Journal of Affective Disorders 304 (2022) 93–101

Contents lists available at ScienceDirect

Journal of Affective Disorders

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

Associations between heart rate variability, peripheral inflammatory markers and major depressive disorder

Andreas Buchmann [a,b,c,*], Christopher Ritter [a,b,c], Sabrina Theresia Müller [a], Melanie Haynes [a], Carmen Ghisleni [c], Ruth Tuura [c], Gregor Hasler [b]

[a] Psychiatric University Hospital, University of Bern, Bolligenstrasse 111, 3000 Bern 60, Switzerland
[b] Unit of Psychiatry Research, University of Fribourg, Chemin du Cardinal-Journet 3, 1752 Villars-sur-Glâne, Fribourg, Switzerland
[c] Center of MR-Research, University Children's Hospital Zurich, Steinwiesstrasse 75, 8032 Zurich, Switzerland

ARTICLE INFO

keywords:
Depression
Vagus
Inflammation
Heartbeat variability
Respiratory sinus arrhythmia
Anxiety

ABSTRACT

Background: Measures for the irregularity of the heartbeat, for example respiratory sinus arrhythmia, have been implicated as a measure for restorative functions of the vegetative nervous system. Methods: In the current observational study, we investigated 265 subjects, 70 of whom had a lifetime history of major depression, with a plethysmographic heartbeat monitor, blood sampling, as well as a range of psychiatric questionnaires. Results: Subjects with a history of MDE had significantly reduced respiratory sinus arrhythmia (RSA) as compared to never-depressed controls; in the whole sample, higher RSA went with lower anxiety/fear variables, especially in subscores related to cardiac symptoms as well as being afraid of dying. A reduced RSA was also associated with an increased concentration of cytokines (TNFa, IL1a, IL6, IFNg) and thyroid-stimulating hormone in the serum, pointing to a possible triangular relationship between immune system, vegetative nervous system, and emotional dysregulation. Limitations: We used a plethysmographic device for the measurement of heartbeat instead of an electrocardiogram, and had a single time point only. Conclusions: This data corroborate the idea that a disequilibrium of the vegetative nervous, especially if accompanied by a dysregulation system in immune function, can increase the risk for depression. Conversely, vagal stimulation and anti-inflammatory treatments may support the treatment with antidepressants.

1. Introduction

Depression is a common illness that severely limits psychosocial functioning (Malhi and Mann, 2018); in 2008, WHO ranked major depression as the third cause of burden of disease worldwide (2004). Very often, depression is comorbid with anxiety (about 85% of patients with depression have significant anxiety, and 90% of patients with anxiety disorder have depression) (Tiller, 2013).

The search for biomarkers of depression has proven difficult (Kennis et al., 2020), partly because there may be subtypes that vary in these biomarkers (as exemplified by cortisol levels after challenge (Juruena et al., 2018)).

One area where biomarkers have been investigated extensively is the autonomic nervous system and its impact on emotion regulation and dysregulation, for example in the model of neurovisceral integration (Thayer and Lane, 2000) and the polyvagal theory (Porges, 2001). One promising biomarker for vagal dysregulation is low heart rate variability (HRV) (Thayer and Lane, 2009). Indeed a large study using two different indicators for heart rate variability showed reduced heart rate variability in both current and remitted depressed as compared to non-depressed controls, which depended strongly on the use of psychoactive medication (Licht et al., 2008). In a meta-analysis on the impact of depression and antidepressant medication on HRV, depressed participants had lower HRV than non-depressed controls, and there was also a depression-severity effect in that more severely depressed had a more strongly reduced HRV (Kemp et al., 2010). In the same meta-analysis, tricyclic medication reduced HRV, whereas SSRIs, mirtazapine and nefazodone did not (see also (Kidwell and Ellenbroek, 2018)).

Several markers of HRV have been implicated as biomarkers for psychopathology, using time or frequency domain analyses (Sgoifo et al., 2015), and indices such as the root mean sum of successive differences (RMSSD) (Jarczok et al., 2018; Koenig et al., 2018), standard deviation of normalized cardiac interbeat intervals (SDNN) (Karavidas

* Corresponding author.
E-mail address: Andreas.Buchmann@kispi.uzh.ch (A. Buchmann).

https://doi.org/10.1016/j.jad.2022.02.017
Received 23 June 2021; Received in revised form 31 December 2021; Accepted 9 February 2022
Available online 20 February 2022

et al., 2007; Licht et al., 2008), the high-frequency component of heart rate variability (HF-HRV) (Beauchaine and Thayer, 2015; Gruber et al., 2015; Koenig et al., 2016), or similarly, respiratory sinus arrhythmia (RSA) (Porges, 1995; Tonhajzerova et al., 2009). While these indicators are all facets of heart rate variability, it is possible that they tap slightly different aspects of autonomic involvement in emotion regulation.

For RSA, it has been implicated as a transdiagnostic biomarker for emotion dysregulation, because it has been found altered in many internalizing and externalizing psychiatric conditions, and it is supposed to reflect prefrontal activity, presumably of the same regions involved in emotion regulation (Beauchaine, 2015). In addition, because it can be quantified in a time frame of roughly 30 s, it can be used for biofeedback and experimental stress studies ('RSA reactivity'). Pharmacological blockade of cholinergic inputs reduces RSA (Coker et al., 1984), and RSA can be influenced by neck suction devices that influence the baroreceptor (Piepoli et al., 1997). Note that historically, RSA has been operationalised and measured in different ways (just as standard deviation of the RR-intervals, or as power in the HF band) (Beauchaine, 2015). RSA has been shown to increase significantly during propofol anaesthesia, and has even be proposed as an indicator to regulate automated propofol application in anaesthesia (Pomfrett et al., 1993).

Many studies highlight relationships between RSA/HF-HRV and various aspects of depression. One study showed that lower resting RSA in the first year of the study predicted depressive symptoms as assessed using the BDI in the second year of the study, even if controlling for state anxiety, body mass index, and medication use (Yaptangco et al., 2015). One paper involving two study samples showed that atypical RSA is an endophenotype of depression, in that atypical RSA patterns predicted current depressive episodes and remission status, were concordant across mothers and their juvenile offspring, and were more prevalent in siblings of depressed than in siblings of never-depressed (Yaroslavsky et al., 2014). One study found that RSA fluctuation was more stably found in depressed as compared to controls than baseline RSA, whereas the latter did not survive correction for health or respiration (Rottenberg et al., 2007). A review found a lower fluctuation in heart rate and heart rate variability in MDD subjects than in controls in well-established stress tasks (Schiweck et al., 2019). For cognition, one study found that low RSA went with longer reaction times in a number-letter switching task (Hoffmann et al., 2017). One study reports a relationship between HF-HRV and anger in a stressful computer task, in that actual anger was uncorrelated with HF-HRV, but low HF-HRV went with a higher persistence of anger (Ellis et al., 2016). In addition, several papers have implicated RSA or HF-HRV in suicidality (e.g. (Tsypes et al., 2018)). In a study of RSA reactivity after stress, RSA reduction was observed both in MDD and non-depressed control subjects in a rumination condition, but for the depressed also in a cognitive distraction condition, which the authors interpret in terms of greater cognitive effort (LeMoult et al., 2016).

In addition to the direct relationship between heart rate variability measures and depression, there may also be bidirectional relationships of each with inflammation (Huston and Tracey, 2011). For example, in a paced respiration study in healthy human adults whose immune systems were challenged with lipopolysaccharide, which induces depression-like behaviors in rodents, higher HRV (high frequency HRV) went with a lower production of IL-6 and TNFalpha (from now on TNFa), whereas the anti-inflammatory cytokine IL-10 was not affected (Marsland et al., 2007a). In patients with hypertension, greater HRV (high-frequency power, baroreflex sensitivity, and RR interval) induced by heart rate biofeedback training went with lower high-sensitivity C-reactive protein concentration in the blood, a marker for inflammatory activity (Nolan et al., 2012). In human macrophage cultures, acetylcholine significantly attenuated the release of pro-inflammatory cytokines (TNF, IL-1beta, IL-6 and IL-18) upon endotoxin challenge; in rats, electrical stimulation of the vagus nerve reduced TNF production in the liver, attenuated TNF in the serum, and prevented the development of shock in endotoxemia (Borovikova et al., 2000). In depressed patients, high-sensitivity C-reactive protein was positively correlated with a lifetime history of suicidal ideation, which was negatively associated with total, low frequency and high frequency HRV (Chang et al., 2017).

