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Article

A First Examination of the Link Between Heart Rate Variability and Networks of Anxiety and Depression Symptoms

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Abstract. The neurovisceral integration model proposes that people low in heart rate variability (HRV) are in a state with strong connections between symptoms of anxiety and depression. So far studies providing support for this hypothesis have relied on classifications or sum scores of a diverse range of symptoms, ignoring observations that anxiety and depression symptoms dynamically influence each other. Here we used network analyses to study if HRV moderates characteristics (density, structure, centrality indices) of network models of generalized anxiety disorder and depression symptoms. We used data (N = 495) from the Dresden Burnout Study where resting levels of HRV were obtained as well as self-reported symptoms of generalized anxiety and depression. Results showed that HRV did not moderate the density and structure of the overall symptom networks. Exploration of the centrality indices suggested that restlessness was a more central node for people low in HRV, a result that remains to be confirmed in larger samples. These findings demonstrate how a network perspective may aid in better understanding the complex relation between symptoms of psychopathology and physiological status.

Keywords: heart rate variability, network analysis, anxiety, depression, worry, physiology

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Low heart rate variability (HRV) is a marker of both somatic and mental health (Dekker et al., 2000; Hillebrand et al., 2013; Koenig et al., 2015; Thayer & Lane, 2000). Numerous studies indicated that people suffering from anxiety and mood disorders are characterized by low variability in their heartbeat series, especially in the high-frequency changes between adjacent beats (Alvares et al., 2016; Koch et al., 2019; Koenig et al., 2016). Low HRV is not only associated with DSM-based classifications of anxiety and mood disorders but also with specific (transdiagnostic) symptoms, such as worry (Chalmers et al., 2016; Ottaviani et al., 2016), exhaustion symptoms (Kanthak et al., 2017), as well as with attentional and memory biases that characterize these disorders (Park, Van Bavel, et al., 2013; Park, Vasey, et al., 2013; Park et al., 2012). In addition, low HRV has been associated with dysregulation in a network of brain areas involved in autonomic and emotion regulation (Mulcahy et al., 2019).

These findings so far provide evidence for the neurovisceral integration model, which was proposed by Thayer and Lane (2000). According to this model, low HRV is indicative of a state of organisms in which they are stuck in an inflexible mode of responding to environmental stimuli (Smith et al., 2017; Thayer & Lane, 2009). So far, however, studies focusing on the association between low resting HRV, anxiety, and mood disorders have mostly studied classifications, specific symptoms, or sum scores on symptom lists. Yet, in the neurovisceral integration model, anxiety and mood disorders were conceptualized from a chaos theory point of view, stating that "…disorders of affect, including anxiety disorders, may be viewed as a kind of distorted emotional state space in which an individual is unable to shift into an attractor or emotion that is appropriate for a given set of environmental demands" (Thayer & Lane, 2000, p. 203). This description closely matches the view of mental disorders that is currently under heavy investigation: the symptom network approach to mental disorders (Borsboom & Cramer, 2013; Fried et al., 2017).

According to the network approach, anxiety and mood disorders are clusters of symptoms that mutually and causally influence each other, with some symptoms being more central to a network of symptoms than others. In a similar way to the neurovisceral integration model, current conceptions of mental disorders propose that people suffering

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from mood and anxiety disorders have reached a tipping point (van de Leemput et al., 2014), after which their symptoms strongly cluster together and reciprocally influence each other (Fried et al., 2017). Network approaches do not assume the underlying causes of the disorders: dense symptom networks are the disorder. It remains a question however who might be vulnerable to develop such dense and strongly connected networks of symptoms. Here we studied if HRV might potentially be such a vulnerability factor by testing if HRV is associated with characteristics of the networks of symptoms of anxiety and depression.

Our main goal was to test if HRV is associated with the density of the network (i.e., the total number of connections) and the overall strength of these connections between the symptoms. The latter seems especially relevant, as stronger positive connections between symptoms of psychopathology might make the total symptom burden less easy to amend by therapeutic interventions. In addition, previous research has shown that *sad mood*, *too much worry,* and *uncontrollable worry* are typically the symptoms with the highest strength in anxiety and depression networks (Beard et al., 2016; Kaiser et al., 2021; Wang et al., 2020), and these symptoms are also the main determinants of depression and anxiety according to the DSM5 (American Psychiatric Association, 2013). Here, we inspected if the centrality of these symptoms depended on the HRV level. A third aim was to inspect bridge centrality indices, which refer to the influence that symptoms belonging to one disorder (i.e., generalized anxiety) have on another disorder (i.e., depression), thereby accounting for comorbidity between these disorders (Jones et al., 2021). In previous research, psychomotor items (e.g., *feeling restless*, *psychomotor agitation, or retardation*) have been found to be bridge symptoms, connecting anxiety and depression symptoms (Kaiser et al., 2021; Wang et al., 2020). However, it remains unclear if HRV levels are associated with bridge centrality.

