Biological Psychology 189 (2024) 108786

Contents lists available at ScienceDirect

Biological Psychology

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

Heart rate and heart rate variability in obsessive-compulsive disorder: Evidence from patients and unaffected first-degree relatives

Franziska Jüres [a,*,1], Christian Kaufmann [a,2], Anja Riesel [a,b,3], Rosa Grützmann [a,c,4], Stephan Heinzel [a,d,e,5], Björn Elsner [a,6], Katharina Bey [f,7], Michael Wagner [f,8], Norbert Kathmann [a,9], Julia Klawohn [a,g,10]

[a] Humboldt-Universität zu Berlin, Department of Psychology, Berlin, Germany
[b] Universität Hamburg, Department of Psychology, Hamburg, Germany
[c] MSB Medical School Berlin, Department of Psychology, Berlin, Germany
[d] Freie Universität Berlin, Department of Education and Psychology, Berlin, Germany
[e] TU Dortmund University, Department of Educational Sciences and Psychology, Dortmund, Germany
[f] University Hospital Bonn, Department of Psychiatry and Psychotherapy, Bonn, Germany
[g] MSB Medical School Berlin, Department of Medicine, Berlin, Germany

ARTICLE INFO

Keywords:
Heart rate
Heart rate variability
Obsessive-compulsive disorder
Resting state
Cardiac vagal control

ABSTRACT

Altered heart rate (HR) and heart rate variability (HRV) are common observations in psychiatric disorders. Yet, few studies have examined these cardiac measures in obsessive-compulsive disorder (OCD). The current study aimed to investigate HR and HRV, indexed by the root mean square of successive differences (RMSSD) and further time domain indices, as putative biological characteristics of OCD. Electrocardiogram was recorded during a five-minute resting state. Group differences between patients with OCD (n = 96), healthy participants (n = 112), and unaffected first-degree relatives of patients with OCD (n = 47) were analyzed. As potential moderators of group differences, we examined the influence of age and medication, respectively. As results indicated, patients with OCD showed higher HR and lower HRV compared to healthy participants. These group differences were not moderated by age. Importantly, subgroup analyses showed that only medicated patients displayed lower HRV compared to healthy individuals, while HR alterations were evident in unmedicated patients. Regarding unaffected first-degree relatives, group differences in HRV remained at trend level. Further, an age-moderated group differentiation showed that higher HRV distinguished relatives from healthy individuals in young adulthood, whereas at higher age lower HRV was indicative of relatives. Both the role of familial risk and medication in HRV alterations need further elucidation. Pending future studies, alterations in HR and potentially HRV might serve as useful indices to characterize the pathophysiology of OCD.

The human cardiovascular system is highly complex and influenced by numerous psychophysiological factors. Cardiac activity, such as heart rate (HR), has been studied as an index of sympathetic and parasympathetic influences of the autonomic nervous system during stressful

* Correspondence to: Humboldt-Universität zu Berlin, Department of Psychology, Unter den Linden 6, 10099 Berlin, Germany.
E-mail address: franziska.jueres@hu-berlin.de (F. Jüres).
[1] https://orcid.org/0000-0003-4146-4488
[2] https://orcid.org/0000-0003-1837-2374
[3] https://orcid.org/0000-0002-1902-6644
[4] https://orcid.org/0000–0001-8706–6894
[5] https://orcid.org/0000-0003-2325-900X
[6] https://orcid.org/0000-0002-4312-4762
[7] https://orcid.org/0000-0001-6392-4997
[8] https://orcid.org/0000-0003-2589-6440
[9] https://orcid.org/0000-0002-1348–7060
[10] https://orcid.org/0000-0002-9436–6948

https://doi.org/10.1016/j.biopsycho.2024.108786
Received 7 December 2022; Received in revised form 16 March 2024; Accepted 22 March 2024
Available online 24 March 2024
0301-0511/© 2024 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

as well as resting and recovery states. During rest, HR is under central inhibitory control by the vagus nerve and thus decreased (Friedman & Thayer, 1998; Grossman et al., 2004). Temporal variability in beat-to-beat intervals of the HR, i.e., heart rate variability (HRV), is supposed to reflect aspects of parasympathetic control over the cardiac system (Smith et al., 2017). The most frequently researched markers of HRV are the root mean square of successive RR interval differences (RMSSD) and the high frequency bins of HRV power (HF-HRV). Both variables are highly correlated and thought to partially reflect parasympathetic (vagal) activity (Allen et al., 2007; Goedhart, van der Sluis, Houtveen, Willemsen, & de Geus, 2007). Generally, HRV has been associated with top-down self-regulation, such as greater capacity for voluntary emotion regulation (Appelhans & Luecken, 2006; Butler et al., 2006; Thayer & Brosschot, 2005; Williams et al., 2015) and higher cognitive functioning (Kim et al., 2013), especially inhibitory control (Hansen et al., 2003; Nashiro et al., 2022; Williams et al., 2016). The link between affective processing, emotion regulation, and the cardiovascular system has been most prominently conceptualized and described in the neurovisceral integration model (Thayer et al., 2009; Thayer & Lane, 2000). Consequently, investigating HR and HRV allows for characterizing autonomic regulatory system function by means of central neural control mechanisms related to affective and cognitive information processing.