In the present study, our main hypothesis was that human subjects with an actual or past depressive episode have a reduced RSA. Secondary research questions were: A) Does RSA explain more variability in internalizing psychiatric symptoms than other measures of heart rate variability, for example the standard deviation of the heart beat interval or root mean square of the successive differences (RMSSD)? B) Is RSA related to specific depressive and anxiety symptoms? and C) Do inter-individual differences in RSA relate to other biomarkers in depression, particularly immune and metabolic markers that have been related to neurovisceral integration (e.g. TNFa, IL1a, IL6, IFNg and thyroid stimulating hormone TSH)?

2. Methods

The ethics committee of the Kanton Zurich approved for all procedures undertaken in the course of the study, and subjects gave written informed consent according to the declaration of Helsinki.

2.1. Subjects

The sample consisted of a group of 296 young adults recruited from the general population via newspaper advertisements or university blackboard webpages. We included psychiatrically healthy or depressed adults between 18 and 40 years of age, right-handed, fulfilling the safety criteria for MRI; we did not include subjects with schizophrenia or subjects who had a first-degree relative with schizophrenia, subjects with drug abuse during the last year, with suicidal plans in the last eight weeks, or subjects with neurological or other medical disorders (such as asthma, diabetes, heart disease); women had to present a negative pregnancy test immediately before MR scans (requirement of the Ethics Commission). Of the 296 participants assessed in the MRI session, two were excluded for mild abnormalities in the structural MRI and one for extrasystoles; of the remaining 294 subjects, 28 were excluded for artefacts in the heartbeat signal, resulting in a dataset of 265 subjects, 70 of whom had a past or present MDE (Major Depressive Episode). Out of the 70 MDE subjects, only seven had taken medication in the past 90 days, in one case thyroid hormones, the other six antidepressants.

Among these 265 subjects, breathing (and consequently RSA) data were excluded in six subjects whose breathing signal did not show a sinusoidal cycling pattern, or artefacts in the heartbeat signal during five or more percent of the time. The relative number of depressed participants was comparable between the excluded subjects (12 out of 31) and included subjects (70 out of 265; chisquare = 2.095, df = 1, p =.148). Further comparison between included and excluded subjects showed only a difference for body mass index (BMI; Students t-test p =.016, with a lower mean for the excluded than for the included subjects) and a nonsignificant trend for neuroticism (t-test p =.067, with a tendency towards higher values in excluded than in included subjects); no differences were found for age, years of education, as well as depression measures (BDI, MADRS, HAMD) or further anxiety measures (BAI, STAI state; see 'procedure' below for the full name of the psychiatric indices).

2.2. Procedure

Subjects filled out an online questionnaire before the study visit, namely ASI (Taylor and Cox, 1998), SKID (German version of SCID; see below), NeoFFI (McCrae and Costa, 1987), STAI trait version (Patterson et al., 1980)), and Aggression questionnaire (AQ) (Buss and Perry, 1992); during the study visit, more questionnaire data (STAI state, BDI (Beck et al., 1961), State-Trait-Anger-Expression Inventory (STAXI) (Spielberger et al., 1995), BAI (Beck et al., 1988), MADRS (Montgomery and Asberg, 1979), HAMD (Hamilton, 1960), PSS (Cohen et al., 1983), PANAS (Crawford and Henry, 2004), PTQ (Ehring et al., 2011)), Mind

Wandering Questionnaire (MWQ) (Mrazek et al., 2013), and blood samples were collected. Subsequently, participants underwent an one hour MR scanning session during which heart and breathing activity were monitored; breathing and heart data were stored only during functional MRI sessions, and evaluated only for the longer resting-state fMRI session (looking at a fixation cross for 601 s). After the scanning session participants were tested with two economic games and an odd-ball reaction time task.

MDE (present and past) diagnoses were posed by a trained clinical psychologist based on the SKID (Wittchen et al., 1997), the German version of SCID (First et al., 1997). We were aware that MDE diagnoses would overlap greatly with other psychiatric diagnoses, especially lifetime presence of any anxiety disorder (specific phobia, social phobia, panic disorder, generalized anxiety disorder, posttraumatic stress disorder; in MDE subjects, 45 out of 70 fulfilled a diagnosis of an anxiety disorder, in non-MDE 20 out of 190; chisquare = 78.85, df = 1, p =.001), for specific phobias (in MDE subjects, 22 out of 70 fulfilled a specific phobia, in non-MDE 14 out of 190; chisquare = 24.82, df = 1, p =.001), but also for obsessive-compulsive disorder (in MDE subjects, 15 out of 70 fulfilled an OCD diagnosis, in non-MDE 1 out of 190; chisquare = 38.70, df = 1, p =.001), MDE diagnosis overlapped with anxiety-related diagnoses.

2.3. Data evaluation

2.3.1. Heartbeat and breathing measurements

For the breathing and respiratory sinus arrhythmia calculations, the first 100 artefact-free inter-beat intervals collected during resting-state fMRI were used for each subject. The breathing signal was aligned to the heartbeat signal, and the R-peaks were timed and inter-peak intervals were calculated. Then offsets from the average inter-beat intervals were calculated. In the breathing signal, breathe-in intervals were separated from breathe-out signals, according to the relative maxima/ minima of the filling of the belt. For the maxima, if two peaks of equal height existed before the signal decreased by at least 250 units (maximum regulated to 3000 units), the second was taken as the cut-off point; if three peaks of equal height existed, the middle one was taken. Offsets from the average inter-beat-interval were summed for all peaks that ended in breathe-in intervals and for all peaks that ended in breathe-out intervals, and total RSA (in milliseconds) was defined as summed deviations from the mean in breathe-out periods minus summed deviations from the mean in breathe-in periods. In addition, relative RSA values (divided by the individual average RR-intervals) were calculated. Out of the 259 subjects with RSA measurements, only 7 had negative RSA values.

As a specificity check for RSA relative to other measures of heart rate variability, we also calculated RMSSD, alpha1 and SD ratio (Tarvainen et al., 2014), based on the full 10-minute dataset.

2.3.2. Blood sampling and evaluation

Venous blood sampling was done by a trained medical-technical assistant roughly 20 min before the MR session started, in the afternoon (2.p.m., SD 1.1 h). Blood samples were centrifuged 60 (plus/minus 15) minutes after collection; cortisol and DHEA were measured immediately after that, and aliquots were frozen and stored at −80 °C for further analysis. Plasma cytokines/ chemokines (CRP, IFNg, IL1, IL6, TNFa) were measured using a multiplex assay using a commercially available human cytokine/ chemokine magnetic bead panel (MILLIPLEX MAP, HCYTMAG-60K-PX41) as per the manufacturer's instructions on Luminex-200 multiplex immunoassay system. Data were analyzed using Milliplex Analyst 5.1 software (EMD Millipore, Billerica, Massachusetts). Blood samples were assayed in duplicate; the Pearson correlation between the concentration values derived from each plate was 0.989 for CRP, 0.901 for TSH, 0.883 for IL1a, 0.988 for IL1b, 0.878 for IL6, and 0.855 for TNFa.

2.4. Statistics

Statistical analyses were performed with IBM SPSS 24/ 27, the mediation analysis with R studio (see below). For the evaluation of our main hypothesis, the relationship between depression status and RSA, we used simple Anovas/ Student's t-tests; for the more exploratory analyses, we used Pearson correlations, partial correlations as well as AnCovas and chisquare tests, because the data scaling and approximately Gaussian distribution of the data allowed the use of these parametric tests. ICAs (with VARIMAX rotation) were used mainly to find out how many independent dimensions explained a set of measured variables. The main hypothesis could be answered with one t-test; for exploratory analyses involving many more variables, we did not correct for multiple comparisons, for two reasons: In the event of a significant main result, we wanted to explore possible candidate mechanisms for further studies; second, the psychiatric variables were highly correlated, so they can be considered as nuances of the same large concept ('internalizing psychiatric symptoms'). The results from these 'exploratory analyses' should therefore be considered with caution until they can be replicated with at least one independent sample. The mediation analysis was calculated with the sem package for RStudio (version 1.3.1093).

