advantages over previous devices, including being non-invasive, low burden, low cost, and allowing the acquisition and processing of a large amount of information in near-real time.

The present study represents a secondary analysis of the Remote Assessment of Disease and Relapse-Major Depressive Disorder (RADAR-MDD) dataset (Matcham et al., 2019, 2022). Previous findings from this dataset identified associations between increased night resting HR (Siddi et al., 2023) and sleep disturbance (Zhang et al., 2021; Matcham et al., 2023) with depression severity in individuals with a history of recurrent MDD during a 24-month follow-up.

In this longitudinal study, we aim to test the following main hypotheses (Fig. 1):

1) Anxiety contributes to elevate night-resting HR (arrow a)
2) Increases in anxiety (arrow b), night resting HR (arrow c) and sleep disturbance (arrow f) are associated with an increase in depression severity.
3) Anxiety (arrow d) and night-resting HR (arrow e) contributes to elevate the sleep disturbance.

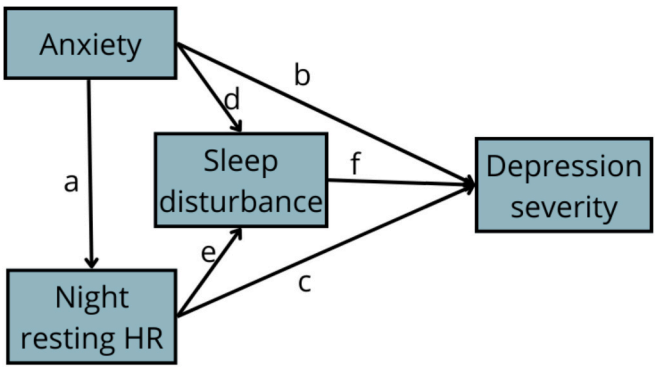

Fig. 1. Causal diagram proposed according to the hypothesis.

2. Methods

2.1. Study design and participants

RADAR-MDD is an international, multicentre, longitudinal, observational cohort study in people with a history of recurrent MDD (the protocol was published here (Matcham et al., 2019), followed up for a median of 541 days (interquartile range.(IQR): 401–730 days) (Matcham et al., 2022). Participants were recruited from three recruitment sites: Centro de Investigación Biomédia en Red (CIBER, Barcelona), King's College London (London, UK); Amsterdam University Medical Centre, location VUmc (Amsterdam, The Netherlands). The RADAR-MDD study, as a part of the research RADAR-CNS project (https://www.radar-cns.org/), was co-developed with service users in our Patient Advisory Board (PAB) (Polhemus et al., 2020; Simblett et al., 2019, 2020). The PAB were involved in the choice of measures, devise, the timing and issues of engagement and have been involved in developing the analysis plan and representative (s) are authors of the papers.

To be eligible for inclusion, individuals needed to: have had at least two episodes of MDD; have experienced with their most recent episode within the previous two years, be able to complete self-reported questionnaires via a smartphone, be fluent in English, Dutch, Catalan or Spanish; be able to give informed consent; be an Android user, or be willing to switch to use an Android phone for the duration of participation; be aged over 18 years. People who had a lifetime history of bipolar disorder, schizoaffective disorder, schizophrenia, MDD with psychotic features dementia, recent drug or alcohol misuse or a major medical illness (requiring long periods of hospitalisation), were not eligible to participate.

2.2. Procedure

The RADAR-MDD study explored the use of active and passive remote monitoring technology (RMT) and then send into the RADARbase platform (Ranjan et al., 2019). The passive RMT included a wrist-worn Fitbit device to measure HR, physical activity and sleep and app to collect information on phone usage, GPS, Bluetooth, while in this manuscript we explored the following variables according to our hypothesis (Table 1). Recruitment took place between November 2017 and June 2020 and follow-up ceased on 30th April 2021. Participants completed the following assessments every 3 months via automated surveys delivered using (REDCap) platform (Harris et al., 2009).

2.3. Assessment

2.3.1. Depression severity

Depression was assessed as total score on the Inventory of Depressive Symptomatology – Self Report (IDSSR) (Rush et al., 2000) to capture symptom severity during the last seven days. The IDS-SR is a 30-item questionnaire, widely used in depression trials and providing detailed information on depressive symptoms, including all 9 Diagnostic and Statistical Manual (DSM) domains, symptoms commonly associated with depression (such as irritability or pain), melancholic symptoms and atypical symptoms. Each item is rated 0–3. For this study, we excluded from the total score the items related to sleep items (Item 1 to 4) that were used to measure sleep disturbance. In this self-rated version (IDS-SR26), a cut-off-point ≥22 indicates the presence of clinically relevant depressive symptomatology (≥26 score were considered in the previous papers (Matcham et al., 2022) including the items 1–4. The new cut-off (≥22) distinguished between patients with clinically significant depression (Rush et al., 2000, 2003) categorized as severe or moderate, and those without depression or with only mild symptoms as the previous cut-off of ≥26 score(275 [59.7 %] vs 186 [40.3 %]).

Table 1
Features Legend: Clinical and HR parameters derived from the app and Fitbit, respectively.

Variable	Features	Assessment
Depression severity	Inventory of Depressive Symptomatology – Self Report IDS-SR 26 items	Every 3 months
Anxiety severity	Generalised Anxiety Disorder-7 items	Every 3 months
Sleep Disturbance	IDS-SR 4 items	Every 3 months
Night resting mHR	Mean HR during resting periods, identified by activity level = resting and number of steps = 0 during the night (0:00–05:59)	Every day

2.3.2. Sleep disturbance

To assess the sleep complaints, we used the sum of the sleep subscale of the IDS-SR30 (from 1 to 4 item) (Gili et al., 2011). The first three items measure (insomnia: sleep onset insomnia, mid-nocturnal insomnia, and early morning insomnia) (Mason et al., 2020) during the last 7 days. The item 4 measure hypersomnia, where participants were asked to rate the longest period slept in a 24 h period over the last 7 days, including naps. This subscale was used previously in various studies (Kaplan et al., 2015). Each item is rated on a 0–3 Likert-type scale, with higher scores representing a greater severity of symptoms.

2.3.3. Anxiety severity

Anxiety was measured via the 7-item Generalised Anxiety Disorder questionnaire (GAD7) (Spitzer et al., 2006), used as a continuous indicator of anxiety symptom severity for the past two weeks (a total of 21, with higher scores indicating increased anxiety severity) and a total score ≥ 10 indicating significant symptoms.181 participants reported high anxiety and 280 reported low anxiety. This threshold has previously been shown to have good levels of sensitivity and specificity (Jordan et al., 2017).

2.3.4. Night resting heart rate feature

The HR was computed from the HR signal provided by Fitbit charge 2 and 3 (Fitbit Inc., San Francisco, CA, USA), which is obtained from the photoplethysmography (PPG) sensor of the device with a narrowest resolution up to 5 s between samples. This device was previously shown to measure HR during the day accurately (Fuller et al., 2020; Liu et al., 2022; Nazari et al., 2019; Nelson and Allen, 2019) and during the night (de Zambotti et al., 2016; Haghayegh et al., 2019).

Night resting mean HR was computed during the night (from 00:00 to 05:59), and resting period was defined when the number of steps and activity level, derived from the accelerometer data, equalled 0.

A previous paper (i.e. Stucky et al., 2021) suggested that the Fitbit underestimated the sleep transition dynamics (transition from deep sleep to light sleep). For this reason, we selected the period from 00:00 to 05:59 as a conservative nighttime that might work for a large part of the population.

We computed the average of each night's resting HR parameter the 2 weeks' prior the IDS-SR26 across the follow-up, excluding the weekends before the IDS-SR26 assessment. People's behaviours follow a quasiperiodic routine during the weekdays, such as working and doing activities during the day and sleeping at night. Meanwhile, the circadian rhythm may be different during the weekends. So, we excluded weekend to avoid differences in the circadian phases between weekdays and weekends (Gander and Paine, 2016) This previous timeframe was also considered previously to detect the association between depression severity measured by the PHQ8 and sleep features in our previous study (Zhang et al., 2021).