In sum, in the present study, we aimed to examine an important tenet of the neurovisceral integration model, namely if people with low levels of HRV show more densely connected networks of anxiety and depression symptoms. Additionally, we explored differences in the centrality of symptoms between participants low and high in HRV.

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Methods

Participants

The current study included participants from the ongoing Dresden Burnout Study (DBS), a large-scale longitudinal study designed to systematically investigate biological, societal, and psychological factors associated with burnout. The design and recruitment strategies of the DBS are described in detail elsewhere (Penz et al., 2018). Shortly summarized, participants had been recruited Germany-wide through public media platforms and the civil register of the city of Dresden. In order to ensure a heterogeneous sample composition, the only inclusion criteria were working age (between 18 and 68 years) at the start of the DBS in January 2015 and language (sufficient language skills to fill out German questionnaires). HRV data used in the present study were assessed during the annual in-person biomarker assessment to which DBS participants with residence in Dresden and within a 60-km radius around the city were invited.

The present study included those participants with complete heart rate data, as well as relevant questionnaire data of the in-person biomarker assessment conducted from October 2016 to February 2017 (see Descriptive Statistics section for more information on the final sample).

All participants received a monetary reward of 15€. All participants gave written informed consent. The DBS was conducted in accordance with the Declaration of Helsinki and therefore approved by the ethics committee of TU Dresden.

Study Design and Procedure

Within one week before the biomarker sampling, participants completed an online questionnaire assessing anxiety and depressive symptoms and provided information on sociodemographic and health-related factors. The full biomarker samplings lasted approximately 50 min and were conducted between 7 AM and 7 PM.

After arriving at the laboratory and signing the consent form, participants were provided with a wireless chest transmitter and a wrist monitor recorder for heart rate recording (Polar RS800CX; Polar Electro OY, Kempele, Finland). Afterwards, they were brought to the blood sampling room, followed by a hair sample collection. At the end of the biomarker sampling procedure, 335 s of seated resting heart rate data were assessed. An interval after venipuncture was chosen to avoid distortions of resting HRV by anticipatory fears.

Assessment of Self-Report Measures

Self-reported age, gender, smoking status, BMI, and health status (presence of high blood pressure, cardiac arrythmia, diabetes, and high cholesterol) were used to describe the two samples (low vs. high HRV).

Depressive symptoms were assessed with the German version (PHQ-9-D; Löwe et al., 2002) of the Patient Health Questionnaire (Kroenke et al., 2001; PHQ-9), which consists of 9 items. The 9 items are scored on a 4-point ranking scale (0 = *not at all*, 1 = *several days*, 2 = *more than half the*

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days, 3 = *nearly every day*) and quantify the frequency, over the last 2 weeks, of each of the nine diagnostic criteria for a depressive disorder defined by the DSM-IV (American Psychiatric Association, 2013). PHQ-9 scores range from 0 to 21, with higher values indicating higher symptom severity and a cut-off point of 10 indicating possible moderate or severe depression as suggested by Manea and colleagues (2012).

Anxiety symptoms were operationalized using the German version (GAD7-D; Löwe et al., 2008) of the Generalized Anxiety Disorder Scale (GAD-7; Spitzer et al., 2006). The GAD-7 consists of 7 items that asses how often, during the last 2 weeks, participants have been bothered by each of the 7 core symptoms of generalized anxiety disorders, according to the DSM-IV diagnostic criteria (American Psychiatric Association, 2000). The items are rated on a 4-point rating scale (0 = *not at all*, 1 = *several days*, 2 = *more than half the days*, 3 = *nearly every day*). Therefore, GAD-7 scores range from 0 to 21, with higher values indicating higher symptom severity and a cut-off point of 10 indicating the possible presence of generalized anxiety disorder, as suggested by Spitzer and colleagues (2006).

Assessment of Heart Rate Data

HRV was assessed via the recording of continuous heart rate (inter-beat intervals; IBI). Of the complete IBI timeline recorded during the first biomarker sampling procedure with a frequency of 1,000 Hz, only a 335-second period of the seated resting condition was analyzed in the present study. A seated rest condition seems especially suited, as this experimental setting has previously been shown to enable the assessment of HRV as a trait-like marker of vagal function (Bertsch et al., 2012).