3. Results

3.1. Depression and RSA

Demographics and sample description of the subjects is given in Table 1. Subjects with lifetime MDD ('MDE subjects') had a highly significantly reduced respiratory sinus arrhythmia as compared to nondepressed controls ('non-MDE subjects', see Fig.1; Table 2a). As can be seen in Table 2a, this difference was relatively specific for RSA and

Table 1
a: Demographics, for whole sample and non-MDE/ MDE subjects p-values according to Students t-tests a), Mann-Whitney U-tests b) resp. Chisquare tests c) b: Descriptives, for whole sample and non-MDE/ MDE subjects p-values according to Students t-tests.

	all	non-MDE	MDE	p
n (%)	265	195 (73.6)	70 (26.4)	
female sex (%)	166 (62.6)	118 (60.5)	48 (68.6)	.146 c
age [y] (M, (SD))	24.7 (4.6)	24.1 (4.0)	26.4 (5.6)	.001 a
education [y] (M, (SD))	13.9 (2.8)	14.0 (2.7)	13.7 (3.1)	.391 a
self-estimated social status (M, (SD))	5.79 (1.60)	6.09 (1.38)	5.06 (1.85)	.001 b
parents' income, categorized (M, (SD))	2.67 (2.33)	2.67 (2.36)	2.65 (2.25)	.964 b
BMI (M, SD)	22.3 (3.0)	22.2 (2.6)	22.7 (3.8)	.228 a
	all	non-MDE	MDE	p
n (%)	265	195 (73.6)	70 (26.4)	
BDI (M, SD)	4.76 (7.00)	2.11 (3.09)	12.38 (9.13)	.001
neuroticism (M, SD)	19.0 (8.8)	15.8 (6.5)	27.7 (8.3)	.001
TSH (M, (SD))	207 (113)	210 (108)	196 (133)	.547
IL-6 (M, (SD))	37.6 (28.5)	37.2 (27.3)	39.3 (33.5)	.714
TNFa (M, (SD))	51.8 (16.4)	51.6 (13.7)	52.7 (24.4)	.743
cortisol in peripheral blood, afternoon [nmol/l] (M, SD)	317 (157)	314 (118)	319 (177)	.917

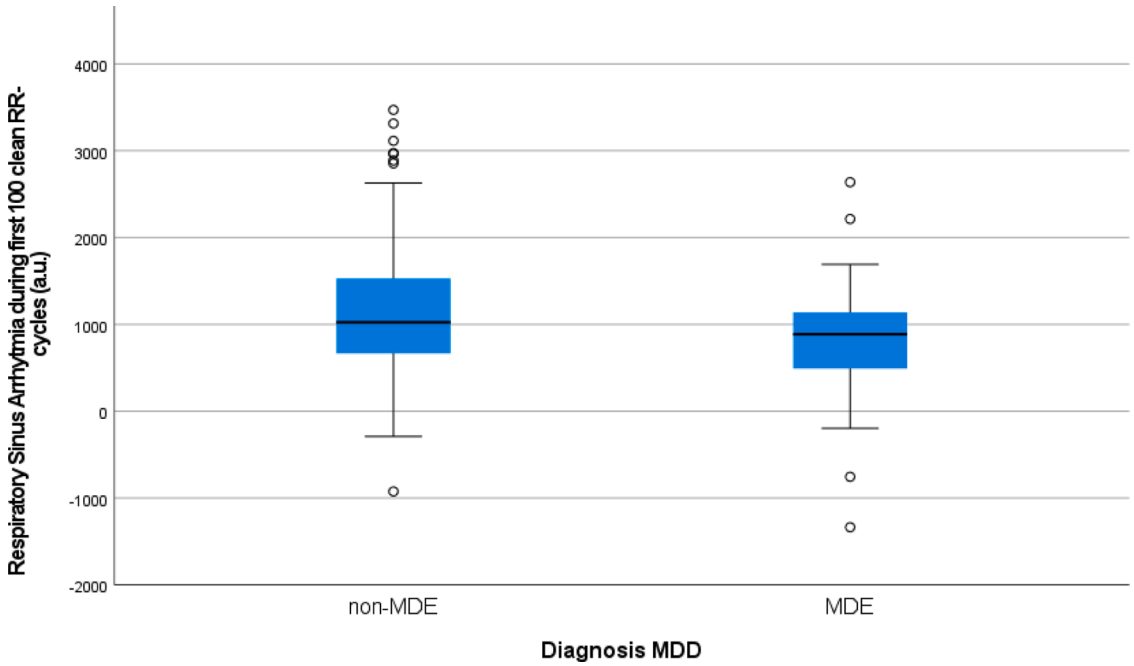

Fig. 1. Relationship between lifetime MDD diagnosis (never-MDE versus actual or past MDE) and Respiratory Sinus Arrhythmia (RSA, measured as half the difference between the summed lags during breathin periods minus the summed lags during breathout periods across the first 100 artefact-free RR-cycles (the single lags are measured in milliseconds) collected during the resting-state scan (fixation, eyes open)).

Table 2a
measures of heart rate variability in subjects with no past or present major depressive episode ('no MDE') or with past or present majore depressive episode ('MDE').

	non-MDE	MDE	eta-squared	p
n	195	70		
average respiration interval (ms) [M(SEM)]	3640(50)	3860(90)	.019	.028
heartbeat variability (SD) [M (SEM)]	72.1(2.2)	69.1(4.1)	.000	.502
mean RR-interval [M(SEM)]	967(10)	953(22)	.002	.518
SD RR-interval [M(SEM)]	54.2(2.1)	50.1(3.1)	.004	.309
RMSSD [M(SEM)]	62.9(2.9)	58.2(4.3)	.003	.388
alpha1 [M(SEM)]	0.859 (0.018)	0.864 (0.034)	.009	.881
SD ratio (high-freq/low-freq) [M(SEM)]	1.51(0.03)	1.58(0.07)	.004	.287
RSA [M(SEM)]	1130(50)	816(75)	.041	.001

Table 2b
measures of heart rate variability in subjects with past (but not actual) major depressive episode ('past MDE') versus subjects with an actual major depressive episode ('actual MDE').

	past MDE	actual MDE	eta-squared	p
n	54	16		
average respiration interval (ms) [M(SEM)]	3870(110)	3810(180)	.001	.770
heartbeat variability (SD) [M (SEM)]	72.6(5.0)	57.7(5.4)	.035	.123
mean RR-interval [M(SEM)]	944(22)	942(45)	.001	.980
SD RR-interval [M(SEM)]	54.1(3.8)	36.9(3.3)	.079	.020
RMSSD [M(SEM)]	61.6(5.1)	42.2(4.9)	.056	.051
alpha1 [M(SEM)]	0.866 (0.040)	0.893 (0.060)	.002	.737
SD ratio (high-freq/low-freq) [M(SEM)]	1.59(0.08)	1.53(0.12)	.003	.675
RSA [M(SEM)]	881(87)	599(143)	.037	.114

could not be seen in other indicators of heart rate variability. We also conducted AnCovas controlling in turn for age, BMI, the average breathing intervals (which was longer in subjects than in non-MDD controls, see Table2a) or the standard deviation of the lengths of 100 inter-beat intervals, but the result remained significant (data not shown). In a subgroup analysis investigating differences in RSA between MDE subjects with and without a current major depressive episode, no significant difference in RSA was evident, but participants with current MDE showed lower variability in the interbeat interval (SD RR-interval and RMSSD; see Table 2b).

3.2. Correlates of psychiatric indices

To elucidate the specificity of this main finding, we correlated RSA with psychopathological features associated with MDE (which were often highly correlated with each other) and found negative associations between RSA and measures of anxiety (Anxiety Sensitivity Index (ASI), Beck's Anxiety Inventory (BAI), state version of the State Trait Anxiety Inventory (STAI state)), introversion and perseverative thinking (PTQ, especially the subindex 'mental capacity captured') (Table 3). We also

Table 3
Pearson correlations of respiratory sinus arrhythmia (RSA) with age and various psychiatric scores.

	all	males	females
age	**-0.245**	n.s.	**-0.308**
anxiety sensitivity (ASI)	-0.191	**-0.279**	-0.166
neuroticism NeoFFI	-0.152	n.s.	-0.201
extraversion NeoFFI	**0.181**	**0.268**	n.s.
MADRS depression score	-0.139	n.s.	n.s.
HAMD depression score	-0.137	(−0.212)	n.s.
state anxiety (STAI state)	**-0.204**	**-0.239**	-0.187
BDI depression score	-0.138	(−0.181)	n.s.
BAI anxiety score	**-0.222**	-0.240	**-0.245**
PTQ sum score	-0.149	-0.298	n.s.
PTQ mental capacity captured score	**-0.222**	**-0.361**	n.s.