We additionally considered the two weeks prior to the IDS.-R26 completion time, considering the weekends and included in the supplementary materials.

2.3.5. Covariates

Baseline sociodemographic, smoking habits and medical health

conditions: Information about sociodemographic (age, gender, education years, partnership status), medical or psychiatric history(yes/no), heaviness of smoking index(yes/no);and current alcohol habit (yes/no) measured through the Alcohol use disorders identification test (Daeppen et al., 2000), self-reported BMI and comorbidity with pre-existing medical or psychiatric health conditions(yes/no), antidepressant medication (yes/no), and time of assessment (every 3 months).

3. Data analysis

The analyses were conducted in four stages.

First, we described the socio-demographic characteristics of the sample at enrolment (baseline) and clinical and physical variables at follow-up using appropriate summary statistics (median and interquartile range (IQR) for continuous variables; frequency and percentage for categorical variables).

Second, Spearman correlation (ρ) was calculated between the night resting HR parameter and IDS-SR26 subscales (1–4 items) and GAD7 items to assess the association of night resting HR with depression, anxiety and sleep disturbance. We also looked at the association between the IDS-SR26 items and the number of observations to explore if depression severity was negatively related to the assessment rate (i.e. patients with severe depression might be significantly less likely to complete the assessment because of their symptoms of abulia and apathy).

We also compared the night resting mean HR between individuals with and without significant depressive symptoms (IDS-SR26 $\geq$ 22) to determine whether HR explained the variance of depression severity. We conducted similar analyses in individuals with anxiety and without anxiety symptoms (GAD7 $\geq$ 10), and those with and without sleep disturbance (IDS1–4 mean $\geq$ 3). Cohen's d effect size was calculated for the comparisons: the effect size is considered small, medium, and large using the 0.2, 0.5 and 0.8 cut-offs.

Third, linear mixed models were conducted in three steps to assess the different association pathways from Fig. 1. Depression severity was the outcome (IDS-SR26 total score) and time of assessment was an explanatory variable included in all the models. In the first step, we included the night resting HR feature as the main explanatory variable (relation c; Fig. 1). The second step, night resting HR was accompanied in various models by anxiety severity (continuous variable 0 to 21), sleep disturbance (continuous variable from 0 to 12), and both together. In the third step, the covariates were included in the same previous models: age and BMI as continuous variables and gender, smoking, alcohol (categorical variables), antidepressant medication, and medical comorbidity as dichotomous variables. We also take into account the time as a covariable, each time is corresponding a 3 month which were the assessments periods. The measures of model fit, such as either the Akaike Information Criterion (AIC) or the Bayesian Information Criterion (BIC), were considered.

To demonstrate the consistencies of our previous findings, we additionally replicated the previous models, including the night resting HR computed during the 2 week including weekends prior the IDS-SR completion time (Table S3).

We then conducted separate linear mixed models to see if anxiety was also associated with night resting HR (relation a; Fig. 1), and if anxiety and night resting HR were related to sleep disturbance (relation d & e; Fig. 1). These models were adjusted for the previous covariates.

Fourth, according to the causal diagram from Fig. 1 and the findings of the previous analyses, we performed the causal mediation analyses using 'lme4' and 'mediation'libraries of R to calculate the effect of each causal pathway of the main variables, night resting HR, sleep disturbance and anxiety, on depression severity considering random effects.

All analyses were performed using the R software (R Core Team, 2016, 2023).

4. Results

4.1. Descriptive characteristics

The sociodemographic characteristics are illustrated in Table 2. A total of 461 individuals with N 1679 observations were included in the analyses; we excluded participants with missing data. Of 623 participants with MDD, only 566 people had HR measures. Of these 461 reported IDS-SR26 score, GAD and sociodemographic data. The majority, 370 (80.3 %), reported sleep disturbance. Individuals with higher depression severity reported higher anxiety and sleep disturbance compared to others (Table S1).

Fig. 2 shows the association between the night resting mean HR, depression, anxiety and sleep disturbance symptoms on the right and the comparisons between groups according to the symptom severity on the left. Night resting mean HR coefficient was correlated to depression severity (IDS-SR26 items) ($\rho = 0.17, p < 0.001$), and anxiety ($\rho = 0.14, p < 0.001$). In the boxplots, we observed that individuals with higher depression and anxiety severity had higher night mean resting HR compared to the other groups with lower severity, however, with a small effect size (Cohen's values were − 0.31and −0.29, respectively). Similarly, there was an association between night resting HR and self-reported sleep disturbance (sum of the items IDS-SR-4 Items) was observed ($\rho = 0.13, p < 0.001$). Then, we compared the individuals who reported sleep disturbance (items IDS1-IDS4 $\geq$ 3) with individuals who did not report sleep disturbance (normal sleepers). The boxplot shows that individuals with sleep disturbance had higher night resting HR compared to normal sleepers.

4.2. Associations between night resting HR, sleep disturbance, anxiety and depression severity

Table 3 shows the results of the different mixed regression models not adjusted and adjusted by covariates. We found that the night mean resting HR was significant in all models except the adjusted model with sleep disturbance (model 3 and 4). Regarding the covariates, BMI, smoking status, comorbidities, and alcohol consumption are the most significant in all the models. All of them are dichotomous variables except for BMI, which is numerical. In model 4, the standardized beta coefficients and *p*-values for these variables are as follows: $\beta = 0.047$ ($\rho = 0.047$), $\beta = 0.065$ ($\rho < 0.001$), $\beta = 0.093$ ($\rho < 0.001$), and $\beta = -0.12$ ($\rho < 0.001$), respectively.

In Table 4, we found a non-significant effect of night resting HR on

Table 2
Baseline, clinical and night resting hear rate (HR) features ($N = 461$).

Variables	Median or N (%)	IQR	Min	Max
Age median	49	27	18	80
Gender (Female) (N,%)	343 (74.4)			
Depression severity (median)	25	19	0	62
High depression (≥ 22) (N %)	275 (59.7)			
Low depression (<22) (N %)	186 (40.3)			
Anxiety severity (median)	8	9	0	21
High anxiety (≥ 10) (N %)	181 (39.3)			
Low anxiety (<10) (N %)	280 (60.7)			
Sleep disturbance (IDS1–4)	4	3	0	11
High (≥ 3) (N %)	370 (80.3)			
Low (<3) (N %)	91 (19.7)			
Body Mass Index (median)	25.8	7.6	14	71.7
Smoking status (yes) (N, %)	77 (16.7)			
Alcohol habit (yes) (n, %)	325 (70.5)			
Antidepressant (yes) (n, %)	239 (51.8)			
Medical comorbidity (yes) (n, %)	236 (51.2)			
Night resting mHR	65.0	12.8	43.7	96.5
Times	3	3	1	12

Note: The table presents the baseline characteristics of the 461 participants. mHR represents the mean heart rate, while 'Times' indicates the number of observations per participant.