Raw data were then transferred to the Polar Precision Performance Software (Polar Electro OY) and exported as raw IBI data for artifact correction conducted by the Center for Neuroscience Research Trier, Germany, according to the guidelines of the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (1996) using the "NEUROCOR® precisionHRV-Algorithm" based on the European Patent "EP2745770B1 Method and device for determining the variability of a creature's heart rate". During this analysis step, artifacts in the electrocardiogram-derived RR intervals are marked and corrected without violation of the phasing and the overall time of the signal. Subsequently, mean heart rate (HR) and HRV measures were calculated. The root mean sum of squares of successive differences between heartbeats (RMSSD) was used to operationalize HRV. RMSSD was chosen because it is an approved short-term measure of HRV reflecting primarily vagal cardiac and it has been shown to be particularly robust against breathing patterns (Bertsch et al., 2012; Hill et al., 2009).

We then used a previously tested and validated cut-off level of RMSSD (cut-off = 25; (Jarczok et al., 2019) to create subgroups (termed "low HRV" and "higher HRV") that we aimed to compare with respect to their network structures. Levels of RMSSD that were below this cut-off have previously been associated with elevated cardiovascular risks (e.g., higher blood pressure, inflammatory markers, blood lipids, and glucose; Jarczok et al., 2019). Similar results were obtained when using a median split to create groups with equal sample sizes. To not solely rely on this dichotomy, we also ran analyses using the continuous RMSSD variable (see the next paragraph).

Statistical Analysis

RMSSD values were not normally distributed and were therefore ln-transformed, but this still did not result in a normal distribution. Inspection of outliers (upper/lower quartile ± 1.5 times the interquartile range) showed the presence of six outliers. Excluding these outliers led to a normal distribution. Yet, the main results (which are largely based on Spearman rank-correlations) did not differ when in- or excluding these outliers. Therefore, we report the results for the total final sample (without excluding the outliers).

In the first step, Spearman correlations were calculated to examine the associations between lnRMSSD values and sum scores on the questionnaires, as well as associations between lnRMSSD values and individual symptoms. In a second step, in order to compare the networks of participants in the low and higher HRV groups, we estimated partial correlation networks for both groups, using the glasso regularization and a hyperparameter gamma set to 0.5, which yields more parsimonious models compared to lower values, thereby increasing the chance of excluding possible spurious edges (i.e., false positives, Epskamp & Fried, 2018; Foygel & Drton, 2010). Due to the ordinal nature of the data, we used Spearman correlations, and pairwise complete observations to handle missing data.

Initially, we estimated the networks based on polychoric correlations. These networks were compared to networks based on Spearman correlations, as the presence of low-frequency items (e.g., suicidality) could yield untrustworthy estimates. This was the case in the present data and we therefore here report the networks based on Spearman correlations. In the visualization of the networks, the symptoms are represented as circles (called "nodes") which are connected by lines ("edges"), with the thickness of the edges representing the strength with which the nodes are connected and the color indicating the direction of the associations.

In the third step, we further quantified how well a node is directly connected to other nodes in the network structure,

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by investigating the Expected Influence as a centrality measure (Epskamp & Fried, 2018). The expected influence of a node is calculated as the sum of the interrelatedness of that node with all the other nodes that it is related to; taking both positive and negative relations into account (Robinaugh et al., 2016).

We used three statistical approaches to compare the networks between the groups. First, the similarity of the networks was examined by correlating both the edge weights of the networks and the expected influence centrality measures (cf. Fried et al., 2018).

Second, to compare the networks in terms of global strength and differences between the expected influence of the edges, a permutation test was conducted (*networkcomparisontest*, Van Borkulo et al., 2022). Third, besides comparing the network structures of participants in the low and higher HRV groups, we also used a data-driven approach to explore if lnRMSSD levels moderated the network structures. We used the approach developed by Jones and colleagues (2020), who describes a recursive partitioning approach (model-based recursive partitioning, MOB) to covariance matrices (e.g., networks) of symptoms (for details see Jones et al., 2020). In this approach, an algorithm explores if significant differences in the covariance matrix (representing the symptoms network) can be detected, using lnRMSSD values as the partitioning variable.

The network analyses were conducted using R-version 3.5.2. For network estimation, we used the *estimateNetwork* function in the *bootnet* package (Epskamp et al., 2018, version 1.5). Networks were subsequently visualized using the *qgraph* package (Epskamp et al., 2012, version 1.9.3). In these network plots, edges represent regularized partial (Spearman) correlations between symptoms. We used the colorblind theme in *qgraph* (Epskamp et al., 2012), fixed the average layout between the two network plots using the average Layout function, and made negative edges dashed; cut-off values were set at 0.1, with a maximum of 0.6.