$p<.05$; **bold**: $p<.01$; (in brackets: $0.05<p<.10$).

looked for physiological correlates that could further elucidate the finding and found relationships of RSA with several pro-inflammatory proteins in the serum (IL1, IL6, IFNg, TNFa) as well as TSH (Table 4). TNFa was strongly correlated with TSH ($r = 0.402$, $p = 0.001$). Given the theoretically tight relationship between cytokines on the one hand and TSH on the other, we conducted partial correlation analyses to estimate which factor is more able to reduce the correlation of the other with RSA; for TSH and IL-6, they were almost identical in reducing the correlation of the effect size of the other with RSA, whereas for TSH and TNFa, TNFa was slightly stronger (reduction in the correlation TSH-RSA 0.080; TSH as control variable for TNFa-RSA just 0.061).

3.3. Reliability and specificity checks

We tested the reliability of the RSA measurements in a random selection of $n = 30$ subjects, in which we used 100 RR-cycles in the middle of the 10min-sequence (versus at the beginning); the Pearson correlation between the two RSA measurements in these 30 subjects was $r = 0.835$, p=.001.

Taking out the 7 medicated subjects did not change the result pattern (data not shown).

To evaluate the specificity of HRV abnormalities with MDD, we compared MDD with anxiety disorders. For specific phobias, there were a reasonable number (14) of cases without depression for comparison. In a 2 × 2 Anova with depression diagnosis and specific phobia (both lifetime) as independent factors, MDD was significant ($p = 0.016$, eta-square=0.023), whereas specific phobiae were not ($p = 0.278$, eta-square=0.005).

In an item-wise analysis, we used an ICA to order all subitems of STAI state, BAI and ASI and extracted five factors ('not being joyful'; 'cardiac symptoms'; 'trembling and being afraid of death'; 'afraid of losing mind' and 'short breath or nausea in public') of which two ('trembling and being afraid of dying' and 'cardiac symptoms') were significantly correlated with RSA.

Among the subitems of the ASI, low RSA was correlated with being afraid of catastrophic processes inside the body (including the heart), rather than being afraid of socially painful situations (Table 5).

In an explorative analysis, we also tested the relationship between emotion dysregulation and RSA in 4 selected items of the SCID, 4 selected items of STAI trait, STAXI and the subscores of the aggression questionnaire and found significant group differences in subjects. For the SCID, item 36 'constantly worrying' was highly significant (not constantly worrying subjects mean RSA 1135(SEM51, $n = 183$), constantly worrying subjects mean RSA 834(72, 76); item 28 'often in a bad mood, quarreling' was also significant (p=.039), whereas items 45 ('not forgetting other's lapses') and 46 ('unforgiving') were not. Pearson correlation with the STAXI total score was significant (r=−.170, p=.006, $n = 259$), and the subscore correlating highest was hostility (r=−.124, p=.046, $n = 259$). For the four selected STAI trait items, all were correlated with RSA, in the order of the effect size item 11 ('I'm inclined to take things hard', r=−.190, p=.002, $n = 259$), 18 ('I take disappointments so keenly that I cannot put them out of my mind', r=−.182, p=.003, $n = 259$), 8 ('I feel that difficulties are piling up so that I can not overcome them', r=−.163, p=.009, $n = 259$), and 20 ('I get in a state of tension or turmoil as I think over my recent concerns and interests', r=−.152, p=.014, $n = 259$).

Table 4
ASI (anxiety sensitivity index) subitems correlating strongly or weakly with RSA (in backtranslation from the German version).

	all	male	female
TSH concentration serum [pg/ml]	**-0.219**	-0.293	n.s.
IFNg concentration serum [pg/ml]	-0.167	**-0.423**	n.s.
IL1a concentration serum [pg/ml]	-0.189	(−.276)	n.s.
IL6 concentration serum [pg/ml]	**-0.226**	-0.305	n.s.
TNFa concentration serum [pg/ml]	**-0.238**	**-0.416**	n.s.

p<.05; **bold**: p<.01; (in brackets: 0.05<p<.10).

Table 5
ASI (anxiety sensitivity index) subitems correlating strongly or weakly with RSA (in backtranslation from the German version).

item number	description	r	p
strongly correlating			
ASI29	"when I feel dizzy, I worry there is something wrong with my brain"	-0.231	0.001
ASI5	"it scares me when my heart beats rapidly."	-0.212	0.001
ASI34	"if I have difficulty thinking clearly, I'm afraid that something is wrong with me"	-0.184	0.003
ASI36	"if I'm feeling a void in my head, I worry that something is not right with me"	-0.174	0.005
weakly correlating			
ASI17	"I'm often feeling tense and nervous"	-0.051	0.418
ASI20	"I'm rarely feeling lonely or sad"	0.018	0.769
ASI24	"I'm rarely sad or down"	-0.017	0.788
ASI30	"in stressful situations, sometimes I'm feeling as if having a breakdown"	-0.041	0.515

3.4. Testing whether cytokines mediate the RSA-Psychiatric outcome association

We conducted a mediation analysis in R. Introducing cytokine concentrations in the serum reduced the betas for the direct paths from RSA to ASI, STAI trait and BDI (from −0.19 to −0.15/−0.14 in the case of ASI as outcome variable, from −0.20 to −0.13/−0.11 in the case of STAI, from −0.14 to −0.11/−0.12 trait for IL6/ TNFa). None of the indirect effects (via cytokines) did not turn out to be significant (p>.2), and indirect effects were always numerically smaller than direct effects (RSA-psychiatric index).

On reviewer's request, we compared the effect sizes of the Pearson correlations between RSA and cytokine concentrations in the serum and found that numerically, the effect sizes were always larger in the MDE subjects than in the non-MDE subjects (in IL1a, the correlation reached significance in MDE, but not in non-MDE).

4. Discussion

The main finding of the present study is that MDE was associated with reduced respiratory sinus arrhythmia (Fig. 1, Table2a). Of note, this association was independent of the presence of an acute major depressive episode at the time of the scan. However, acute depression was related to reduction of other measures of heart rate variability (Table 2b). Earlier studies already showed a link between depression and reduced heart rate variability, and that antidepressants can influence heart rate variability (Kemp et al., 2010). Our study corroborates the view that reduced heart rate variability can be found in subjects with at least one lifetime depressive episode; with our sample of overwhelmingly unmedicated subjects (except $n = 7$, and excluding the medicated subjects did not have any influence on the pattern of results). However, given the small number of medicated subjects we are not able to assess whether medication influences heart rate variability.

In an exploratory analysis of the relationships between psychiatric indices and RSA, RSA was associated with a wide range of mood and anxiety symptoms (Table3). Our item-wise analyses pointed to a relatively specific dominance of heart symptoms (also in contrast to breathing symptoms) and being afraid of dying in subjects with low RSA. As a specificity check, we compared the RSA of non-MDE and MDE cases with or without specific phobias and found a significant result only for MDE, but not for specific phobia status, providing further evidence for a relatively specific link between MDE and RSA (see also (Licht et al., 2008)). Similarly, we did not find a difference between subjects with traumatic memories (39%) and subjects without traumatic memories in

RSA (data not shown).

According to a review paper (Berk et al., 2013), depression is associated with a chronic, low-grade inflammatory response and activation of cell-mediated immunity, as well as activation of the compensatory anti-inflammatory reflex system. This can be seen in the blood increases of the cytokines IL-6, TNF, and CRP (Dowlati et al., 2010), prostaglandine E2 (Nishino et al., 1989). Inflammation seems to increase serotonin turnover (Godbout et al., 2008; Janssen et al., 2010).A possible pathophysiological process is that cytokines from the innate immune system reach the brain by crossing the blood-brain barrier, activating microglia, which can disrupt the plasticity and development of nerve cells (Weber et al., 2017). Note that two possible PET tracers for neuroinflammatory processes are being tested (Berdyyeva et al., 2019; Setiawan et al., 2015). Conversely, parasympathetic and cholinergic influences seem to inhibit inflammation in depression (Borovikova et al., 2000; Halaris, 2013). At least some antidepressants seem to normalize cytokines in the blood (Janssen et al., 2010; Kubera et al., 2001), and anti-inflammatory agents have been tried to treat depression (Husain et al., 2017; Kohler et al., 2014; Muller et al., 2006). Interestingly, ECT seems to have a pro-inflammatory effect (Beurel et al., 2020).