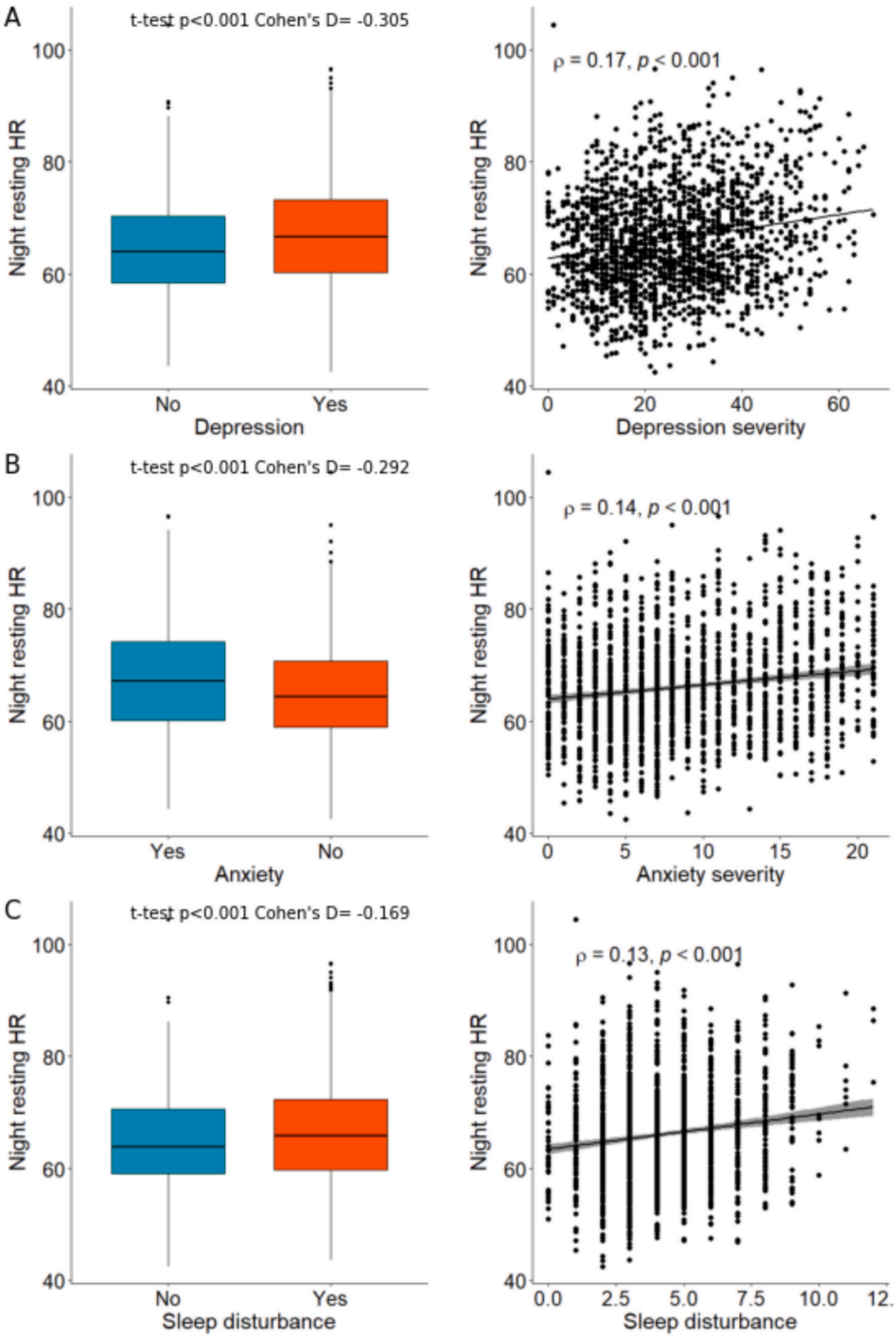

Fig. 2. The scatter plots show the relation between the clinical variables and night resting mean heart rate (HR) on the right side, while the boxplots on the left show the comparison between the groups with different clinical severity.
Note: All the observations were included in the plots.

anxiety. In Table 5, we observed that night resting HR and anxiety had a significant effect on sleep disturbance.

Table S2 compares the models from Table 3 to explore which model provides a better fit for the data. First, we compared the first two models: adjusted model 1 with only HR and adjusted model 2 with anxiety and HR. The results showed the most significant model was model 2 with anxiety ($\rho < 0.001$). We also compared the models with the sleep disturbance (model 1) with (model 3) to observe if this model provided a significantly better fit to the data than model 1. The results showed that model 3 with sleep disturbance provided a better fit to model 1. Last, we compared the adjusted model containing sleep disturbance, anxiety, and night resting HR with all previous models (lower AIC); we observed that the final model demonstrated a better fit than the other models. Thus, the night mean resting HR, sleep disturbance, and anxiety showed an increasing effect on depression severity.

The additional linear mixed models including the night resting HR computed during the 2-week prior, including the weekends, the IDS-SR26 completion time, showed that the previous associations were maintained (Please see Table S3).

Table 3
Mixed regression models of night resting heart rate (HR) and Time of assessment on depression severity (IDS-SR26), alone and accompanied by the explanatory variables anxiety and sleep disturbance, and non-adjusted and adjusted by other covariates*.

	Model 1				Adjusted Model*	
Features	Bstd	95 % CI	p-value	βstd	95 % CI	p-value
Night Resting mHR	**0.10**	**0.07–0.22**	**<0.001**	**0.06**	**0.01–0.16**	**0.025**
Time	**−0.03**	**−0.11–0.01**	**0.020**	**−0.03**	**−0.11–0.01**	**0.021**
R2 marginal	0.010			0.187		
R2 conditional	0.779			0.786		
AIC	12,742			12,652		
BIC	12,770			12,717		
	Model 2			**Adjusted Model***		
Features	**Bstd**	**95 % CI**	**p-value**	**βstd**	**95 % CI**	**p-value**
Night Resting mHR	**0.06**	**0.04–0.15**	**0.001**	**0.04**	**0.00–0.11**	**0.040**
Anxiety	**0.59**	**1.34–1.49**	**<0.001**	**0.57**	**1.29–1.45**	**<0.001**
Time	−0.02	−0.08-0.00	0.070	−0.04	−0.08-0.00	0.055
R2 marginal	0.463			0.544		
R2 conditional	0.819			0.834		
AIC	11,818			11,775		
BIC	11,852			11,846		
	Model 3			**Adjusted Model***		
Features	**Bstd**	**95 % CI**	**p-value**	**βstd**	**95 % CI**	**p-value**
Night Resting mHR	**0.08**	**0.05–0.19**	**0.001**	0.04	−0.01-0.13	0.076
Sleep disturbance	**0.24**	**1.27–1.71**	**<0.001**	**0.23**	**1.23–1.66**	**<0.001**
Time	−0.02	−0.10- -0.00	0.044	−0.02	−0.10 − 0.01	0.054
R2 marginal	0.079			0.255		
R2 conditional	0.768			0.781		
AIC	12,581			12,497		
BIC	12,614			12,568		
	Model 4			**Adjusted Model***		
Features	**B**	**95 % CI**	**p-value**	**Bstd**	**95 % CI**	**p-value**
Night Resting mHR	**0.05**	**0.03–0.13**	**0.003**	0.03	-0.01-0.10	0.089
Sleep disturbance	**0.14**	**0.72–1.08**	**<0.001**	**0.14**	**0.64–1.04**	**<0.001**
Anxiety	**0.56**	**1.26–1.41**	**<0.001**	**0.54**	**1.21–1.37**	**<0.001**
Time	−0.02	−0.08-0.01	0.108	−0.02	−0.08- -0.00	0.091
R2 marginal	0.515			0.581		
R2 conditional	0.824			0.839		
AIC	11,732			11,695		
BIC	11,770			11,772		

* Note: Models on the left include night mean resting HR and anxiety and/or sleep disturbance (continuous score) as indicated. Adjusted models on the right include all the previous variables and covariates (age, gender, smoking status, antidepressant medication, and medical comorbidity). Night resting HR was calculated 2 weeks (excluding weekend) prior the IDS-SR26 completion.

Table 4
Mixed regression model of anxiety and wave of assessment on night resting heart rate (HR), non-adjusted and adjusted by covariates*.

	Model 1				Adjusted Model*	
Features	βstd	95 % CI	p-value	βstd	95 % CI	p-value
Anxiety	0.04	0.01–013	0.028	0.02	−0.02-0.10	0.225
Time	0.03	0.01–0.07	0.017	0.03	0.01–0.07	0.017
R2 marginal	0.002			0.117		
R2 conditional	0.839			0.841		
AIC	11052			11000		
BIC	11079			11066		

Note: Covariates are age, gender, smoking status, antidepressant medication, and medical comorbidity.
* Adjusted model by the following covariates: age, gender, smoking status, antidepressant medication, and medical comorbidity.