In terms of psychopathology, altered patterns in cardiac activation, as reflected in higher HR and lower HRV, are shared across the spectrum of internalizing disorders and symptoms. Accordingly, reduced HRV has been discussed as a transdiagnostic biomarker of psychopathology (Beauchaine & Thayer, 2015). For patients with depression, not only a higher resting HR and lower HRV, as measured by RMSSD and HF-HRV, have been found, but a decrease in RMSSD and HF-HRV has also been linked to greater severity of depressive symptoms (Agelink et al., 2002; Kemp et al., 2010; Koenig et al., 2016). Patients with depression and comorbid anxiety disorders seem to display the greatest reductions in HRV (RMSSD and HF-HRV) compared to patients without comorbidities and compared to healthy participants (Kemp et al., 2012), pointing to a cardiac vagal imbalance linked to anxiety. Indeed, the same pattern of altered resting cardiac activity as reported in depression has been repeatedly observed across several anxiety disorders (for meta-analysis, see Chalmers et al., 2014). Studies among children and adolescents with anxiety disorder or depression report similar findings compared to adult samples (for meta-analysis, see Koenig et al., 2016; for review, see Paniccia et al., 2017; Sharma et al., 2011; Srinivasan, 2006).

Obsessive-compulsive disorder (OCD) is a severe mental disorder considered part of the internalizing spectrum and mainly characterized by intrusive, anxiety or discomfort inducing obsessions and/or burdensome compulsions (American Psychiatric Association, 2020) that affects about 3% of the general population in their lifetime (Ruscio et al., 2010). Most patients with OCD develop comorbidities (Ruscio et al., 2010), with comorbid anxiety or affective disorders burdening up to 73% of patients with OCD (Fineberg et al., 2013). On the psychophysiological level, the disorder has been associated with several alterations, such as increased and less flexibly adapted neural indices of performance monitoring (Grützmann et al., 2021; Riesel, 2019; Riesel et al., 2019), conflict resolution (Bey, Kloft, et al., 2017; Chamberlain et al., 2007), and altered functional connectivity of the default mode network (Beucke et al., 2013). Cardiac indices of autonomic regulation have only scarcely been investigated in OCD so far. Whereas some studies reported no differences in HR or HF-HRV between patients with OCD and healthy participants (McCarthy et al., 1995; Slaap et al., 2004), others found higher HR and/ or lower HF-HRV in patients with OCD compared to healthy individuals (Olbrich et al., 2022; Pittig et al., 2013). In the most recent study on cardiac activity in OCD, 51 untreated and drug-naïve patients with OCD exhibited significantly higher HR at rest, but no group differences in resting HRV (pNN50 and HF-HRV) were found (Olbrich et al., 2022). In the studies cited above, sample size was comparatively small, leaving a necessity for further research in OCD with larger study samples. Importantly, both HR and HRV seem to carry potential for a more comprehensive explanation of the pathogenesis of internalizing disorders, such as OCD. Previous results in healthy adolescents indicated a moderating role of low HRV, indexed by the respiratory sinus arrhythmia (RSA), on the association between psychosocial stress and internalizing symptoms (McLaughlin et al., 2015). In terms of HR, a longitudinal study in healthy adolescent Swedish men found a higher resting HR to be related to higher risk for OCD, schizophrenia, and anxiety disorders (Latvala et al., 2016). Lower HR and higher HRV (RMSSD and HF-HRV) seemingly predict reduced likelihood of depression in former healthy men over a ten year follow up (Jandackova et al., 2016). Thus, low cardiac vagal tone in healthy individuals could represent a vulnerability marker for internalizing psychopathological symptoms. Considering this notion, study findings robustly point to genetic influences on resting HR and HRV in adults as well as adolescents. For resting HR, heritability varies between 61 – 68% (De Geus et al., 2007; Snieder et al., 2003; Wang et al., 2015) and for resting HRV between 31 – 64% (Golosheykin et al., 2017; Kupper et al., 2004; Uusitalo et al., 2007). With HR and HRV being considered as potential biomarkers of some psychiatric disorders, research focus has shifted onto individuals with high familiar risk of developing a psychiatric disorder. On the basis of these findings and concepts, we further aimed to explore HR and HRV in unaffected first-degree relatives of patients with OCD.