In our study, lower RSA correlated with increased inflammation-related cytokines (most strongly TNFa, but also IL-6, IL1a and IFNg; not with CRP). Relationships between heart rate variability and cytokines have been reported earlier in patients with a broad range of diseases such as those with heart failure (Malave et al., 2003; Nikolic et al., 2013), obesity and diabetes (Parish et al., 2016; Wegeberg et al., 2020), obstructive sleep apnea (Xie et al., 2020), infants with hypoxic ischemic encephalopathy (Al-Shargabi et al., 2017; Yasova Barbeau et al., 2019), in traumatic brain injury (Deepika et al., 2018), to name just a few, and in larger samples of healthy subjects (Cooper et al., 2015; Lampert et al., 2008; von Kanel et al., 2008). Note that all papers cited demonstrated a low-HRV-associated-with-high-cytokines relationship, although not always using the same measures for HRV/cytokines, but according to a recent meta-analysis, SDNN and HF-HRV should show the largest effect sizes (Williams et al., 2019). An experimental study in rats showed a decrease in heart rate and temperature going with a peak in TNFa, followed by a longer reaction with reduced HRV and increased levels of other cytokines, including IL-6, after receiving a bacterial endotoxin (Fairchild et al., 2009). Human studies with low-dose endotoxin also found increases in TNFa and IL-6 and reductions in HRV (Herlitz et al., 2015; Koeneman et al., 2021; Marsland et al., 2007b). Interestingly, studies in arthritic patients showed that an implantable vagus nerve stimulator was able to reduce TNF and IL-6 (Koopman et al., 2017), and that patients with low HRV profited less from anti-TNFa therapy (Holman and Ng, 2008). In addition, at least one paper on a genetic polymorphism in humans demonstrates that a common proinflammatory polymorphism in the IL-6 promoter reduces heart rate variability in subjects older than 50 years, along with a higher sensitivity to air-pollution on HRV, which the authors interpret in terms of an influence of inflammation on HRV (Adam et al., 2014). Note that this discussion is also relevant for the reported relationship between depression and coronary heart disease (Halaris, 2013). Theoretical and review papers highlight the influence of the cholinergic anti-inflammatory pathway, based on the observation that macrophages can be deactivated by cholinergic inputs from the vagus nerve (Borovikova et al., 2000; Huston and Tracey, 2011; Pavlov and Tracey, 2005; Tracey, 2002), but could also noradrenergic influences (Fitzgerald, 2020).

Another factor strongly correlating with RSA was TSH in the serum (note that this was strongly correlated with cytokine concentration, especially TNFa). This finding was not based on a hypothesis and needs replication in future studies; here we are not able to give an in-depth discussion on possible pathophysiological mechanisms.

So far, few studies collected data about depressed mood, immune activation and measures of heart rate variability in the same subjects; as a notable exception, one study in older subjects found higher CRP and IL-6 as well as lower heart rate variability (SDNN, SDANN, RMSSD) in depressed than in nondepressed subjects, along with higher cardiovascular risk factors (higher cholesterol and reduced flow-mediated dilation) (Pizzi et al., 2008). Beyond replicating these relationships in a single sample, our study also indicates that RSA, despite the critique for its age dependency in the literature, may be a more specific trait marker for the diathesis of internalizing psychiatric disorders than other measures of heart rate variability, whereas other measures (e.g. standard deviation of the RR-intervals) may be better indicators for acute depressive episodes.

As a next step, it would be important to collect longitudinal data to investigate potential intraindividual variability in RSA, whether it reflects changes in psychiatric symptoms, and whether they precede or follow changes in internalizing psychiatric symptomology. The relationship between depression and inflammation seems to have trait-like aspects, as exemplified by genetic studies involving cytokines and monocyte chemoattractant protein-1 (Barnes et al., 2017), but also state-like aspects, as demonstrated in a psycho-social stress study (Fagundes et al., 2013).

Our data are consistent with earlier theories that a dysregulated vegetative nervous system, especially if combined with chronic activation of the immune system, may increase the risk for depressive episodes. As discussed in the literature, this may apply especially to a subgroup of depressed participants (Lopresti et al., 2014; Lotrich, 2015); specifically those with a poor response to antidepressant medication (Lanquillon et al., 2000), reversed vegetative symptoms (Hickman et al., 2014), or the suicidal and non-melancholic patients (Beurel et al., 2020; Chang et al., 2017; Dunjic-Kostic et al., 2013; Woelfer et al., 2019), patients with childhood adversity (Miller and Cole, 2012) or with cumulated episodes (Copeland et al., 2012). An increased risk may not only be seen for depression, but also for bipolar disorder, schizophrenia (Goldsmith et al., 2016) or PTSD (Gill et al., 2008), but note that another source claims specificity for depression (Baune et al., 2012). While the direction of cause and effect is not fully clear, vagal stimulation may be able to improve the depressive symptoms of long-term depressed (Rush et al., 2005), and anti-inflammatory medication can support the treatment with antidepressants (Beurel et al., 2020; Kohler et al., 2014; Muller et al., 2006), but there are no large studies in non-comorbid depression yet (Bullmore, 2018) although clinical trials are on the way (Sakamoto et al., 2021).

5. Strengths and limitations

We did not use ECG to measure the heartbeat, but a plethysmographic device as used in MRI scanners for cardiac triggering or to control for heartbeat artefacts. We evaluated only a single dataset roughly in the middle of a one-hour MR session (we collected a second one during task fMRI, but did not evaluate it since it may have been influenced by task demands), so we were not able to check day-to-day reliability and could not ensure if the measured RSA values constitute rather a state or trait variables. The setting may have been relaxing for a subset of the subjects but more arousing for other (presumably fearful) subjects; this could have increased situation-related differences between subjects, but also reduced trait-like differences between subjects. However, our sample was quite large, and we collected enough questionnaire data to search for psychological correlates of reduced RSA/ heart rate variability. In addition, anxiety diagnoses could not be excluded in the actual study.

6. Conclusion

Our data, although being purely observational, corroborate the idea that a disequilibrium of the vegetative nervous system, especially if accompanied by a dysregulation in immune function, can increase the risk for depression. Conversely, vagal stimulation and anti-inflammatory treatments may support the treatment with antidepressants, at least in some MDD patients.

Funding

This work was supported by the University of Berne, Switzerland, and the University Children's Hospital Zurich, Switzerland, as well as the University of Fribourg, Switzerland.

CRediT authorship contribution statement

Andreas Buchmann: Conceptualization. **Christopher Ritter:** Investigation. **Sabrina Theresia Müller:** Investigation. **Melanie Haynes:** Investigation. **Carmen Ghisleni:** Investigation. **Ruth Tuura:** Conceptualization, Supervision, Writing – review & editing. **Gregor Hasler:** Conceptualization, Supervision, Writing – review & editing.

Declaration of Competing Interest

None of the authors declares conflicts of interest.

Acknowledgment

We are grateful to Dr. Julian Koenig and Prof. Dr. Michael Kaess and their group at Universitäre Psychiatrische Dienste Bern for calculation of the non-RSA heartbeat variability indices. We are grateful to Sarah Rindlisbacher, Julia Rüegsegger, Fabia Colombo, Isabelle Fischer and Sarela Brechbühl for data collection and data entry. We are grateful to Prof. Dr. Martin Hersberger and his team at the Kinderspital Zürich for producing aliquots and clinical chemistry analyses, and Seunghee Kim-Schulze and her team at the Icahn School of Medicine at Mount Sinai in New York.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2022.02.017.

References

Adam, M., Imboden, M., Boes, E., Schaffner, E., Kunzli, N., Phuleria, H.C., Kronenberg, F., Gaspoz, J.M., Carballo, D., Probst-Hensch, N., 2014. Modifying effect of a common polymorphism in the interleukin-6 promoter on the relationship between long-term exposure to traffic-related particulate matter and heart rate variability. PLoS One 9.