4.3. Identification of causal mediation mechanism

According to our hypothesis and based on the findings observed in the previous steps, we executed two mediation models to explore the role of sleep disturbance between night resting HR and depression severity and between anxiety and depression severity (Fig. 3).

In the first mediation model, the total effect of night resting HR on depression was $\beta = 0.010$ ($\rho = 0.016$). This total effect was composed by the direct effect that was equal to $\beta = 0.064$ ($\rho = 0.074$) and the indirect effect that was $\beta = 0.025$ ($\rho = 0.014$).

In the second model, the total effect of anxiety on depression severity was $\beta = 1.386$ ($p < 0.001$), the direct effect was $\beta = 1.294$ ($\rho < 0.001$) and the indirect effect was $\beta = 0.09$ ($\rho < 0.001$), being a 7 % of the total effect.

5. Discussion

To the best of our knowledge, this is the first study that explored how night resting HR, sleep disturbance, and anxiety symptoms are interrelated, as well as the mediating pathways through which they contribute to depression severity among individuals with a history of recurrent MDD (Correia et al., 2023). The findings are in line with our hypothesis; night resting HR was associated with depression severity through sleep disturbance. The association found between increased night resting HR and depression severity confirmed the findings observed in our prior study (Siddi et al., 2023), where depression severity was assessed with a different tool (Patient Health Questionnaire 8 items) every 2 weeks; and the association between depression severity and sleep disturbance features collected passively using the Fitbit (Zhang et al., 2021).

Table 5
Mixed regression model of night resting HR, anxiety and time of assessment on sleep disturbance (IDS-SR 1–4), non-adjusted and adjusted by covariates*.

	Model 1			Adjusted Model*		
Features	Bstd	95 % CI	*p-value*	βstd	95 % CI	*p-value*
Night Resting Mhr	**0.11**	**0.01–0.04**	**<0.001**	**0.07**	**0.00–0.03**	**0.018**
Time	−0.02	−0.02- 000	0.071	-0.03	−0.02-0.00	0.150
R2 marginal	0.012			0.079		
R2 conditional	0.597			0.603		
AIC	7030			7024		
BIC	7058			7089		
	Model 2			Adjusted Model		
Features	**Bstd**	**95 % CI**	***p-value***	**Bstd**	**95 % CI**	***p-value***
Anxiety	**0.29**	**0.09–0.13**	**<0.001**	**0.28**	**0.09–0.13**	**<0.001**
Time	−0.01	−0.02-0.01	0.456	−0.02	−0.02-0.01	0.318
R2 marginal	0.086			0.144		
R2 conditional	0.591			0.600		
AIC	6921			6921		
BIC	6949			6987		
	Model 3			Adjusted Model		
Features	**Bstd**	**95 % CI**	***p-value***	**βstd**	**95 % CI**	***p-value***
Night Resting Mhr	**0.08**	**0.01–0.03**	**0.006**	**0.06**	**0.00–0.03**	**0.036**
Anxiety	**0.28**	**0.09–0.13**	**<0.001**	**0.28**	**0.09–0.12**	**<0.001**
Time	−0.02	−0.02-0.01	0.454	−0.02	−0.02 -0.00	0.267
R2 marginal	0.096			0.147		
R2 conditional	0.593			0.601		
AIC	6924			6927		
BIC	6957			6998		

Note: Covariates are age, gender, smoking status, antidepressant medication, medical comorbidity. AIC = Akaike information criterion; BIC = Bayesian information criterion.
* Adjusted model by the covariates age, gender, smoking status, antidepressant medication, medical comorbidity.

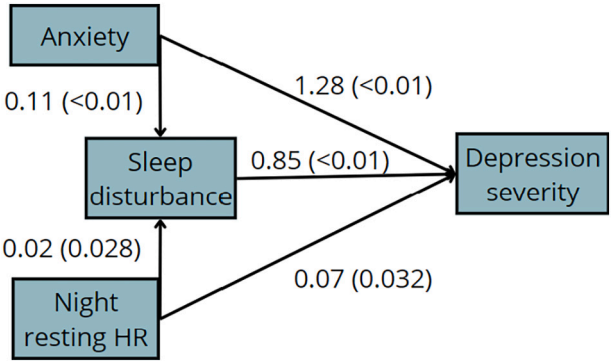

Fig. 3. Causal diagrams on the mediation role of sleep disturbance between night resting HR or anxiety and depression severity.

Heightened anxiety levels often perceive everyday situations as stressful, leading to a more frequent release of adrenaline and other stress hormones, consequently increasing HR (Kim et al., 2018; Steimer, 2002). However, in the present study, a direct association between anxiety levels and night resting HR was not observed. Night resting HR might depend on individual variation in stress susceptibility, resilience and reactivity (Halaris, 2016).

Despite the lack of a direct association between anxiety and night resting HR, anxiety did contribute to the amplification of depressive severity and sleep disturbance. The association between anxiety and depression severity was partially mediated by sleep disturbance (6 %). This means that both anxiety and sleep disturbance have a direct increasing effect on depression severity. People who suffer from both MDD and elevated levels of anxiety often can have a lower their ability to either fall asleep initially or maintain uninterrupted sleep (Cox and Olatunji, 2016; Nutt et al., 2008). The presence of significant anxiety symptoms and sleep disturbance generally predicts worse of depression severity (da Estrela et al., 2021; Jansson-Fröjmark and Lindblom, 2008; Kalin, 2020). Various studies demonstrated that patients with anxious MDD were more likely to be severely depressed and to have more suicidal ideation (Fava et al., 2004; Kessler et al., 2015).

These findings underscore the intertwined relationship between anxiety, sleep disturbance, and depression severity, providing a foundation to explore how physiological markers, such as night resting HR, may contribute to this complex interaction.

In this study, the association between night resting HR and depression severity was mediated by sleep disturbance. Previous studies have demonstrated that changes in HR across sleep may be a physiological marker of depression severity in a sample with MDD and sleep disturbance (da Estrela et al., 2021; Saad et al., 2019, 2020). Increased night resting HR is linked with an altered balance of the ANS clinically manifested as increased HR and cardiac output. It is associated with reduced melatonin secretion (Sewerynek, 2002; Simko et al., 2016), responsible for circadian variability and the sleep quality (Pandi-Perumal et al., 2020). Thus, elevated night resting HR may indicate a set of physiological changes, which lead to sleep disturbance including challenges initiating sleep or maintaining uninterrupted sleep, which in turn impede sleep quality. This suggests that the physiological manifestation of increased night resting HR may contribute to the complexities of sleep patterns observed in individuals grappling with depressive symptoms. These disruptions in sleep, in turn, may exacerbate the depression symptoms (Cox and Olatunji, 2016; Fang et al., 2019), perpetuate the course of depression, or increase the risk of recurrence of MDD (Baglioni et al., 2011).

Understanding these connections is crucial for developing targeted interventions and comprehensive approaches to addressing sleep-related challenges in the context of depression. In conclusion, there are intricate associations among anxiety, sleep complaints, and increased night HR in MDD. Recognizing and addressing these interconnections is vital for providing comprehensive care and improving the overall well-being of individuals affected by MDD. An integrated approach that addresses all three components is often the most effective way to manage the condition.

5.1. Strengths and limitations

This study includes objective and subjective measures and are collected over months. Moreover, it includes data collected from

clinically relevant sample in their natural environment. We controlled our models for multiple variables known to impact HR, sleep and depression anxiety, including gender, BMI, alcohol smoking and antidepressant medication, however there may still have been incomplete control of these covariates leading to residual confounding - for example, we did not take account of antidepressant doses, and other medications and/or physical illnesses were no included in our models. Finally, although we report a causal mediation between night resting HR, sleep disturbance, anxiety with depression severity, this type of analysis precluding inferences of directionality among the associations observed such as depressive symptoms may have preceded night resting HR irregularities and sleep disturbance.

6. Conclusion

In summary, this study reveals that the link between depression severity and night resting HR is mediated by sleep disturbance. This underscores the necessity of accounting for sleep quality when assessing how HR abnormalities relate to depression severity. Prolonged elevation of resting HR during nighttime can disrupt sleep, exacerbating depressive symptoms. Long-term monitoring in real-world setting of these indicators may aid in preventing depression relapse.