In order to investigate first-degree relatives of patients with OCD in this study, we included unaffected parents, siblings, and children of patients with OCD. Patients with OCD were seeking therapy at an outpatient clinic and a minimum of constraints were applied to the clinical sampling procedure (for detailed sample and exclusion criteria, see below). This sampling approach resulted in groups spanning a wide age range. Since healthy participants were recruited with a similar age distribution to that of patients, the overall study comprises a relatively heterogenous sample with an age range of 18 – 65 years. This in turn lead to the secondary study aim of investigating the relation between age, cardiac activity, and psychopathology. Cardiac autonomic measures have generally been found to show considerable developmental effects in healthy individuals. As existing findings suggest, the cardiac vagal system develops from birth throughout young childhood. Resting HR in infants, young children, and adolescents is negatively correlated with age (Alkon et al., 2011; Alkon et al., 2003; Fernandes et al., 2013; Rabbia et al., 2002). Several studies report an age-related increase in parasympathetic activation, measured by HRV or RSA, which seems to stabilize around the age of 10 years (Alkon et al., 2011; Bar-Haim et al., 2000; De Rogalski Landrot et al., 2007; Galeev et al., 2002; Michels et al., 2013; Silvetti et al., 2001). Whereas a decrease in HR in adulthood is only moderate or not detectable (Agelink et al., 2001; Boettger et al., 2010; Fukusaki et al., 2000; Sloan et al., 2008; Umetani et al., 1998; Voss et al., 2012), HRV shows a decline until the age of approximately 60 years (Sloan et al., 2008; Umetani et al., 1998; Voss et al., 2012; 2015). In sum, it is conceivable that group differences in cardiac measures might vary at different age levels, indicating a potential interaction of psychopathology and developmental effects on cardiac regulation. Gentzler et al. (2012) reported such developmental interaction in children at high-risk or low-risk for depression. They found an increase in resting HRV, indicated by the RSA, with age in low-risk children but no HRV increase in children with high-risk for depression. To this end, we investigated the effects of age on HR and HRV and the overlap with psychopathology by taking into consideration age variation within the three participant groups.

The current study aimed to extend research on altered HR and HRV as biological characteristics of internalizing psychopathology by investigating resting state cardiac activity, captured in HR and HRV (e.g., RMSSD), in individuals diagnosed with OCD. We hypothesized that cardiac alterations would be in line with previous observations in anxiety disorders, suggesting higher resting HR and lower HRV (RMSSD) in patients compared to healthy individuals. Moreover, we were interested

Table 1
Demographic and Clinical Characteristics of Patients With Obsessive-Compulsive Disorder (OCD), Healthy Control Participants (HC), and Unaffected First-Degree Relatives of Patients With OCD (REL)

Measure	OCD (n = 96)	HC (n = 112)	REL (n = 47)	Test statistic	p
Age (years)	30.8 (8.8)	32.4 (10.5)	45.0 (15.6)	$F(2, 110.65) = 16.94$[a]	**< .001**
Gender (n female:male)	51:45	60:52	30:17	$\chi^2(2) = 1.70$	.427
Body mass index[b]	24.1 (4.7)	25.2 (5.6)	23.5 (3.3)	$F(2, 246) = 2.20$	.113
Smoking (n yes:no)[c]	28:62	40:71	10:36	$\chi^2(2) = 3.09$	.213
Verbal intelligence (WST)[d]	102.6 (10.6)	103.9 (9.7)	106.2 (9.0)	$F(2, 249) = 1.97$	.142
BDI-II[e]	19.7 (11.0)	2.8 (3.5)	3.7 (4.4)	$F(2, 111.37) = 102.14$[a]	**< .001**
OCI-R[e]	27.9 (12.7)	3.9 (3.9)	5.7 (6.1)	$F(2, 103.19) = 155.34$[a]	**< .001**
STAI trait[f]	53.8 (10.2)	32.3 (7.3)	33.5 (7.3)	$F(2, 123.32) = 146.88$[a]	**< .001**
MADRS	13.3 (9.1)	–	–	–	–
Y-BOCS total score	23.5 (5.5)	–	–	–	–

Note. Means with standard deviation in parentheses are reported. Boldface p values indicate significant group differences ($p < .05$). WST = Wortschatztest; BDI-II = Beck Depression Inventory-II; OCI-R = Obsessive-Compulsive Inventory-Revised; STAI = State-Trait Anxiety Inventory; MADRS = Montgomery-Asberg Rating Depression Scale; Y-BOCS = Yale-Brown Obsessive Compulsive Scale. [a] Welch univariate analysis of variance was performed due to unequal group variances. [b] Data on body mass index was missing for five patients with OCD and one healthy control participant. [c] Smoking status was missing for six patients with OCD, one healthy control participant, and one unaffected first-degree relative. [d] WST scores were missing for three individuals. [e] BDI-II and OCI-R scores were missing for two participants. [f] STAI trait scores were missing for nine participants.

in whether unaffected individuals with increased familial risk for OCD would show similar alterations as the patient group with a current OCD diagnosis, which would suggest cardiac alterations as potential risk markers. As to the best of our knowledge, no previous studies on cardiac activity in unaffected first-degree relatives of patients with OCD are available yet, we thus studied this question exploratively. Since numerous factors have been demonstrated to influence the cardiovascular system, effects of several sociodemographic (gender, body mass index, smoking) and psychological (obsessive-compulsive, affective, and anxious symptoms, medication) factors on HR and HRV were tested exploratively. So far, studies on HR and HRV in OCD were either conducted in medication-free samples (McCarthy et al., 1995; Olbrich et al., 2022; Slaap et al., 2004) or were limited in investigating the impact of medication due to small sample size (Pittig et al., 2013). Lastly, we investigated whether group differences between patients with OCD and a healthy comparison sample would be moderated by age. We expected that with age, HRV (RMSSD) would decrease in healthy participants, whereas in patients with OCD, we expected HRV (RMSSD) to be low across the entire age span. Further, if increased familiar risk relates to alterations in HRV compared to patients with OCD, unaffected first-degree relatives might show a similar pattern of age and HRV (RMSSD) as described for patients with OCD. Yet, due to the overall higher age of unaffected first-degree relatives in the study, age and HRV effects could overlap. We thus did not specify any hypothesis for cardiac differences in unaffected relatives. No hypothesis regarding HR and age was made due to inconsistencies in study reports of a decrease in HR with age; examination of the relation between HR and age was thus performed exploratively.