Al-Shargabi, T., Govindan, R.B., Dave, R., Metzler, M., Wang, Y., du Plessis, A., Massaro, A.N., 2017. Inflammatory cytokine response and reduced heart rate variability in newborns with hypoxic-ischemic encephalopathy. J. Perinatol. 37, 668–672.

Barnes, J., Mondelli, V., Pariante, C.M., 2017. Genetic contributions of inflammation to depression. Neuropsychopharmacology 42, 81–98.

Baune, B.T., Smith, E., Reppermund, S., Air, T., Samaras, K., Lux, O., Brodaty, H., Sachdev, P., Trollor, J.N., 2012. Inflammatory biomarkers predict depressive, but not anxiety symptoms during aging: the prospective sydney memory and aging study. Psychoneuroendocrinology 37, 1521–1530.

Beauchaine, T.P., 2015. Respiratory sinus arrhythmia: a transdiagnostic biomarker of emotion dysregulation and psychopathology. Curr. Opin. Psychol. 3, 43–47.

Beauchaine, T.P., Thayer, J.F., 2015. Heart rate variability as a transdiagnostic biomarker of psychopathology. Int. J. Psychophysiol. 98, 338–350.

Beck, A.T., Epstein, N., Brown, G., Steer, R.A., 1988. An inventory for measuring clinical anxiety: psychometric properties. J. Consult. Clin. Psychol. 56, 893–897.

Beck, A.T., Ward, C.H., Mendelson, M., Mock, J., Erbaugh, J., 1961. An inventory for measuring depression. Arch. Gen. Psychiatry 4, 561–571.

Berdyyeva, T., Xia, C., Taylor, N., He, Y., Chen, G., Huang, C., Zhang, W., Kolb, H., Letavic, M., Bhattacharya, A., Szardenings, A.K., 2019. PET Imaging of the P2X7 ion channel with a novel tracer [(18)F]JNJ-64413739 in a rat model of neuroinflammation. Mol. Imaging Biol. 21, 871–878.

Berk, M., Williams, L.J., Jacka, F.N., O'Neil, A., Pasco, J.A., Moylan, S., Allen, N.B., Stuart, A.L., Hayley, A.C., Byrne, M.L., Maes, M., 2013. So depression is an inflammatory disease, but where does the inflammation come from? BMC Med. 11, 200.

Beurel, E., Toups, M., Nemeroff, C.B., 2020. The bidirectional relationship of depression and inflammation: double trouble. Neuron 107, 234–256.

Borovikova, L.V., Ivanova, S., Zhang, M., Yang, H., Botchkina, G.I., Watkins, L.R., Wang, H., Abumrad, N., Eaton, J.W., Tracey, K.J., 2000. Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin. Nature 405, 458–462.

Bullmore, E., 2018. The art of medicine: inflamed depression. Lancet 392, 1189–1190.

Buss, A.H., Perry, M., 1992. The Aggression Questionnaire. J. Personal. Soc. Psychol. 63, 452–459.

Chang, C.C., Tzeng, N.S., Kao, Y.C., Yeh, C.B., Chang, H.A., 2017. The relationships of current suicidal ideation with inflammatory markers and heart rate variability in unmedicated patients with major depressive disorder. Psychiatry Res. 258, 449–456.

Cohen, S., Kamarck, T., Mermelstein, R., 1983. A global measure of perceived stress. J. Health Soc. Behav. 24, 385–396.

Coker, R., Koziell, A., Oliver, C., Smith, S.E., 1984. Does the sympathetic nervous system influence sinus arrhythmia in man? Evidence from combined autonomic blockade. J. Physiol. 356, 459–464.

Cooper, T.M., McKinley, P.S., Seeman, T.E., Choo, T.H., Lee, S., Sloan, R.P., 2015. Heart rate variability predicts levels of inflammatory markers: evidence for the vagal anti-inflammatory pathway. Brain Behav. Immun. 49, 94–100.

Copeland, W.E., Shanahan, L., Worthman, C., Angold, A., Costello, E.J., 2012. Cumulative depression episodes predict later C-reactive protein levels: a prospective analysis. Biol. Psychiatry 71, 15–21.

Crawford, J.R., Henry, J.D., 2004. The positive and negative affect schedule (PANAS): construct validity, measurement properties and normative data in a large non-clinical sample. Br. J. Clin. Psychol. 43, 245–265.

Deepika, A., Devi, B.I., Shukla, D., Sathyaprabha, T.N., Christopher, R., Ramesh, S.S., 2018. Neuroimmunology of traumatic brain injury: a longitudinal study of interdependency of inflammatory markers and heart rate variability in severe traumatic brain injury. J. Neurotrauma 35, 1124–1131.

Dowlati, Y., Herrmann, N., Swardfager, W., Liu, H., Sham, L., Reim, E.K., Lanctot, K.L., 2010. A meta-analysis of cytokines in major depression. Biol. Psychiatry 67, 446–457.

Dunjic-Kostic, B., Ivkovic, M., Radonjic, N.V., Petronijevic, N.D., Pantovic, M., Damjanovic, A., Poznanovic, S.T., Jovanovic, A., Nikolic, T., Jasovic-Gasic, M., 2013. Melancholic and atypical major depression–connection between cytokines, psychopathology and treatment. Prog. Neuropsychopharmacol. Biol. Psychiatry 43, 1–6.

Ehring, T., Zetsche, U., Weidacker, K., Wahl, K., Schonfeld, S., Ehlers, A., 2011. The perseverative thinking questionnaire (PTQ): validation of a content-independent measure of repetitive negative thinking. J. Behav. Ther. Exp. Psy. 42, 225–232.

Ellis, A.J., Shumake, J., Beevers, C.G., 2016. The effects of respiratory sinus arrhythmia on anger reactivity and persistence in major depression. Psychophysiology 53, 1587–1599.

Fagundes, C.P., Glaser, R., Hwang, B.S., Malarkey, W.B., Kiecolt-Glaser, J.K., 2013. Depressive symptoms enhance stress-induced inflammatory responses. Brain Behav. Immun. 31, 172–176.

Fairchild, K.D., Saucerman, J.J., Raynor, L.L., Sivak, J.A., Xiao, Y., Lake, D.E., Moorman, J.R., 2009. Endotoxin depresses heart rate variability in mice: cytokine and steroid effects. Am. J. Physiol. Regul. Integr. Comp. Physiol. 297, R1019–R1027.

First, M.B., Spitzer, R.L., Gibbon, M., Williams, J.B.W., 1997. Structured Clinical Interview For DSM-IV Axis I Disorders, Research Version, Patient/Non-patient Edition (SCID-I/P). Biometrics Research/ New York State Psychiatric Institute, New York.

Fitzgerald, P.J., 2020. Serious infection may systemically increase noradrenergic signaling and produce psychological effects. Med. Hypotheses 139, 109692.

Gill, J., Vythilingam, M., Page, G.G., 2008. Low cortisol, high DHEA, and high levels of stimulated TNF-alpha, and IL-6 in women with PTSD. J. Trauma Stress 21, 530–539.

Godbout, J.P., Moreau, M., Lestage, J., Chen, J., Sparkman, N.L., O'Connor, J., Castanon, N., Kelley, K.W., Dantzer, R., Johnson, R.W., 2008. Aging exacerbates depressive-like behavior in mice in response to activation of the peripheral innate immune system. Neuropsychopharmacology 33, 2341–2351.

Goldsmith, D.R., Rapaport, M.H., Miller, B.J., 2016. A meta-analysis of blood cytokine network alterations in psychiatric patients: comparisons between schizophrenia, bipolar disorder and depression. Mol. Psychiatry 21, 1696–1709.

Gruber, J., Mennin, D.S., Fields, A., Purcell, A., Murray, G., 2015. Heart rate variability as a potential indicator of positive valence system disturbance: a proof of concept investigation. Int. J. Psychophysiol. 98, 240–248.

Halaris, A., 2013. Inflammation, heart disease, and depression. Curr. Psychiatry Rep. 15, 400.

Hamilton, M., 1960. A rating scale for depression. J. Neurol. Neurosurg. Psychiatry 23, 56–62.