CRediT authorship contribution statement

Elena Condominas: Writing – original draft, Software, Methodology, Funding acquisition, Formal analysis, Data curation. **Albert Sanchez-Niubo:** Formal analysis, Data curation. **Joan Domènech-Abella:** Writing – review & editing, Supervision, Conceptualization. **Josep Maria Haro:** Writing – original draft, Formal analysis. **Raquel Bailon:** Writing – original draft, Formal analysis, Data curation. **Iago Giné-Vázquez:** Writing – original draft, Formal analysis, Data curation. **Gemma Riquelme:** Validation, Supervision. **Faith Matcham:** Writing – review & editing, Data curation. **Femke Lamers:** Writing – review & editing, Supervision, Data curation. **Spyridon Kontaxis:** Writing – review & editing. **Estela Laporta:** Writing – review & editing. **Esther Garcia:** Writing – review & editing, Validation, Supervision, Data curation. **Maria Teresa Peñarrubia Maria:** Writing – review & editing. **Katie M. White:** Writing – review & editing. **Carolin Oetzmann:** Writing – review & editing. **Peter Annas:** Writing – review & editing. **Matthew Hotopf:** Writing – review & editing, Funding acquisition. **Brenda W.J.H. Penninx:** Writing – review & editing. **Vaibhav A. Narayan:** Writing – review & editing. **Amos Folarin:** Writing – review & editing. **Daniel Leightley:** Writing – review & editing. **Nicholas Cummins:** Writing – review & editing. **Yathart Ranjan:** Writing – review & editing. **Giovanni de Girolamo:** Writing – review & editing. **Antonio Preti:** Writing – review & editing. **Sara Simblett:** Writing – review & editing. **Til Wykes:** Writing – review & editing. **Inez Myin-Germeys:** Writing – review & editing. **Richard Dobson:** Writing – review & editing. **Sara Siddi:** Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization.

Role of funding

The RADAR-CNS project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 115902. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA, www.imi.europa.eu. This communication reflects the views of the RADAR-CNS consortium and neither IMI nor the European Union and EFPIA are liable for any use that may be made of the information contained herein. The funding body has not been involved in the design of the study, the collection or analysis of data, or the interpretation of data.

This work was also funded by TED2021-131106B-I00 (Ministerio de Ciencia e Innovación and European Social Fund), Spain, and by European Social Fund (EU) and Aragón Government, Spain through BSICoS group, Spain T39_23R.

Declaration of competing interest

Vaibhav A Narayan is employee of Janssen Research and Development LLC. Peter Annas is employed by the pharmaceutical company H. Lundbeck A/S. Josep Maria Haro has received economic compensation for participating in advisory boards or giving educational lectures from Eli Lilly & Co, Sanofi, Lundbeck, and Otsuka. No other authors have competing interests to declare.

Acknowledgment

The RADAR-CNS project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 115902. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA, www.imi.europa.eu. This communication reflects the views of the RADAR-CNS consortium and neither IMI nor the European Union and EFPIA are liable for any use that may be made of the information contained herein. The funding body has not been involved in the design of the study, the collection or analysis of data, or the interpretation of data.

This work was also funded by TED2021-131106B-I00 (Ministerio de Ciencia e Innovación and European Social Fund), Spain, and by European Social Fund (EU) and Aragón Government, Spain through BSICoS group, Spain T39_23R.

Participants in the CIBER site came from following four clinical communities in Spain: Parc Sanitari Sant Joan de Déu Network services, Institut Català de la Salut, Institut Pere Mata, and Hospital Clínico San Carlos. Participant recruitment in Amsterdam was partially accomplished through Hersenonderzoek.nl, a Dutch online registry that facilitates participant recruitment for neuroscience studies Hersenonderzoek.nl is funded by ZonMw-Memorabel project no 73305095003, a project in the context of the Dutch Deltaplan Dementie, Gieskes-Strijbis Foundation, the Alzheimer's Society in the Netherlands and Brain Foundation Netherlands. We thank all GLAD Study volunteers for their participation, and gratefully acknowledge the NIHR BioResource, NIHR BioResource centres, NHS Trusts and staff for their contribution. We also acknowledge NIHR BRC, King's College London, South London and Maudsley NHS Trust and King's Health Partners. We thank the National Institute for Health Research, NHS Blood and Transplant, and Health Data Research UK as part of the Digital Innovation Hub Programme. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

This paper represents independent research part funded by the National Institute for Health Research NIHR Maudsley Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care. We thank all the members of the RADAR-CNS patient advisory board for their contribution to the device selection procedures, and their invaluable advice throughout the study protocol design. This research was reviewed by a team with experience of mental health problems and their careers who have been specially trained to advise on research proposals and documentation through the Feasibility and Acceptability Support Team for Researchers FAST-R: a free, confidential service in England provided by the National Institute for Health Research Maudsley Biomedical Research Centre via King's College London and South London and Maudsley NHS Foundation Trust. RADAR-MDD will be conducted per the Declaration of Helsinki and Good Clinical Practice, adhering to principles outlined in the NHS Research Governance Framework for Health and Social Care 2nd edition.

Ethical approval has been obtained in London from the Camberwell St Giles Research Ethics Committee REC reference: 17/LO/1154, in London from the CEIC Fundacio Sant Joan de Deu CI: PIC-128-17 and in the Netherlands from the Medische Ethische Toetsingscommissie VUms METc VUmc registratienummer: 2018.012 – NL63557.029.17.

All authors acknowledged the contribution of the Patient Advisory Board.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2025.02.010.

Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

References

Angermann, C.E., Ertl, G., 2018. Depression, anxiety, and cognitive impairment: Comorbid mental health disorders in heart failure. In: Current Heart Failure Reports, Vol. 15, Issue 6. Current Science Inc., pp. 398–410. https://doi.org/10.1007/s11897-018-0414-8

Baglioni, C., Battagliese, G., Feige, B., Spiegelhalder, K., Nissen, C., Voderholzer, U., Lombardo, C., Riemann, D., 2011. Insomnia as a predictor of depression: A meta-analytic evaluation of longitudinal epidemiological studies. J. Affect. Disord. 135 (1–3), 10–19. https://doi.org/10.1016/j.jad.2011.01.011.

Carney, R.M., Steinmeyer, B., Freedland, K.E., Blumenthal, J.A., Stein, P.K., Steinhoff, W. A., Howells, W.B., Berkman, L.F., Watkins, L.L., Czajkowski, S.M., Domitrovich, P.P., Burg, M.M., Hayano, J., Jaffe, A.S., 2008. Nighttime heart rate and survival in depressed patients post acute myocardial infarction. Psychosom. Med. 70 (7), 757–763. https://doi.org/10.1097/PSY.0b013e3181835ca3.

Correia, A.T.L., Lipinska, G., Rauch, H.G.L., Forshaw, P.E., Roden, L.C., Rae, D.E., 2023. Associations between sleep-related heart rate variability and both sleep and symptoms of depression and anxiety: A systematic review. Sleep Med. 101, 106–117. https://doi.org/10.1016/j.sleep.2022.10.018.

Correll, C.U., Solmi, M., Veronese, N., Bortolato, B., Rosson, S., Santonastaso, P., Thapa-Chhetri, N., Fornaro, M., Gallicchio, D., Collantoni, E., Pigato, G., Favaro, A., Monaco, F., Kohler, C., Vancampfort, D., Ward, P.B., Gaughran, F., Carvalho, A.F., Stubbs, B., 2017. Prevalence, incidence and mortality from cardiovascular disease in patients with pooled and specific severe mental illness: a large-scale meta-analysis of 3,211,768 patients and 113,383,368 controls. World Psychiatry 16 (2), 163–180. https://doi.org/10.1002/wps.20420.

Cox, R.C., Olatunji, B.O., 2016. A systematic review of sleep disturbance in anxiety and related disorders. J. Anxiety Disord. 37, 104–129. https://doi.org/10.1016/j.janxdis.2015.12.001.