1. Method

1.1. Participants

The sample included a total of 328 participants with resting state electrocardiogram (ECG) data (150 healthy participants, 126 patients with current OCD, and 52 unaffected first-degree relatives). Due to exclusion criteria defined below for the present investigation, 12 healthy participants (current anxiety disorder $n = 5$, current OCD/tic disorder $n = 4$, and drug misuse $n = 3$) and one patient with OCD (drug misuse) had to be excluded. Data from nine patients with OCD were discarded from current analyses due to intake of tricyclic antidepressant medication, which have been shown to affect cardiac activity (Alvares et al., 2016). Due to insufficient data quality, a total of 18 patients with OCD, 25 healthy participants, and four unaffected relatives were also excluded from further analyses. Finally, two patients with OCD, one healthy participant, and one unaffected relative were defined as outliers as their mean HRV (RMSSD) was three standard deviations from the group mean. Consequently, these four participants were also removed from analyses. The final sample consisted of 96 patients with OCD, 112 healthy participants, and 47 unaffected first-degree relatives of patients with OCD (see Table 1).

Participants in the analyzed sample were aged between 18 and 65 years, native German speakers, had normal or corrected-to-normal vision, and did not report any current or past neurological diseases. Psychiatric disorders were assessed by trained psychologists with the Structural Clinical Interview for DSM-IV (SCID; Wittchen et al., 1997). Exclusion criteria for all participants were a lifetime diagnosis of any psychotic, bipolar, or substance use disorder, use of benzodiazepines in the previous four weeks or of antipsychotics three months before the study appointment. The study was conducted in accordance with the Declaration of Helsinki and approved by the ethical review board at Humboldt-Universität zu Berlin. Participants gave written consent and received a compensation of 10 Euros per hour.

Patients were diagnosed with OCD as primary disorder and recruited via the specialized outpatient clinic at Humboldt-Universität zu Berlin. All patients were awaiting treatment with cognitive behavioral psychotherapy. A total of 74 patients with OCD had one or more comorbid diagnoses, namely affective disorders ($n = 64$), anxiety disorders ($n = 23$), somatoform disorders ($n = 6$), eating disorders ($n = 3$), and personality disorders ($n = 11$). Thirty-eight patients received medical treatment, including selective serotonin reuptake inhibitors (SSRI; $n = 33$), serotonin–norepinephrine reuptake inhibitors (SNRI; $n = 4$), or a combination of SSRI and SNRI ($n = 1$).

Healthy participants were recruited via online advertisement with similar age and gender distribution to that of patients. They were free of any current or past psychiatric disorder and without a positive family history of OCD.

Unaffected first-degree relatives of patients with OCD were contacted via the outpatient clinic after consent of the respective patient. They were excluded if they met criteria for diagnosis of OCD at any time or for any other psychiatric disorder at the time of participation.

1.2. Self-report questionnaires and clinical interviews

Participants completed several self-report questionnaires. Obsessive-compulsive symptoms were assessed with the Obsessive-Compulsive Inventory-Revised (OCI-R; 20 items, 5-point Likert scale ranging from 0–4; Cronbach's α = .85; Foa et al., 2002; Gönner et al., 2008),

depressive symptoms with the Beck Depression Inventory-II (BDI-II; 21 items, 4-point rating scale ranging from 0–3; Cronbach's α = .92; Beck et al., 1996; Hautzinger et al., 2006) and trait anxiety level with the trait scale of the State-Trait Anxiety Inventory (STAI trait; 20 items, 4-point Likert scale ranging from 1–4; Cronbach's α = .89; Laux et al., 1981; Spielberger et al., 1983). We further estimated verbal intelligence with a German vocabulary test (WST; 42 items, each with one real target word and five pseudowords; Cronbach's α = .94; Schmidt & Metzler, 1992). Patients with OCD were interviewed by trained clinical psychologists using the Yale-Brown Obsessive Compulsive Scale (Y-BOCS; 10 items, 5-point rating scale ranging from 0–4; r = .90; Goodman et al., 1989; Hand & Büttner-Westphal, 1991; Jacobsen et al., 2003), to assess the severity of obsessive-compulsive symptoms, and the Montgomery-Asberg Depression Rating Scale (MADRS; 10 items, 7-point rating scale ranging from 0–6; r = .76; Montgomery & Asberg, 1979; Neumann & Schulte, 1989) to assess the severity of depressive symptoms.