To test if the networks of the low and higher HRV groups differed significantly from each in terms of structure (i.e., whether there are edge weights that differed between the networks) or global strength (the sum of all absolute edge weights for each network), the package *networkcomparisontest* (Van Borkulo et al., 2022, version 2.2.2) was used. We also used this package to test if there were differences between the networks in expected influence and bridge the expected influence of the nodes. However, it should be noted that this procedure has not been validated yet (Van Borkulo et al., 2022). Finally, the package *networktree* (Jones et al., 2020, version 1.0.1) was used to detect significant differences in the network structure. By using the rank-ordered version of the original data as input to this package, we were able to estimate the networks based on Spearman correlations.

To assess the accuracy of the edge estimates and the centrality estimates, we conducted the routine implemented in the *bootnet* package, using nonparametric bootstrapping with 1,000 bootstrap samples. The results of these stability and accuracy analyses can be found in the Electronic Supplementary Material (ESM, Figures E3–E12).

Results

Descriptive Statistics

Of the 526 participants who provided heart rate data, 23 had to be excluded due to an artifact load of $\geq$ 5%. The mean resting level of RMSSD of these 503 participants was 38.14 ms (*SD* = 22.75). Of them, 165 were assigned to the low HRV group (resting level of RMSSD < 25 ms), and 338 individuals were assigned to the higher HRV group (resting level of RMSSD > 25 ms) based on the cut-off values suggested by Jarczok and colleagues (2019). For the low HRV group 164 filled in the PHQ-9 and 163 filled in the GAD-7. In the higher HRV group, 332 participants provided answers on the PHQ-9 and GAD-7. This yielded a final total sample size of N = 495. In Table 1 the descriptive statistics of these groups are provided. The groups differed statistically with respect to age, gender distribution, and resting HR, with individuals in the low HRV group being older, consisting of more men, and having a higher resting HR, compared to the higher HRV group. As expected, self-reported health status in the low HRV group was compromised when compared to the higher HRV group, with more participants reporting high blood pressure, diabetes, and high cholesterol (ps < .05).

With respect to the likelihood of the presence of psychopathology, 27.7% of the total sample scored above the clinical cut-off of 10 on the PHQ-9 (suggesting the presence of moderate or more severe depression), and 17.8% scored above the cut-off of 10 on the GAD-7 (suggesting the presence of generalized anxiety disorder) – possible comorbidity was present in 15.2% of the participants.

Association Between Resting lnRMSSD and Symptoms

Spearman correlations showed no significant associations between resting lnRMSSD levels and both, the total PHQ-9 ($r(493) = -.08$, $p = .07$) and the total GAD-7 ($r(493) = -.06$, $p = .15$). Next, Spearman correlation coefficients between resting lnRMSSD levels and individual symptoms

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Table 1. Descriptive statistics and statistical differences between the groups

		Low HRV (n = 163)		Higher HRV (n = 332)		Overall (n = 495)	
Scale/item	Label	*M*	*SD*	*M*	*SD*	*M*	*SD*
Age*		46.82	10.81	37.61	11.61	40.64	12.14
Gender (n; % female)*		102 (62.5%)		237 (71.4%)		339 (68.5%)	
BMI		27.81	22.48	26.38	26.67	26.85	25.34
Resting HR*		75.95	8.95	67.47	9.11	70.26	9.89
Smoking (n; % smokers)		25 (15.3%)		45 (13.6%)		40 (14.1%)	
High blood pressure (n; %)*[a]		33 (22.6%)		35 (11.1%)		68 (14.8)	
Cardiac arrythmia (n; %)[b]		4 (2.8%)		6 (2.0%)		10 (2.2%)	
Diabetes (n; %)*,[c]		10 (6.8%)		4 (1.3%)		14 (3.0%)	
High cholesterol (n; %)*,[d]		23 (16.2%)		21 (6.9%)		44 (9.9%)	
Depression (PHQ-9)		8.31	5.48	7.62	5.14	7.85	5.26
Little interest or pleasure in doing things	interest	1.13	0.86	1.03	0.81	1.06	0.83
Feeling down, depressed, or hopeless	down	0.87	0.90	0.82	0.84	0.84	0.86
Trouble falling or staying asleep, or sleeping too much	sleep	1.44	0.99	1.27	0.97	1.32	0.98
Feeling tired or having little energy	tired	1.60	0.93	1.42	0.87	1.47	0.89
Poor appetite or overeating	appetite	0.96	0.98	0.91	0.96	0.92	0.96
Feeling bad about yourself – or that you are a failure or have let yourself or your family down	selfesteem	0.64	0.85	0.67	0.81	0.66	0.83
Trouble concentrating on things, such as reading the newspaper or watching television	concentration	1.07	0.88	0.93	0.83	0.98	0.85
Moving or speaking so slowly that other people could have noticed? Or the opposite – being so fidgety or restless that you have been moving around a lot more than usual?	psychomotor	0.44	0.71	0.40	0.68	0.41	0.69
Thoughts that you would be better off dead or of hurting yourself in some way?	suicidality	0.17	0.52	0.17	0.41	0.17	0.45
Depression (PHQ > 10)		49 (30.1%)		88 (26.5%)		137 (27.7%)	
Anxiety (GAD-7)		6.40	4.64	6.25	4.66	6.30	4.65
Feeling nervous, anxious, or on edge	nervous	0.99	0.84	1.05	0.85	1.03	0.85
Not being able to stop or control worrying	uncontrolworry	0.87	0.84	0.79	0.90	0.81	0.88
Worrying too much about different things	worry	0.96	0.87	0.92	0.89	0.93	0.88
Trouble relaxing	troublerelax	1.33	0.94	1.27	0.94	1.29	0.94
Being so restless that it's hard to sit still	restless	0.64	0.83	0.60	0.81	0.62	0.82
Becoming easily annoyed or irritable	irritable	1.06	0.80	1.06	0.82	1.06	0.81
Feeling afraid as if something awful might happen	awful	0.55	0.72	0.56	0.77	0.56	0.76
Generalized anxiety disorder (GAD > 10)		30 (18.4%)		58 (17.4%)		88 (17.8%)	