Daeppen, J.-B., Yersin, B., Landry, U., Pecoud, A., Decrey, H., 2000. Reliability and validity of the alcohol use disorders identification test (AUDIT) imbedded within a general health risk screening questionnaire: results of a survey in 332 primary care patients. Alcohol. Clin. Exp. Res. 24 (5), 659–665. https://doi.org/10.1111/j.1530-0277.2000.tb02037.x.

Eddie, D., Bentley, K.H., Bernard, R., Yeung, A., Nyer, M., Pedrelli, P., Mischoulon, D., Winkelman, J.W., 2020. Major depressive disorder and insomnia: exploring a hypothesis of a common neurological basis using waking and sleep-derived heart rate variability. J. Psychiatr. Res. 123, 89–94. https://doi.org/10.1016/j.jpsychires.2020.01.015.

da Estrela, C., McGrath, J., Booij, L., Gouin, J.-P., Kalin, N.H., 2021. Heart rate variability, sleep quality, and depression in the context of chronic stress. Ann. Behav. Med. 55 (2), 155–164. https://doi.org/10.1093/abm/kaaa039.

Fang, H., Tu, S., Sheng, J., Shao, A., 2019. Depression in sleep disturbance: A review on a bidirectional relationship, mechanisms and treatment. J. Cell. Mol. Med. 23 (4), 2324–2332. https://doi.org/10.1111/jcmm.14170.

Fava, M., Alpert, J.E., Carmin, C.N., Wisniewski, S.R., Trivedi, M.H., Biggs, M.M., Shores-Wilson, K., Morgan, D., Schwartz, T., Balasubramani, G.K., John Rush, A., 2004. Clinical correlates and symptom patterns of anxious depression among patients with major depressive disorder in STAR*D. Psychol. Med. 34 (7), 1299–1308. https://doi.org/10.1017/S0033291704002612.

Felez-Nobrega, M., Haro, J.M., Koyanagi, A., 2022. Multimorbidity, depression with anxiety symptoms, and decrements in health in 47 low- and middle-income countries. J. Affect. Disord. 317, 176–184. https://doi.org/10.1016/j.jad.2022.08.110.

Fuller, D., Colwell, E., Low, J., Orychock, K., Tobin, M.A., Simango, B., Buote, R., Van Heerden, D., Luan, H., Cullen, K., Slade, L., Taylor, N.G.A., 2020. Reliability and validity of commercially available wearable devices for measuring steps, energy expenditure, and heart rate: systematic review. JMIR Mhealth Uhealth 8 (9), e18694. https://doi.org/10.2196/18694.

Gander, P.H., Paine, S.-J., 2016. Differences in circadian phase and weekday/weekend sleep patterns in a sample of middle-aged morning types and evening types. Chronobiol. Int. 33 (8), 1009–1017. https://doi.org/10.1080/07420528.2016.1192187.

Gaspersz, R., Nawijn, L., Lamers, F., Penninx, B.W.J.H., 2018. Patients with anxious depression. Curr. Opin. Psychiatry 31 (1), 17–25. https://doi.org/10.1097/YCO.0000000000000376.

Geoffroy, P.A., Hoertel, N., Etain, B., Bellivier, F., Delorme, R., Limosin, F., Peyre, H., 2018. Insomnia and hypersomnia in major depressive episode: prevalence, sociodemographic characteristics and psychiatric comorbidity in a population-based study. J. Affect. Disord. 226, 132–141. https://doi.org/10.1016/j.jad.2017.09.032.

Gili, M., Luciano, J.V., Bauzá, N., Aguado, J., Serrano, M.J., Armengol, S., Roca, M., 2011. Psychometric properties of the IDS-SR30 for the assessment of depressive symptoms in spanish population. BMC Med. Res. Methodol. 11 (1), 131. https://doi.org/10.1186/1471-2288-11-131.

Gordan, R., Gwathmey, J., Xie, L., 2015. Autonomic and endocrine control of cardiovascular function. World J. Cardiol. 7 (4), 204–214. https://doi.org/10.4330/wjc.v7.i4.204.

Haghayegh, S., Khoshnevis, S., Smolensky, M.H., Diller, K.R., 2019. Accuracy of PurePulse photoplethysmography technology of Fitbit charge 2 for assessment of heart rate during sleep. Chronobiol. Int. 36 (7), 927–933. https://doi.org/10.1080/07420528.2019.1596947.

Halaris, A., 2016. Inflammation-associated co-morbidity between depression and cardiovascular disease. In: Current Topics in Behavioral Neurosciences, vol. 31. Springer Verlag, pp. 45–70. https://doi.org/10.1007/7854_2016_28.

Harris, P.A., Taylor, R., Thielke, R., Payne, J., Gonzalez, N., Conde, J.G., 2009. Research electronic data capture (REDCap)-A metadata-driven methodology and workflow process for providing translational research informatics support. J. Biomed. Inform. 42 (2), 377–381. https://doi.org/10.1016/j.jbi.2008.08.010.

James, S.L., Abate, D., Abate, K.H., Abay, S.M., Abbafati, C., Abbasi, N., Abbastabar, H., Abd-Allah, F., Abdela, J., Abdelalim, A., Abdollahpour, I., Abdulkader, R.S., Abebe, Z., Abera, S.F., Abil, O.Z., Abraha, H.N., Abu-Raddad, L.J., Abu-Rmeileh, N. M.E., Accrombessi, M.M.K., Murray, C.J.L., 2018. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the global burden of disease study 2017. Lancet 392 (10159), 1789–1858. https://doi.org/10.1016/S0140-6736(18)32279-7.

Jansson-Fröjmark, M., Lindblom, K., 2008. A bidirectional relationship between anxiety and depression, and insomnia? A prospective study in the general population. J. Psychosom. Res. 64 (4), 443–449. https://doi.org/10.1016/j.jpsychores.2007.10.016.

Jordan, P., Shedden-Mora, M.C., Löwe, B., 2017. Psychometric analysis of the Generalized Anxiety Disorder scale (GAD-7) in primary care using modern item response theory. PloS One 12 (8), e0182162. https://doi.org/10.1371/journal.pone.0182162.

Kalin, N.H., 2020. The critical relationship between anxiety and depression. Am. J. Psychiatry 177 (5), 365–367. https://doi.org/10.1176/appi.ajp.2020.20030305.

Kaplan, K.A., McGlinchey, E.L., Soehner, A., Gershon, A., Talbot, L.S., Eidelman, P., Gruber, J., Harvey, A.G., 2015. Hypersomnia subtypes, sleep and relapse in bipolar disorder. Psychol. Med. 45 (8), 1751–1763. https://doi.org/10.1017/S0033291714002918.

Kemp, A.H., Quintana, D.S., Gray, M.A., Felmingham, K.L., Brown, K., Gatt, J.M., 2010. Impact of depression and antidepressant treatment on heart rate variability: A review and meta-analysis. Biol. Psychiatry. https://doi.org/10.1016/j.biopsych.2009.12.012.

Kessler, R.C., Sampson, N.A., Berglund, P., Gruber, M.J., Al-Hamzawi, A., Andrade, L., Bunting, B., Demyttenaere, K., Florescu, S., de Girolamo, G., Gureje, O., He, Y., Hu, C., Huang, Y., Karam, E., Kovess-Masfety, V., Lee, S., Levinson, D., Medina Mora, M.E., Wilcox, M.A., 2015. Anxious and non-anxious major depressive disorder in the World Health Organization world mental health surveys. Epidemiol. Psychiatr. Sci. 24 (3), 210–226. https://doi.org/10.1017/S2045796015000189.

Kim, H.-G., Cheon, E.-J., Bai, D.-S., Lee, Y.H., Koo, B.-H., 2018. Stress and heart rate variability: A meta-analysis and review of the literature. Psychiatry Investig. 15 (3), 235–245. https://doi.org/10.30773/pi.2017.08.17.