1.3. Resting state paradigm

The data were collected as part of a larger research study investigating several biomarkers and potential endophenotypes in OCD during different tasks and conditions, such as neural markers of brain activity (e.g., frontal alpha asymmetry, error-related negativity, working memory), eye movement markers (e.g., smooth pursuit eye movements) or genetic markers (e.g., oxytocin receptor gene). Results from other analyses within the study are presented and discussed elsewhere (Bey et al., 2022; Bey et al., 2018; Bey, Kloft, et al., 2017; Bey, Lennertz, et al., 2017; Bey et al., 2019; Bey et al., 2020; Grützmann et al., 2021; Heinzel, Bey, et al., 2021; Heinzel et al., 2018; Heinzel, Kaufmann, et al., 2021; Kathmann et al., 2016; Riesel et al., 2019). Participants completed several consecutive tasks: First a flanker task followed by the here reported five-minute resting state paradigm, then a passive viewing paradigm using emotional pictures was administered followed by another five-minute resting state. During all tasks, electroencephalogram (EEG) and ECG were recorded. This study only considers ECG data assessed during the first five-minute resting state paradigm, due to possible confounding factors of the passive viewing paradigm in the second resting state period. In the five minutes of the resting state paradigm, participants were instructed to sit still, to keep their gaze on the white fixation cross, to stay awake and to not think of anything in particular. The white fixation cross was presented against a black background on a 19-inch computer monitor and in a .4° viewing angle. The task was presented with Presentation software (Neurobehavioral Systems Inc, Albany, CA).

1.4. ECG recording and preprocessing

ECG was recorded continuously, together with the EEG, using three Ag/AgCl electrodes, one above the collarbone, one on the left mastoid, and one placed on the cheek as ground electrode. Data were recorded at a sampling rate of 1000 Hz using BrainVision amplifiers (Brain Products, München, Germany). An online band-pass filter of 0.05 – 250 Hz was applied to reduce respiratory influences.

Raw data were extracted, band-passed filtered (10 – 40 Hz), and imported into QRS Tool (Allen et al., 2007). In QRS Tool, inter-beat intervals (IBIs) were calculated, manually screened, and hand-corrected for artifacts and ectopic beats. Data with unreliable R peaks identification (e.g., due to excessive noise, movement artifacts, arrhythmias) were excluded from analysis. Data with few ectopic beats were manually interpolated but excluded in case of excessive anomalies. A total of 47 out of 306 (15.36%) participants (18 patients with OCD, 25 healthy participants, four unaffected relatives) were excluded from all analyses after this screening process. Following R peak detection, IBIs were then exported to Cardiac Metric X (CMetX; Allen et al., 2007) to compute the mean HR and time domain HRV variables, such as the RMSSD, SDNN (standard deviation of all RR intervals), pNN50 (percentage of successive normal sinus RR intervals more than 50 ms) and logRSA (logarithm of the respiratory sinus arrhythmia). Both time and frequency domain analyses are most frequently used across studies investigating parasympathetic activation (Malik, 1996). As CMetX computes time domain analyses and as this is the most precise and commonly used assessment (Huikuri et al., 2009), we will thus focus on time domain variables measuring the differences between subsequent R-R intervals in this study. All HRV analyses are based on the RMSSD as one of the most reported time domain measure with superior statistical properties and considered to partially reflect variations in cardiac vagal activity (Ciccone et al., 2017; Kleiger, Stein, & Bigger, 2005; Laborde et al., 2017; Malik, 1996). For the above-mentioned variables SDNN, pNN50, and logRSA, we will report descriptive statistics and main analyses to provide a more comprehensive picture of the autonomic profile of participant groups (see Table 2). Both the RMSSD as well as the logRSA highly correlate with HF-HRV (Allen et al., 2007; Kleiger et al., 2005). The logRSA represents the natural log of the time series filtered in

Table 2
Cardiac Measures During Rest in the Groups of Patients With Obsessive-Compulsive Disorder (OCD), Healthy Control Participants (HC), and Unaffected First-Degree Relatives of Patients With OCD (REL)

Measure	OCD (n = 96)	HC (n = 112)	REL (n = 47)	Test statistic	η^2	p
Mean HR	73.11 (10.20)[1]	69.56 (8.22)[2]	70.78 (8.65)	$F(2, 252) = 3.98$	.031	**.020**
Adjusted for age	72.67 (0.93)[1]	69.33 (0.86)[2]	72.21 (1.43)	$F(2, 251) = 3.97$	.031	**.020**
RMSSD (log)	3.40 (0.50)[1]	3.58 (0.45)[2]	3.35 (0.60)	$F(2, 114.98) = 5.12$[a]	.039	**.007**
Adjusted for age	3.34 (0.05)[1]	3.55 (0.04)[2]	3.55 (0.07)	$F(2, 251) = 6.07$	.046	**.003**
SDNN (log)	3.86 (0.43)	3.96 (0.35)	3.84 (0.53)	$F(2, 111.13) = 2.24$[a]	.017	.112
Adjusted for age	3.81 (0.40)	3.94 (0.37)	3.99 (0.06)	$F(2, 251) = 3.77$	.029	**.024**
pNN50 (log)	2.00 (1.42)	2.37 (1.29)	1.85 (1.62)	$F(2, 239) = 2.90$	.024	.057
Adjusted for age	1.87 (0.14)[1]	2.32 (0.13)[2]	2.29 (0.22)	$F(2, 238) = 3.19$	.026	**.043**
RSA (log)	5.83 (1.03)	6.13 (0.93)	5.71 (1.34)	$F(2, 113) = 3.28$[a]	.026	**.041**
Adjusted for age	5.69 (0.10)[1]	6.05 (0.09)[2]	6.20 (0.15)[2]	$F(2, 251) = 5.51$	.042	**.005**