Note. HRV = heart rate variability; BMI = body mass index, HR = heart rate, PHQ-9 = Patient Health Questionnaire-9; GAD-7 = Generalized Anxiety Disorder-7. [a]18 participants reported to not know their status; [b]23 participants reported to not know their status; [c]12 participants reported to not know their status; [d]27 participants reported to not know their status. *$p < .05$

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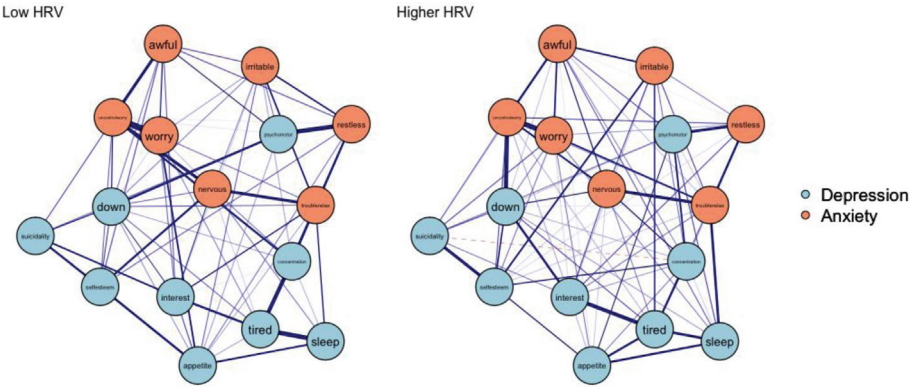

Figure 1. Network plots for participants with low heart rate variability (root mean sum of squares of successive differences between heart beats RMSSD < 25) and higher heart rate variability (RMSSD > 25).

were calculated. Overall, the correlation coefficients were negative and small. The largest associations were observed between lnRMSSD and *sleep problems* ($r(493) = -.13$, $p = .004$), *feeling tired* ($r(493) = -.10$, $p = .02$), and *uncontrollable worry* ($r(493) = -.10$, $p = .02$).

Network Characteristics

The symptom networks of participants in the low and higher HRV groups are presented in Figure 1. Tables E1 and E2 (in ESM 1) show the edge weights; Figures E1 and E2 (in ESM 1) show bootstrapped 95% confidence intervals (CIs) around the edge weights.

Edge weights in the low HRV group were all positive with the strongest edge (0.39) between *worry* and *uncontrollable worry*. The mean weight of the network was 0.0599. The strongest connection between anxiety and depression symptoms was the edge between *restlessness* and *psychomotor agitation* or retardation (0.28).

Edge weights in the higher HRV group contained two negative values, and ranged from −0.04 (*concentration – suicidality*; *restless – tired*) to 0.32 (*worry – uncontrollable worry*), with a mean weight of 0.0593. Here, the strongest connection between anxiety and depression symptoms was the edge between *uncontrollable worry* and *feeling down* (0.27).

We first computed the density of the networks by dividing the number of detected edges by the total number of possible edges (i.e., in a full network). For the low HRV network, this ratio was 73/120 (density = 0.61). In contrast to the expectation, for the higher HRV network, this ratio was higher, namely 83/120 (density = 0.69).

To test for the similarity of the networks, a Spearman correlation was calculated which showed that, overall, the edge weights were not moderately correlated ($r = .49$) suggesting differences between the networks.