Herlitz, G.N., Arlow, R.L., Cheung, N.H., Coyle, S.M., Griffel, B., Macor, M.A., Lowry, S. F., Calvano, S.E., Gale, S.C., 2015. Physiologic variability at the verge of systemic inflammation: multiscale entropy of heart rate variability is affected by very low doses of endotoxin. Shock 43, 133–139.

Hickman, R.J., Khambaty, T., Stewart, J.C., 2014. C-reactive protein is elevated in atypical but not nonatypical depression: data from the National Health and Nutrition Examination survey (NHANES) 1999-2004. J. Behav. Med. 37, 621–629.

Hoffmann, A., Ettinger, U., Reyes Del Paso, G.A., Duschek, S., 2017. Executive function and cardiac autonomic regulation in depressive disorders. Brain Cogn. 118, 108–117.

Holman, A.J., Ng, E., 2008. Heart rate variability predicts anti-tumor necrosis factor therapy response for inflammatory arthritis. Auton. Neurosci. 143, 58–67.

Husain, M.I., Strawbridge, R., Stokes, P.R., Young, A.H., 2017. Anti-inflammatory treatments for mood disorders: systematic review and meta-analysis. J. Psychopharmacol. 31, 1137–1148.

Huston, J.M., Tracey, K.J., 2011. The pulse of inflammation: heart rate variability, the cholinergic anti-inflammatory pathway and implications for therapy. J. Intern. Med. 269, 45–53.

Janssen, D.G., Caniato, R.N., Verster, J.C., Baune, B.T., 2010. A psychoneuroimmunological review on cytokines involved in antidepressant treatment response. Hum. Psychopharmacol. 25, 201–215.