Koenig, J., Kemp, A.H., Beauchaine, T.P., Thayer, J.F., Kaess, M., 2016. Depression and resting state heart rate variability in children and adolescents - A systematic review and meta-analysis. Clin. Psychol. Rev. 46, 136–150. https://doi.org/10.1016/j.cpr.2016.04.013.

Kontaxis, S., Gil, E., Marozas, V., Lazaro, J., Garcia, E., Posadas-de Miguel, M., Siddi, S., Bernal, M.L., Aguilo, J., Haro, J.M., de la Camara, C., Laguna, P., Bailon, R., 2021. Photoplethysmographic waveform analysis for autonomic reactivity assessment in depression. I.E.E.E. Trans. Biomed. Eng. 68 (4), 1273–1281. https://doi.org/10.1109/TBME.2020.3025908.

Leistedt, S.J.-J., Linkowski, P., Lanquart, J.-P., Mietus, J.E., Davis, R.B., Goldberger, A.L., Costa, M.D., 2011. Decreased neuroautonomic complexity in men during an acute major depressive episode: analysis of heart rate dynamics. Transl. Psychiatry 1 (7), e27. https://doi.org/10.1038/tp.2011.23.

Lett, H.S., Blumenthal, J.A., Babyak, M.A., Sherwood, A., Strauman, T., Robins, C., Newman, M.F., 2004. Depression as a risk factor for coronary artery disease: Evidence, mechanisms, and treatment. In: Psychosomatic Medicine, Vol. 66, Issue 3. Lippincott Williams and Wilkins, pp. 305–315. https://doi.org/10.1097/01.psy.0000126207.43307.c0.

Liu, S., Han, J., Puyal, E.L., Kontaxis, S., Sun, S., Locatelli, P., Dineley, J., Pokorny, F.B., Costa, G.D., Leocani, L., Guerrero, A.I., Nos, C., Zabalza, A., Sørensen, P.S., Buron, M., Magyari, M., Ranjan, Y., Rashid, Z., Conde, P., Consortium, R. A. D. A. R. C. N. S, 2022. Fitbeat: COVID-19 estimation based on wristband heart rate using a contrastive convolutional auto-encoder. Pattern Recogn. 123, 108403. https://doi.org/10.1016/J.PATCOG.2021.108403.

Mason, B.L., Davidov, A., Minhajuddin, A., Trivedi, M.H., 2020. Focusing on insomnia symptoms to better understand depression: A STAR*D report. J. Affect. Disord. 260, 183–186. https://doi.org/10.1016/j.jad.2019.08.094.

Matcham, F., Di San, Barattieri, Pietro, C., Bulgari, V., De Girolamo, G., Dobson, R., Eriksson, H., Folarin, A.A., Haro, J.M., Kerz, M., Lamers, F., Li, Q., Manyakov, N.V., Mohr, D.C., Myin-Germeys, I., Narayan, V., Bwjh, P., Ranjan, Y., Rashid, Z., Rintala, A., Meyer, N., 2019. Remote assessment of disease and relapse in major depressive disorder (RADAR-MDD): A multi-Centre prospective cohort study protocol. In: BMC Psychiatry, vol. 19, Issue 1. BioMed Central Ltd. https://doi.org/10.1186/s12888-019-2049-z.

Matcham, F., Leightley, D., Siddi, S., Lamers, F., White, K.M., Annas, P., de Girolamo, G., Difrancesco, S., Haro, J.M., Horsfall, M., Ivan, A., Lavelle, G., Li, Q., Lombardini, F., Mohr, D.C., Narayan, V.A., Oetzmann, C., Penninx, B.W.J.H., Bruce, S., RADAR-CNS consortium., 2022. Remote assessment of disease and relapse in major depressive disorder (RADAR-MDD): recruitment, retention, and data availability in a longitudinal remote measurement study. BMC Psychiatry 22 (1), 136. https://doi.org/10.1186/s12888-022-03753-1.

Matcham, F., Carr, E., Meyer, N., White, K.M., Oetzmann, C., Leightley, D., Hotopf, M. W., 2023. Wearable-derived sleep features predict relapse in Major Depressive Disorder. https://doi.org/10.31234/osf.io/epftv.

Möller, H.-J., 2002. Anxiety associated with comorbid depression. J. Clin. Psychiatry 63 (Suppl. 1), 22–26. http://www.ncbi.nlm.nih.gov/pubmed/12562115.

Monroe, S.M., Simons, A.D., 1991. Diathesis-stress theories in the context of life stress research: implications for the depressive disorders. Psychol. Bull. 110 (3), 406–425. https://doi.org/10.1037/0033-2909.110.3.406.

Nabi, H., Kivimäki, M., Empana, J.-P., Sabia, S., Britton, A., Marmot, M.G., Shipley, M.J., Singh-Manoux, A., 2011. Combined effects of depressive symptoms and resting heart rate on mortality. J. Clin. Psychiatry 72 (09), 1199–1206. https://doi.org/10.4088/JCP.09m05901blu.

Nazari, G., Macdermid, J.C., Sinden, K.E., Richardson, J., Tang, A., 2019. Inter-instrument reliability and agreement of fitbit charge measurements of heart rate and activity at rest, during the modified Canadian aerobic fitness test, and in recovery. Physiother. Can. 71 (3), 197–206. https://doi.org/10.3138/ptc.2018-25.

Nelson, B.W., Allen, N.B., 2019. Accuracy of consumer wearable heart rate measurement during an ecologically valid 24-hour period: Intraindividual validation study. JMIR Mhealth Uhealth 7 (3), e10828. https://doi.org/10.2196/10828.

Nilsson, P.M., Nilsson, J.-Å., Hedblad, B., Berglund, G., 2001. Sleep disturbance in association with elevated pulse rate for prediction of mortality – consequences of mental strain? J. Intern. Med. 250 (6), 521–529. https://doi.org/10.1046/j.1365-2796.2001.00913.x.

Nutt, D., Wilson, S., Paterson, L., 2008. Sleep disorders as core symptoms of depression. Dialogues Clin. Neurosci. 10 (3), 329–336. https://doi.org/10.31887/DCNS.2008.10.3/dnutt.

Ottaviani, C., Shahabi, L., Tarvainen, M., Cook, I., Abrams, M., S. D., 2015. Cognitive, behavioral, and autonomic correlates of mind wandering and perseverative cognition in major depression. Front. https://doi.org/10.3389/fnins.2014.00433.

Pandi-Perumal, S.R., Monti, J.M., Burman, D., Karthikeyan, R., BaHammam, A.S., Spence, D.W., Brown, G.M., Narashimhan, M., 2020. Clarifying the role of sleep in depression: A narrative review. Psychiatry Res. 291, 113239. https://doi.org/10.1016/j.psychres.2020.113239.

Pawlowski, M.A., Gazea, M., Wollweber, B., Dresler, M., Holsboer, F., Keck, M.E., Steiger, A., Adamczyk, M., Mikoteit, T., 2017. Heart rate variability and cordance in rapid eye movement sleep as biomarkers of depression and treatment response. J. Psychiatr. Res. 92, 64–73. https://doi.org/10.1016/j.jpsychires.2017.03.026.

Perlis, M.L., Gehrman, P., 2013. Types of insomnia. In: Encyclopedia of Sleep. Elsevier, pp. 199–202. https://doi.org/10.1016/B978-0-12-378610-4.00175-3.

Polhemus, A.M., Novák, J., Ferrao, J., Simblett, S., Radaelli, M., Locatelli, P., Matcham, F., Kerz, M., Weyer, J., Burke, P., Huang, V., Dockendorf, M.F., Temesi, G., Wykes, T., Comi, G., Myin-Germeys, I., Folarin, A., Dobson, R., Manyakov, N.V., Hotopf, M., 2020. Human-centered design strategies for device selection in mHealth programs: development of a novel framework and case study. JMIR Mhealth Uhealth 8 (5), e16043. https://doi.org/10.2196/16043.

R Core Team, 2016. R Development Core Team. R: A Language and Environment for Statistical Computing. http://www.R-project.org.