Next, to test whether there were differences between the global strength of the networks and whether there were edges that significantly differed between the networks, a permutation test (network comparison test, Van Borkulo et al., 2022) was conducted. Since we did not have a priori expectations about which edges could differ, an omnibus test was used to test the null hypothesis that all edges were equal, a so-called network invariance test. Overall, there were no differences in global strength of connectivity between the networks (global strength per group: low HRV = 7.19; higher HRV = 7.27, difference S = 0.08, $p = .72$). Additionally, the omnibus test for equality of the edges was not significant (maximum difference in edge weight, $M = .16$, $p = .89$). Given the exploratory nature of this study and since the correlation analysis suggested only moderate similarity between the edges, we decided to inspect whether any of the edges differed between the networks. Of the 120 edges, only 4 edges were significantly stronger in the network of the low HRV group compared to those in the higher HRV group (*down – psychomotor*: $E = 0.14$, $p = .02$; *self-esteem – nervous*: $E = 0.14$, $p = .03$; *concentration – uncontrollable worry*: $E = 0.16$, $p = .003$; *interest – awful*: $E = 0.07$, $p = .02$). Thus, according to these exploratory tests, which were conducted without a correction for multiple testing, only in 3% of the edges differences were observed.

We additionally conducted an explorative analysis using the *networktree* package (Jones et al., 2020). In this analysis, all resting lnRMSSD values were used as a continuous covariate to detect if lnRMSSD values are associated with alterations in the network structure. The networktree algorithm automatically detects influential lnRMSSD values at which level the sample can be partitioned into two (differing) networks. In line with the network comparison test, no association between lnRMSSD levels and network structure was observed (see Figure E13 in ESM 1).

Centrality of Symptoms

Subsequently, we were interested in the expected influence indices of the symptoms within the networks. Figure 2 shows the expected influence values for the two groups. A Spearman correlation showed that the expected influence

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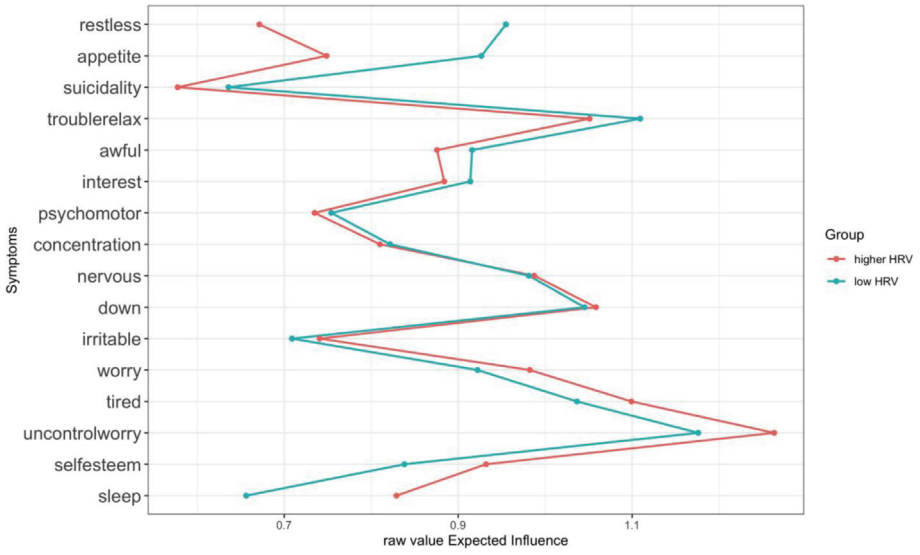

Figure 2. Expected influence values per HRV group (ordered by largest differences between the two groups, with the low HRV group as reference) – low HRV = root mean sum of squares of successive differences between heart beats, RMSSD < 25; higher HRV = higher heart rate variability (RMSSD > 25).

estimates for the two groups were correlated (ρ = .75). For both HRV groups, the symptom with the highest expected influence was *uncontrollable worry*. This indicates that, for both groups, *uncontrollable worry* is the symptom with the strongest connection to the other symptoms. From Figure 2 it can also be observed that the largest difference in expected influence was apparent for the symptom of *restlessness*, which in the low HRV group had a higher expected influence (raw value = 0.95) than in the higher HRV group (0.67). *Appetite* also seemed more central in the low HRV group, and *sleep* seemed more central in the higher HRV group. The network comparison test showed that the difference in *restlessness* centrality was significant (difference C = 0.28, p = .02), whereas *appetite* (C = 0.17, p = .17) and *sleep* centrality (C = 0.17, p = .15) did not differ between the networks.

Bridge Centrality

Next, we examined whether specific symptoms could be identified as bridge symptoms, driving comorbidity between anxiety and depression, and whether these differed between the low and higher HRV groups. The results are depicted in Figure 3.