Jarczok, M.N., Aguilar-Raab, C., Koenig, J., Kaess, M., Borniger, J.C., Nelson, R.J., Hall, M., Ditzen, B., Thayer, J.F., Fischer, J.E., 2018. The Heart s rhythm 'n' blues: sex differences in circadian variation patterns of vagal activity vary by depressive symptoms in predominantly healthy employees. Chronobiol. Int. 35, 896–909.
Juruena, M.F., Bocharova, M., Agustini, B., Young, A.H., 2018. Atypical depression and non-atypical depression: is HPA axis function a biomarker ? A systematic review. J. Affect Disorders 233, 45–67.
Karavidas, M.K., Lehrer, P.M., Vaschillo, E., Vaschillo, B., Marin, H., Buyske, S., Malinovsky, I., Radvanski, D., Hassett, A., 2007. Preliminary results of an open label study of heart rate variability biofeedback for the treatment of major depression. Appl. Psychophysiol. Biofeedback 32, 19–30.
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 67, 1067–1074.
Kennis, M., Gerritsen, L., van Dalen, M., Williams, A., Cuijpers, P., Bockting, C., 2020. Prospective biomarkers of major depressive disorder: a systematic review and meta-analysis. Mol. Psychiatry 25, 321–338.
Kidwell, M., Ellenbroek, B.A., 2018. Heart and soul: heart rate variability and major depression. Behav. Pharmacol. 29, 152–164.
Koeneman, M., Koch, R., van Goor, H., Pickkers, P., Kox, M., Bredie, S., 2021. Wearable patch heart rate variability is an early marker of systemic inflammation during experimental human endotoxemia. Shock 56, 537–543.
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.
Koenig, J., Westlund Schreiner, M., Klimes-Dougan, B., Ubani, B., Mueller, B.A., Lim, K. O., Kaess, M., Cullen, K.R., 2018. Increases in orbitofrontal cortex thickness following antidepressant treatment are associated with changes in resting state autonomic function in adolescents with major depression - preliminary findings from a pilot study. Psychiatry Res. Neuroimaging 281, 35–42.
Kohler, O., Benros, M.E., Nordentoft, M., Farkouh, M.E., Iyengar, R.L., Mors, O., Krogh, J., 2014. Effect of anti-inflammatory treatment on depression, depressive symptoms, and adverse effects: a systematic review and meta-analysis of randomized clinical trials. JAMA Psychiatry 71, 1381–1391.
Koopman, F.A., van Maanen, M.A., Vervoordeldonk, M.J., Tak, P.P., 2017. Balancing the autonomic nervous system to reduce inflammation in rheumatoid arthritis. J. Intern. Med. 282, 64–75.
Kubera, M., Lin, A.H., Kenis, G., Bosmans, E., van Bockstaele, D., Maes, M., 2001. Anti-Inflammatory effects of antidepressants through suppression of the interferon-gamma/interleukin-10 production ratio. J. Clin. Psychopharmacol. 21, 199–206.
Lampert, R., Bremner, J.D., Su, S., Miller, A., Lee, F., Cheema, F., Goldberg, J., Vaccarino, V., 2008. Decreased heart rate variability is associated with higher levels of inflammation in middle-aged men. Am. Heart J. 156, 759 e751-757.
Lanquillon, S., Krieg, J.C., Bening-Abu-Shach, U., Vedder, H., 2000. Cytokine production and treatment response in major depressive disorder. Neuropsychopharmacology 22, 370–379.
LeMoult, J., Yoon, K.L., Joormann, J., 2016. Rumination and Cognitive Distraction in Major Depressive Disorder: an Examination of Respiratory Sinus Arrhythmia. J. Psychopathol. Behav. Assess 38, 20–29.
Licht, C.M., de Geus, E.J., Zitman, F.G., Hoogendijk, W.J., van Dyck, R., Penninx, B.W., 2008. Association between major depressive disorder and heart rate variability in the netherlands study of depression and anxiety (NESDA). Arch. Gen. Psychiatry 65, 1358–1367.
Lopresti, A.L., Maker, G.L., Hood, S.D., Drummond, P.D., 2014. A review of peripheral biomarkers in major depression: the potential of inflammatory and oxidative stress biomarkers. Prog. Neuropsychopharmacol. Biol. Psychiatry 48, 102–111.
Lotrich, F.E., 2015. Inflammatory cytokine-associated depression. Brain Res. 1617, 113–125.
Malave, H.A., Taylor, A.A., Nattama, J., Deswal, A., Mann, D.L., 2003. Circulating levels of tumor necrosis factor correlate with indexes of depressed heart rate variability: a study in patients with mild-to-moderate heart failure. Chest 123, 716–724.
Malhi, G.S., Mann, J.J., 2018. Depression. Lancet 392, 2299–2312.
Marsland, A.L., Gianaros, P.J., Prather, A.A., Jennings, J.F., Neumann, S.A., Manuck, S. B., 2007a. Stimulated production of proinflarnmatory cytokines covaries inversely with heart rate variability. Psychosom. Med. 69, 709–716.
Marsland, A.L., Gianaros, P.J., Prather, A.A., Jennings, J.R., Neumann, S.A., Manuck, S. B., 2007b. Stimulated production of proinflammatory cytokines covaries inversely with heart rate variability. Psychosom. Med. 69, 709–716.
McCrae, R.R., Costa Jr., P.T., 1987. Validation of the five-factor model of personality across instruments and observers. J. Pers. Soc. Psychol. 52, 81–90.
Miller, G.E., Cole, S.W., 2012. Clustering of depression and inflammation in adolescents previously exposed to childhood adversity. Biol. Psychiatry 72, 34–40.
Montgomery, S.A., Asberg, M., 1979. A new depression scale designed to be sensitive to change. Br. J. Psychiatry 134, 382–389.
Mrazek, M.D., Phillips, D.T., Franklin, M.S., Broadway, J.M., Schooler, J.W., 2013. Young and restless: validation of the mind-wandering questionnaire (MWQ) reveals disruptive impact of mind-wandering for youth. Front Psychol. 4, 560.
Muller, N., Schwarz, M.J., Dehning, S., Douhe, A., Cerovecki, A., Goldstein-Muller, B., Spellmann, I., Hetzel, G., Maino, K., Kleindienst, N., Moller, H.J., Arolt, V., Riedel, M., 2006. The cyclooxygenase-2 inhibitor celecoxib has therapeutic effects in major depression: results of a double-blind, randomized, placebo controlled, add-on pilot study to reboxetine. Mol. Psychiatry 11, 680–684.
Nikolic, V.N., Jevtovic-Stoimenov, T., Stokanovic, D., Milovanovic, M., Velickovic-Radovanovic, R., Pesic, S., Stoiljkovic, M., Pesic, G., Ilic, S., Deljanin-Ilic, M., Marinkovic, D., Stefanovic, N., Jankovic, S.M., 2013. An inverse correlation between TNF alpha serum levels and heart rate variability in patients with heart failure. J. Cardiol. 62, 37–43.
Nishino, S., Ueno, R., Ohishi, K., Sakai, T., Hayaishi, O., 1989. Salivary prostaglandin concentrations: possible state indicators for major depression. Am. J. Psychiatry 146, 365–368.
Nolan, R.P., Floras, J.S., Ahmed, L., Harvey, P.J., Hiscock, N., Hendrickx, H., Talbot, D., 2012. Behavioural modification of the cholinergic anti-inflammatory response to C-reactive protein in patients with hypertension. J. Intern. Med. 272, 161–169.
Parish, R.C., Todman, S., Jain, S.K., 2016. Resting Heart Rate Variability, Inflammation, and Insulin Resistance in Overweight and Obese Adolescents. Metab Syndr. Relat. Disord. 14, 291–297.
Patterson, R.L., Osullivan, M.J., Spielberger, C.D., 1980. Measurement of state and trait anxiety in elderly mental-health clients. J. Behav. Assess 2, 89–97.
Pavlov, V.A., Tracey, K.J., 2005. The cholinergic anti-inflammatory pathway. Brain Behav. Immun. 19, 493–499.
Piepoli, M., Sleight, P., Leuzzi, S., Valle, F., Spadacini, G., Passino, C., Johnston, J., Bernardi, L., 1997. Origin of respiratory sinus arrhythmia in conscious humans. An important role for arterial carotid baroreceptors. Circulation 95, 1813–1821.
Pizzi, C., Manzoli, L., Mancini, S., Costa, G.M., 2008. Analysis of potential predictors of depression among coronary heart disease risk factors including heart rate variability, markers of inflammation, and endothelial function. Eur. Heart J. 29, 1110–1117.
Pomfrett, C.J., Barrie, J.R., Healy, T.E., 1993. Respiratory sinus arrhythmia: an index of light anaesthesia. Br. J. Anaesth. 71, 212–217.
Porges, S.W., 1995. Cardiac vagal tone: a physiological index of stress. Neurosci. Biobehav. Rev. 19, 225–233.
Porges, S.W., 2001. The polyvagal theory: phylogenetic substrates of a social nervous system. Int. J. Psychophysiol. 42, 123–146.
Rottenberg, J., Clift, A., Bolden, S., Salomon, K., 2007. RSA fluctuation in major depressive disorder. Psychophysiology 44, 450–458.
Rush, A.J., Sackeim, H.A., Marangell, L.B., George, M.S., Brannan, S.K., Davis, S.M., Lavori, P., Howland, R., Kling, M.A., Rittberg, B., Carpenter, L., Ninan, P., Moreno, F., Schwartz, T., Conway, C., Burke, M., Barry, J.J., 2005. Effects of 12 months of vagus nerve stimulation in treatment-resistant depression: a naturalistic study. Biol. Psychiatry 58, 355–363.
Sakamoto, S., Zhu, X., Hasegawa, Y., Karma, S., Obayashi, M., Alway, E., Kamiya, A., 2021. Inflamed brain: targeting immune changes and inflammation for treatment of depression. Psychiatry Clin. Neurosci. 75, 304–311.
Schiweck, C., Piette, D., Berckmans, D., Claes, S., Vrieze, E., 2019. Heart rate and high frequency heart rate variability during stress as biomarker for clinical depression. A systematic review. Psychol. Med. 49, 200–211.
Setiawan, E., Wilson, A.A., Mizrahi, R., Rusjan, P.M., Miler, L., Rajkowska, G., Suridjan, I., Kennedy, J.L., Rekkas, P.V., Houle, S., Meyer, J.H., 2015. Role of translocator protein density, a marker of neuroinflammation, in the brain during major depressive episodes. JAMA Psychiatry 72, 268–275.
Sgoifo, A., Carnevali, L., Alfonso Mde, L., Amore, M., 2015. Autonomic dysfunction and heart rate variability in depression. Stress 18, 343–352.
Spielberger, C.D., Reheiser, E.C., Sydeman, S.J., 1995. Measuring the experience, expression, and control of anger. Issues Compr. Pediatr. Nurs. 18, 207–232.
Tarvainen, M.P., Niskanen, J.P., Lipponen, J.A., Ranta-Aho, P.O., Karjalainen, P.A., 2014. Kubios HRV–heart rate variability analysis software. Comput. Methods Programs Biomed. 113, 210–220.
Taylor, S., Cox, B.J., 1998. An expanded anxiety sensitivity index: evidence for a hierarchic structure in a clinical sample. J. Anxiety Disord. 12, 463–483.
Thayer, J.F., Lane, R.D., 2000. A model of neurovisceral integration in emotion regulation and dysregulation. J. Affect. Disord. 61, 201–216.
Thayer, J.F., Lane, R.D., 2009. Claude Bernard and the heart-brain connection: further elaboration of a model of neurovisceral integration. Neurosci. Biobehav. Rev. 33, 81–88.
The Global Burden of disease, 2004. World Health Organization, Geneva.
Tiller, J.W., 2013. Depression and anxiety. Med. J. Aust. 199, S28–S31.
Tonhajzerova, I., Ondrejka, I., Javorka, M., Adamik, P., Turianikova, Z., Kerna, V., Javorka, K., Calkovska, A., 2009. Respiratory sinus arrhythmia is reduced in adolescent major depressive disorder. Eur. J. Med. Res. 14 (Suppl 4), 280–283.
Tracey, K.J., 2002. The inflammatory reflex. Nature 420, 853–859.
Tsypes, A., James, K.M., Woody, M.L., Feurer, C., Kudinova, A.Y., Gibb, B.E., 2018. Resting respiratory sinus arrhythmia in suicide attempters. Psychophysiology 55.
von Kanel, R., Nelesen, R.A., Mills, P.J., Ziegler, M.G., Dimsdale, J.E., 2008. Relationship between heart rate variability, interleukin-6, and soluble tissue factor in healthy subjects. Brain Behav. Immun. 22, 461–468.
Weber, M.D., Godbout, J.P., Sheridan, J.F., 2017. Repeated social defeat, neuroinflammation, and behavior: monocytes carry the signal. Neuropsychopharmacology 42, 46–61.
Wegeberg, A.L., Okdahl, T., Floyel, T., Brock, C., Ejskjaer, N., Riahi, S., Pociot, F., Storling, J., Brock, B., 2020. Circulating inflammatory markers are inversely associated with heart rate variability measures in type 1 diabetes. Mediators Inflamm. 2020, 3590389.
Williams, D.P., Koenig, J., Carnevali, L., Sgoifo, A., Jarczok, M.N., Sternberg, E.M., Thayer, J.F., 2019. Heart rate variability and inflammation: a meta-analysis of human studies. Brain Behavior Immun. 80, 219–226.
Wittchen, H.-U., Zaudig, M., Fydrich, T., 1997. Skid. strukturiertes klinisches interview für DSM-IV. Achse I und II. Handanweisung. Hogrefe.
Woelfer, M., Kasties, V., Kahlfuss, S., Walter, M., 2019. The role of depressive subtypes within the neuroinflammation hypothesis of major depressive disorder. Neuroscience 403, 93–110.

Xie, J.Y., Liu, W.X., Ji, L., Chen, Z., Gao, J.M., Chen, W., Chen, G.F., Zhu, Q., 2020. Relationship between inflammatory factors and arrhythmia and heart rate variability in OSAS patients. Eur. Rev. Med. Pharmacol. Sci. 24, 2037–2053.
Yaptangco, M., Crowell, S.E., Baucom, B.R., Bride, D.L., Hansen, E.J., 2015. Examining the relation between respiratory sinus arrhythmia and depressive symptoms in emerging adults: a longitudinal study. Biol. Psychol. 110, 34–41.
Yaroslavsky, I., Rottenberg, J., Kovacs, M., 2014. Atypical patterns of respiratory sinus arrhythmia index an endophenotype for depression. Dev. Psychopathol. 26, 1337–1352.
Yasova Barbeau, D., Krueger, C., Huene, M., Copenhaver, N., Bennett, J., Weaver, M., Weiss, M.D., 2019. Heart rate variability and inflammatory markers in neonates with hypoxic-ischemic encephalopathy. Physiol. Rep. 7, e14110.