Note. For each cardiac measure, means with standard deviation in parentheses as well as adjusted means for age with standard error in parentheses are reported. RMSSD, SDNN, pNN50, and RSA are time-domain measures of heart rate variability (Allen et al., 2007). All variables, except Mean HR, were log-transformed before analyses due to non-normal distribution. Mean HR is in beats per minutes. Boldface p values represent statistical significance of the main effect group ($p < .05$). Within a row, different numerical superscripts indicate significant differences in post hoc group comparisons ($p < .05$) after Bonferroni correction. Absence of numerical superscript indicates no significant group difference. HR = heart rate; RMSSD = root mean square of successive RR interval differences; SDNN = standard deviation of all RR intervals; pNN50 = percentage of successive normal sinus RR intervals more than 50 ms; RSA = respiratory sinus arrhythmia.
[a] Welch's univariate analysis of variance was performed due to unequal group variances.

Table 3
Logistic Regression Models to Predict Group Status From Cardiac Measures and Age

Variable	R^2	χ^2	*p*	Adj. OR	95% CI	*p*
Patients with OCD vs. healthy participants						
DV: Group	.06	8.85	.031			
Mean HR				1.042	[1.010, 1.075]	**.010**
Age				0.987	[0.958, 1.017]	.395
Mean HR × Age				0.999	[0.996, 1.002]	.407
DV: Group	.09	14.18	.003			
RMSSD				0.341	[0.178, 0.653]	**.001**
Age				0.974	[0.944, 1.005]	.100
RMSSD × Age				1.053	[0.989, 1.122]	.108
Healthy participants vs. unaffected first-degree relatives						
DV: Group	.26	31.92	< .001			
Mean HR				1.039	[0.991, 1.089]	.115
Age				1.080	[1.048, 1.112]	**< .001**
Mean HR × Age				0.999	[0.996, 1.003]	.752
DV: Group	.32	40.40	< .001			
RMSSD				2.106	[0.767, 5.783]	.148
Age				1.082	[1.042, 1.123]	**< .001**
RMSSD × Age				0.906	[0.851, 0.965]	**.002**

Note. Logistic regressions were performed to predict the dichotomous dependent variable group, comprising either patients with OCD and healthy participants (0 = healthy participants, 1 = patients with OCD) or healthy participants and unaffected first-degree relatives of patients with OCD (0 = healthy participants, 1 = unaffected first-degree relatives). The Nagelkerke R^2 and χ^2 statistics are reported for the logistic regression models. RMSSD was log-transformed for analyses. Mean HR is in beats per minute. All predictors were grand mean-centered. Boldface *p* values indicate significant group differences ($p < .05$). Adj. OR = adjusted odds ratio; OCD = obsessive-compulsive disorder; DV = dependent variable; HR = heart rate; RMSSD = root mean square of successive RR interval differences.

the .12 – .40 Hz band, the same band HF-HRV is defined by. Hence, HF-HRV is commonly referred to as respiration band (Eckberg & Eckberg, 1982), and therefore sometimes used interchangeably with logRSA (Lane et al., 2013).

1.5. Statistical analysis

Statistical analyses and figures were performed using SPSS (Version 28.0, SPSS Inc., Chicago, IL, USA) and R (Version 4.0.4; R Core Team, 2021). All statistical tests were two-tailed and a significance level of .05 was applied. For significant results, effect sizes (Cohen's *d*, eta squared η^2, or partial eta squared η_p^2) are reported. For univariate analysis of variance (ANOVA), post hoc comparisons were conducted and corrected for multiple comparisons using the Bonferroni correction. In case of unequal group variances as indexed by significant Levene's tests, *p* values were adjusted with Games-Howell correction.

Group differences in demographics and clinical data were examined using ANOVAs and followed up by independent samples Student's or Welch's *t*-tests or χ^2-tests.

All HRV variables were non-normally distributed in participant groups (Shapiro-Wilk and Kolmogorv-Smirnov tests, all $ps < .002$). Thus, the following analyses are performed with log-transformed cardiac indices, except for Mean HR, as determined by the Box-Cox method (Box & Cox, 1964). The variable Mean HR was normally distributed.

To investigate group differences in HR and HRV between patients with OCD, healthy participants, and unaffected first-degree relatives, univariate ANOVAs were performed. As age ranged widely in the group of unaffected relatives and as it significantly influences HR and HRV, we accounted for the effect of age in the group comparison on HR and HRV by computing a univariate analysis of covariance (ANCOVA) with age as continuous covariate. To promote comparison across studies and to provide a broad autonomic profile of participant groups, ANOVAs with group as between-subjects factor as well as ANCOVAs with age as covariate and group as between-subjects factor on the log-transformed variables SDNN, pNN50, and LogRSA are also displayed in Table 2.