A Spearman correlation of the bridge expected influence values showed what can also be observed in Figure 3: the correspondence between the bridge expected influence values was low (ρ = .26). Especially, the more physically oriented symptoms had higher bridge expected influence values in the low HRV group than in higher HRV group. However, these differences were not significant. That is, the largest differences were observed for *restlessness* (C = 0.27, p = .06), *appetite* (C = 0.22, p = .06), *concentration* (C = 0.20, p = .16), *troubles relaxing* (C = 0.18, p = .21), and *psychomotor problems* (C = 0.17, p = .22).

Stability Analyses

Results from the stability analyses can be found in ESM 1 (Figures E3-E12). These analyses showed that the centrality estimates were stable (CS > .25) and could be interpreted. Furthermore, the bootstrap analyses showed that overall there were few significantly different edges within the networks, as also demonstrated above. With respect to bridge expected influence (S9-S10), for the low HRV group suicidality was the item that showed the most significant differences with other nodes and had the lowest bridge expected influence. For the higher HRV group appetite demonstrated the lowest bridge expected influence.

Discussion

While previous studies on the relation between HRV and depression and anxiety symptoms relied on sum scores or focused on specific symptoms, here we explored if HRV levels were associated with the network structure of these symptoms. This approach was inspired by the neurovisceral integration model, which posits that low - vagally mediated - HRV is a marker for a negative emotional state characterized by strong positive feedback loops between symptoms of psychopathology (Smith et al., 2017; Thayer & Lane, 2000, 2009).

First of all, we could not replicate previous findings of HRV being related to sum scores of the anxiety and depression scales (Koch et al., 2019). However, we observed that HRV levels were associated with individual symptoms, namely *sleep problems, tiredness,* and *uncontrollable worry*. Although these associations were small, explaining about 1% of the variance, this is in line with previous studies (Chalmers et al., 2016; Gouin et al., 2015; Kanthak et al.,

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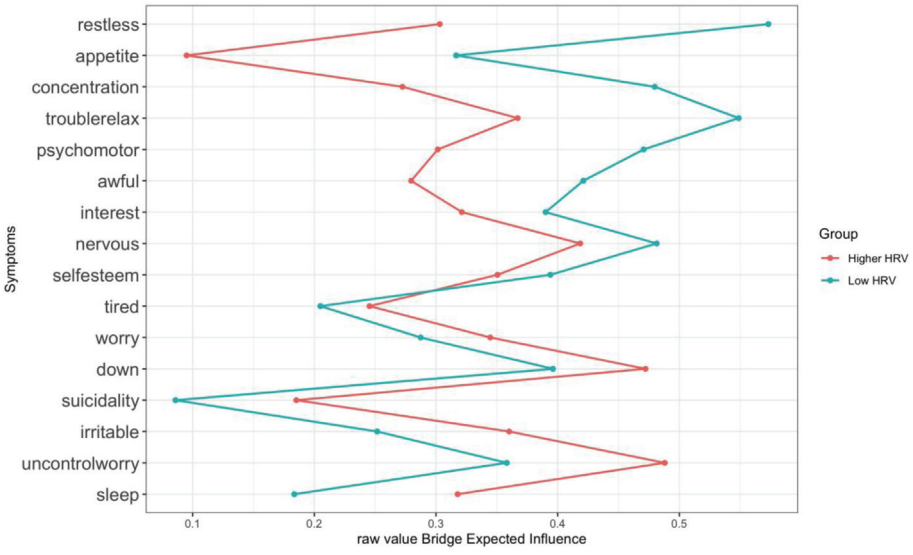

Figure 3. Bridge expected influence values per HRV group, indicating the influence that nodes belonging to one disorder (eg., generalized anxiety) have on another disorder (e.g., depression). Symptoms are ordered by largest differences between the two groups, with the low HRV group as reference. Low HRV = root mean sum of squares of successive differences between heart beats, RMSSD < 25; higher HRV = higher heart rate variability (RMSSD > 25).

2017). More importantly for the aim of this particular study, we also did not find that HRV strongly moderated the network structures, as expressed by the similarities in the density of the networks, their global strength of connectivity, and the connectivity between specific edges. Yet, correlation analyses showed that the bridge centrality indices of both groups (low vs. higher HRV) were only weakly associated and that the more physical symptoms (e.g., *restlessness, appetite*) were stronger bridge symptoms in the low HRV group compared to the higher HRV group, even though these differences were not significant. A significant difference in the expected influence of *restlessness* was observed, however, which was stronger in the low HRV group. Overall, these findings offer a first insight into how short-term resting HRV levels might be associated with symptoms of anxiety and depression. Furthermore, the results from the stability analyses (see ESM 1) showed that the estimates were stable (CS > .25) and could be interpreted. However, the relatively small sample size still warrants caution when interpreting the findings.