R Core Team, 2023. R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna. https://www.R-project.org/.

Ranjan, Y., Rashid, Z., Stewart, C., Conde, P., Begale, M., Verbeeck, D., Boettcher, S., Hyve, Dobson, R., Folarin, A., RADAR-CNS Consortium, 2019. RADAR-base: open source Mobile health platform for collecting, monitoring, and analyzing data using sensors, wearables, and mobile devices. JMIR Mhealth Uhealth 7 (8), e11734. https://doi.org/10.2196/11734.

Rashid, S., Qureshi, A.G., Noor, T.A., Yaseen, K., Sheikh, M.A.A., Malik, M., Malik, J., 2023. Anxiety and depression in heart failure: an updated review. Curr. Probl. Cardiol. 48 (11), 101987. https://doi.org/10.1016/j.cpcardiol.2023.101987.

Reyes del Paso, G.A., Langewitz, W., Mulder, L.J.M., van Roon, A., Duschek, S., 2013. The utility of low frequency heart rate variability as an index of sympathetic cardiac tone: A review with emphasis on a reanalysis of previous studies. Psychophysiology 50 (5), 477–487. https://doi.org/10.1111/psyp.12027.

Rush, A.J., Carmody, T., Reimitz, P.-E., 2000. The inventory of depressive symptomatology (IDS): clinician (IDS-C) and self-report (IDS-SR) ratings of depressive symptoms. Int. J. Methods Psychiatr. Res. 9 (2), 45–59. https://doi.org/10.1002/mpr.79.

Rush, A.J., Trivedi, M.H., Ibrahim, H.M., Carmody, T.J., Arnow, B., Klein, D.N., Markowitz, J.C., Ninan, P.T., Kornstein, S., Manber, R., Thase, M.E., Kocsis, J.H., Keller, M.B., 2003. The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. Biol. Psychiatry 54 (5), 573–583.

Saad, M., Ray, L.B., Bujaki, B., Parvaresh, A., Palamarchuk, I., De Koninck, J., Douglass, A., Lee, E.K., Soucy, L.J., Fogel, S., Morin, C.M., Bastien, C., Merali, Z., Robillard, R., 2019. Using heart rate profiles during sleep as a biomarker of depression. BMC Psychiatry 19 (1), 168. https://doi.org/10.1186/s12888-019-2152-1.

Saad, M., Ray, L.B., Bradley-Garcia, M., Palamarchuk, I.S., Gholamrezaei, A., Douglass, A., Lee, E.K., Soucy, L., Robillard, R., 2020. Autonomic modulation of cardiac activity across levels of sleep depth in individuals with depression and sleep complaints. Psychosom. Med. 82 (2), 172–180. https://doi.org/10.1097/PSY.0000000000000766.

Sauvet, F., Leftheriotis, G., Gomez-Merino, D., Langrume, C., Drogou, C., Van Beers, P., Bourrilhon, C., Florence, G., Chennaoui, M., 2010. Effect of acute sleep deprivation on vascular function in healthy subjects. J. Appl. Physiol. 108 (1), 68–75. https://doi.org/10.1152/japplphysiol.00851.2009.

Sewerynek, E., 2002. Melatonin and the cardiovascular system. Neuro Endocrinol. Lett. 23 (Suppl. 1), 79–83. http://www.ncbi.nlm.nih.gov/pubmed/12019357.

Siddi, S., Bailon, R., Giné-Vázquez, I., Matcham, F., Lamers, F., Kontaxis, S., Laporta, E., Garcia, E., Lombardini, F., Annas, P., Hotopf, M., Penninx, B.W.J.H., Ivan, A., White, K.M., Difrancesco, S., Locatelli, P., Aguiló, J., Peñarrubia-Maria, M.T., Narayan, V.A., Haro, J.M., 2023. The usability of daytime and night-time heart rate dynamics as digital biomarkers of depression severity. Psychol. Med. 53 (8), 3249–3260. https://doi.org/10.1017/S0033291723001034.

Simblett, S., Matcham, F., Siddi, S., Bulgari, V., Barattieri di San Pietro, C., Hortas López, J., Ferrão, J., Polhemus, A., Haro, J.M., de Girolamo, G., Gamble, P., Eriksson, H., Hotopf, M., Wykes, T., RADAR-CNS Consortium, 2019. Barriers to and facilitators of engagement with mHealth Technology for Remote Measurement and Management of depression: qualitative analysis. JMIR Mhealth Uhealth 7 (1), e11325. https://doi.org/10.2196/11325.

Simblett, S., Matcham, F., Curtis, H., Greer, B., Polhemus, A., Novák, J., Ferrao, J., Gamble, P., Hotopf, M., Narayan, V., Wykes, T., 2020. Patients' measurement priorities for remote measurement technologies to aid chronic health conditions: qualitative analysis. JMIR Mhealth Uhealth 8 (6), e15086. https://doi.org/10.2196/15086.

Simko, F., Baka, T., Paulis, L., Reiter, R.J., 2016. Elevated heart rate and nondipping heart rate as potential targets for melatonin: a review. J. Pineal Res. 61 (2), 127–137. https://doi.org/10.1111/jpi.12348.

Spitzer, R.L., Kroenke, K., Williams, J.B.W., Löwe, B., 2006. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch. Intern. Med. https://doi.org/10.1001/archinte.166.10.1092.

Steimer, T., 2002. The biology of fear- and anxiety-related behaviors. Dialogues Clin. Neurosci. 4 (3), 231–249. https://doi.org/10.31887/DCNS.2002.4.3/tsteimer.

Stucky, B., Clark, I., Azza, Y., Karlen, W., Achermann, P., Kleim, B., Landolt, H.-P., 2021. Validation of Fitbit charge 2 sleep and heart rate estimates against polysomnographic measures in shift workers: naturalistic study. J. Med. Internet Res. 23 (10), e26476. https://doi.org/10.2196/26476.

Thayer, J.F., Åhs, F., Fredrikson, M., Sollers Iii, J.J., Wager, T.D., 2011. A meta-analysis of heart rate variability and neuroimaging studies: implications for heart rate variability as a marker of stress and health. Neurosci. Biobehav. Rev. 36, 747–756. https://doi.org/10.1016/j.neubiorev.2011.11.009.

Tiller, J.W.G., 2013. Depression and anxiety. Med. J. Aust. 199 (S6). https://doi.org/10.5694/mja12.10628.

Yang, A.C., Tsai, S.-J., Yang, C.-H., Kuo, C.-H., Chen, T.-J., Hong, C.-J., 2011. Reduced physiologic complexity is associated with poor sleep in patients with major depression and primary insomnia. J. Affect. Disord. 131 (1–3), 179–185. https://doi.org/10.1016/j.jad.2010.11.030.

de Zambotti, M., Baker, F.C., Willoughby, A.R., Godino, J.G., Wing, D., Patrick, K., Colrain, I.M., 2016. Measures of sleep and cardiac functioning during sleep using a multi-sensory commercially-available wristband in adolescents. Physiol. Behav. 158, 143–149. https://doi.org/10.1016/j.physbeh.2016.03.006.

Zhang, Y., Folarin, A.A., Sun, S., Cummins, N., Bendayan, R., Ranjan, Y., Rashid, Z., Conde, P., Stewart, C., Laiou, P., Matcham, F., White, K.M., Lamers, F., Siddi, S., Simblett, S., Myin-Germeys, I., Rintala, A., Wykes, T., Haro, J.M., Dobson, R.J., 2021. Relationship between major depression symptom severity and sleep collected using a wristband wearable device: multicenter longitudinal observational study. JMIR Mhealth Uhealth 9 (4), e24604. https://doi.org/10.2196/24604.

Zou, H., Zhou, H., Yan, R., Yao, Z., Lu, Q., 2022. Chronotype, circadian rhythm, and psychiatric disorders: recent evidence and potential mechanisms. Front. Neurosci. 16. https://doi.org/10.3389/fnins.2022.811771.