Additionally, to test our hypothesis whether age interacts with HRV (RMSSD) and HR in the classification of group status (patient with OCD, unaffected relative with high-risk for OCD, or healthy participant with low risk for OCD), classification analyses with age as a moderator were performed. Specifically, we used binary logistic regressions to predict group status (patients with OCD vs. healthy participants, healthy participants vs. unaffected relatives) with HR or HRV, respectively, and age as independent predictors, as well as the interaction between the predictors (see Table 3). All variables were grand mean-centered for the regression analyses. Significant interactions were followed-up with Johnson-Neyman analyses using the PROCESS Macro for SPSS (Version 4.1; Hayes, 2017) to resolve the moderation. We exploratively analyzed the effect of medication status on group differences in HR and HRV (RMSSD), respectively, with subgroup analyses (medicated vs. unmedicated patients with OCD, medicated patients with OCD vs. healthy individuals, unmedicated patients with OCD vs. healthy individuals) using univariate ANOVAs as well as univariate ANCOVAs with age as covariate (see Table 4).

The following exploratory analyses are presented in detail in the Supplemental Material. We performed univariate ANCOVAs on HR or HRV (RMSSD) with gender, body mass index, or smoking as a covariate and group as between-subject factor to test whether observed group effects remain significant after accounting for potential influence of these variables (see Supplemental Material, page 3). In an explorative manner, we ran Pearson correlations within participant groups to further explore relationships between obsessive-compulsive, anxiety, or depressive symptom dimensions and cardiac activity (see Table S1).

2. Results

2.1. Demographic and clinical data

Demographic and clinical data of patients with OCD, healthy participants, and unaffected first-degree relatives of patients with OCD along with statistics of group comparisons are depicted in Table 1. Groups did not differ regarding gender, body mass index, verbal intelligence (WST), or status of smoking (all $ps > .113$). Groups differed significantly in age, with unaffected relatives on average being older than patients with OCD, $t(60.67) = 5.83$, $p < .001$, $d = -1.25$, and healthy participants, $t(64.23) = -5.11$, $p < .001$, $d = -1.04$. Patients with OCD and healthy participants did not differ in age ($p = .991$).

As expected, patients with OCD scored significantly higher on obsessive-compulsive symptoms (OCI-R), $t(109.01) = -17.68$,

Table 4
Exploratory Analyses on Medication Effects on HR and HRV With Age as Covariate

Model	Variables		Test statistic	η^2	p
	DV	Factors			
Unmedicated patients with OCD vs. *healthy participants*					
1	Mean HR	Group	$F(1, 87.22) = 6.58$[a]	.046	**.012**
2	Mean HR	Group	$F(1, 167) = 7.54$	.043	**.007**
		Age	$F(1, 167) = 4.68$	.027	**.032**
3	RMSSD (log)	Group	$F(1, 168) = 2.01$	.012	.158
4	RMSSD (log)	Group	$F(1, 167) = 3.08$	.018	.081
		Age	$F(1, 167) = 18.29$	.099	**< .001**
Medicated patients with OCD vs. *healthy participants*					
1	Mean HR	Group	$F(1, 148) = 2.23$	.015	.138
2	Mean HR	Group	$F(1, 147) = 1.82$	.012	.179
		Age	$F(1, 147) = 2.85$	.019	.093
3	RMSSD (log)	Group	$F(1, 148) = 11.86$	.074	**< .001**
4	RMSSD (log)	Group	$F(1, 147) = 15.76$	.097	**< .001**
		Age	$F(1, 147) = 17.10$	.104	**< .001**
Medicated patients with OCD vs. *unmedicated patients with OCD*					
1	Mean HR	Group	$F(1, 93.95) = 1.22$[a]	.011	.272
2	Mean HR	Group	$F(1, 93) = 1.23$	.013	.271
		Age	$F(1, 93) = 4.15$	.043	**.045**
3	RMSSD (log)	Group	$F(1, 94) = 3.24$	.033	.075
4	RMSSD (log)	Group	$F(1, 93) = 3.62$	.037	.060
		Age	$F(1, 93) = 3.86$	.040	.052

Note. Analyses of variance on HR and HRV (RMSSD) with group as between-subjects factor were computed. Analyses of covariance on HR and HRV (RMSSD) included group as between-subjects factor and age as covariate. RMSSD was log-transformed due to non-normal distribution. Boldface p values represent statistical significance of the main effect group or of age ($p < .05$). HR = heart rate in beats per minute; HRV = heart rate variability; RMSSD = root mean square of successive RR interval differences; DV = dependent variable; OCD = obsessive-compulsive disorder.
[a] Welch's univariate analysis of variance was performed due to unequal group variances.