Our finding that HRV was not associated with the network structure was surprising. There were no differences in the density of the networks, neither in global strength of connectivity and only in four specific edges. In line with previous studies (Beard et al., 2016; Kaiser et al., 2021; Wang et al., 2020), the relation between *worrying too much* and *uncontrollable worry* provided to be the strongest connection in both subgroups. When exploring differences in the centrality indices, we did however observe that restlessness was a more central node for people low in HRV. Additionally, when exploring connections across disorders, some differences appeared. Even though the network comparison test did not point towards specific symptoms that were having a different impact on comorbidity, the weak-moderate correlation between the indices, and the pattern of absolute differences between the bridge centrality values, suggested that different types of symptoms may account for comorbidity depending on the respective HRV level. Whereas in the higher HRV group, this connection was driven by the main DSM symptoms of each disorder (i.e., *feeling down* and *uncontrollable worry*) in the low HRV group, this appeared to be driven by more physical symptoms (i.e., *psychomotor retardation or agitation* and *restlessness* (cf. Kaiser et al., 2021). In addition, the largest differences in bridge centrality were observed for *restlessness*, *appetite*, *concentration*, *troubles relaxing* and *psychomotor problems*. Yet, overall these differences in bridge centrality were not significant according to the network comparison test. In addition, the networktree analyses did not yield clear differences. In fact, the only method providing some indication of low similarity between the networks was the correlation analysis.

How may we – very cautiously – interpret the lack of similarity as derived from the correlation analyses? In previous studies, physical symptoms have also been found to be the most important bridge symptoms (Kaiser et al., 2021). Yet, here we observed this to be the case, particularly for people with low HRV. One tentative option could be that in people with low HRV, parasympathetic activity (associated with resting and digesting) is reduced and that – as a consequence – somatic expressions of the stress response are more easily evoked, felt and reported (feeling restless, disturbances in the vegetative system). This physical expression of stress could in turn easily trigger both excessive worrying and feeling downhearted. Still, the findings were not consistent across the approaches we used, and further attempts to understand the role of physiological measures in networks of psychopathology symptoms are warranted. So far, only little is known about these interactions, and besides measures of vagal cardiac activity (as in the present study), and measures of inflammation (Fried et al., 2020),

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researchers can rely on a wide range of physical and physiological measures; for example, it has been recently shown that actigraphy can be used to more objectively measure restlessness (Franklin et al., 2021)

Additionally, it is important to keep track of the limitations of this study. Participants in the low HRV group were older and the group consisted of more men. As gender differences in the relation between HRV and depression (Chambers & Allen, 2007), sadness (Verkuil et al., 2015), and worry (Verkuil et al., 2009) have been previously reported, we cannot rule that these differences possibly affected the present results. Large-scale studies are warranted that are able to take these variables into account, for example by using a matched design. Another limitation is that we did not focus on clinical participants, although our sample included participants scoring in the clinical ranges on our measures of anxiety and depression (Kroenke et al., 2001; Spitzer et al., 2006). This limits the generalizability of the current findings, and it remains possible that with a more clinical (and larger) sample more moderating effects of HRV can be detected. One could also argue that the use of a cut-off of an RMSSD level of 25 is problematic. First of all, this led to group size differences. Although we relied on a previous study when selecting this cut-off (Jarczok et al., 2019), other cut-points (such as the upper and lower quartiles) could be used. Furthermore, dichotomizing in its own right has disadvantages and can lead to spurious results (Maxwell & Delaney, 1993). In this respect, it is important to mention that we cross-validated the results for the overall network structures using RMSSD values as a continuous variable, which led to similar results. In addition, several studies that examined the test-retest reliability of HRV values suggest that absolute values of HRV indices are not stable over time, and within-subject variance is substantial (Uhlig et al., 2020). This is a general limitation of physiological measures and obtaining robust results when combining physiology with psychological networks will therefore require multiple larger studies testing the associations under different circumstances.

Conclusion

To conclude, in contrast to the hypothesis based on the neurovisceral integration model, HRV levels were not associated with the connectivity of anxiety and depression symptoms in the current sample. Exploration of the centrality indices suggested that *restlessness* was a more central symptom for people low in HRV, but this remains to be confirmed in future larger studies. Data derived from larger and more clinical samples could be used to further disentangle the complex relation between HRV levels and symptoms of psychopathology.

Electronic Supplementary Material

The electronic supplementary material is available with the online version of the article at https://doi.org/10.1027/0269-8803/a000322

ESM 1. Edge weights low HRV group (Table E1), Edge weights higher HRV group (Table E2), Accuracy and stability of the estimated networks (Figures E1–E12), output of the networktree analysis (E13).

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Bart Verkuil, conceptualization, writing – original draft, data analysis; Magdalena K. Wekenborg: writing – review & editing.
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