$p < .001$, $d = -2.64$, depressive symptoms (BDI-II), $t(110.47) = -14.32$, $p < .001$, $d = -2.13$, and anxiety symptoms (STAI trait), $t(153.57) = -16.67$, $p < .001$, $d = -2.46$, than healthy participants. They also scored significantly higher on symptom measures than unaffected relatives, OCI-R: $t(139.89) = 14.06$, $p < .001$, $d = 2.02$; BDI-II: $t(135.91) = 12.23$, $p < .001$, $d = 1.70$; STAI trait: $t(134) = 12.07$, $p < .001$, $d = 2.18$. Healthy participants and unaffected relatives did not differ regarding depressive, obsessive-compulsive, or anxious symptom severity (all $ps > .152$).

Medicated and unmedicated patients did not differ in age ($p = .704$), gender ($p = .619$), or severity of obsessive-compulsive (Y-BOCS: $p = .085$), depressive (BDI-II: $p = .242$), or anxious symptoms (STAI trait: $p = .287$), respectively.

2.2. Relation between cardiac measures and age within groups

Pearson correlations between the main variables of interest in each group are presented in Fig. 1 and in the Supplemental Material (see Table S1). HR was marginally negatively correlated with age in patients with OCD, $r(94) = -.20$, 95% CI [−.39, −.00], $p = .049$. No correlation between HR and age was observed in healthy participants, $r(110) = -.13$, 95% CI [−.31,.05], $p = .163$, or in unaffected relatives, $r(45) = -.17$, 95% CI [−.44,.12], $p = .256$. Opposed to this, age was negatively correlated with HRV (RMSSD) within healthy participants, $r(110) = -.37$, 95% CI [−.52, −.20], $p < .001$, and unaffected relatives, $r(45) = -.68$, 95% CI [−.81, −.48], $p < .001$, but only on trend level within patients with OCD, $r(94) = -.19$, 95% CI [−.38,.01], $p = .065$.

2.3. Group differences in HR

Data and descriptive statistics on HR per group are displayed in Fig. 2 and Table 2. Results of the ANOVA on resting HR revealed a main effect of group. Post hoc comparisons revealed that patients with OCD exhibited a higher HR at rest than healthy participants, $t(182.03) = -2.73$, $p = .016$, $d = -0.39$, whereas there were no group differences between unaffected first-degree relatives and patients with OCD or between unaffected relatives and healthy participants (all $ps > .455$).

2.3.1. Accounting for sociodemographic effects

When adding age as a covariate, results indicated a significant influence on HR, $F(1, 251) = 6.54$, $p = .011$, $\eta_p^2 = .025$. Yet, after accounting for age, the main effect of group remained significant (see Table 2), that is patients with OCD showed a higher resting HR than healthy participants, $p = .025$, $M_{Diff} = 3.34$, 95% CI [0.32, 6.36]. Neither gender nor body mass index nor smoking were significant covariates (all $ps > .268$; see Supplemental Material, page 3). Thus, accounting for them did not change the above reported group differences in HR.

2.3.2. Group classification with age as a moderator

Results of all binary logistic regression models of HR as a classifier of group status are presented in Table 3. The regression model with HR, age, and the interaction of both predicting group status of patients with OCD versus healthy participants was significant ($p = .031$, overall classification accuracy of 60.6%). Yet, the interaction of interest between age and HR was not. The analogous logistic regression with HR, age, and their interaction as predictors for status of healthy participants or of unaffected first-degree relatives showed a significant regression model ($p < .001$, overall classification accuracy of 77.4%), but the interaction between HR and age did not contribute to the prediction of group status.

2.3.3. Exploratory subgroup analyses on medication effects

As depicted in Table 4, unmedicated patients showed a higher HR than healthy individuals. No differences in HR were observed between medicated and unmedicated patients or medicated patients and healthy participants. These findings in group differences did not change after accounting for age.

2.4. Group differences in HRV

Data and descriptive statistics on HRV variables per group are displayed in Table 2, the distribution of the main HRV variable RMSSD is illustrated in Fig. 2. Analysis of RMSSD by means of a univariate ANOVA yielded a significant main effect of group, reflecting that groups differed in their resting HRV (RMSSD). Post hoc comparisons revealed a group difference between patients with OCD and healthy participants in RMSSD, $t(206) = 2.76$, $p = .029$, $d = 0.38$, with patients exhibiting a lower HRV (RMSSD) than healthy participants. Furthermore, healthy participants showed a higher HRV (RMSSD) than unaffected relatives but only on trend level, $t(68.39) = 2.37$, $p = .053$. There was no group difference between unaffected relatives and patients with OCD ($p > .99$). Importantly, further indices of HRV support the group effects in HRV (see Table 2).

2.4.1. Accounting for sociodemographic effects

In the ANCOVA on RMSSD, a main effect of the covariate age was observed, $F(1, 251) = 49.41$, $p < .001$, $\eta_p^2 = .164$. Yet, the main effect of group remained significant, as displayed in Table 2. Post hoc tests revealed that patients with OCD showed a significantly reduced HRV (RMSSD) compared to healthy participants, $p = .003$, $M_{Diff} = -0.21$, 95% CI [− 0.36, − 0.06], and compared to unaffected relatives but only on trend level, $p = .056$, $M_{Diff} = -0.21$, 95% CI [− 0.43, 0.00]. There

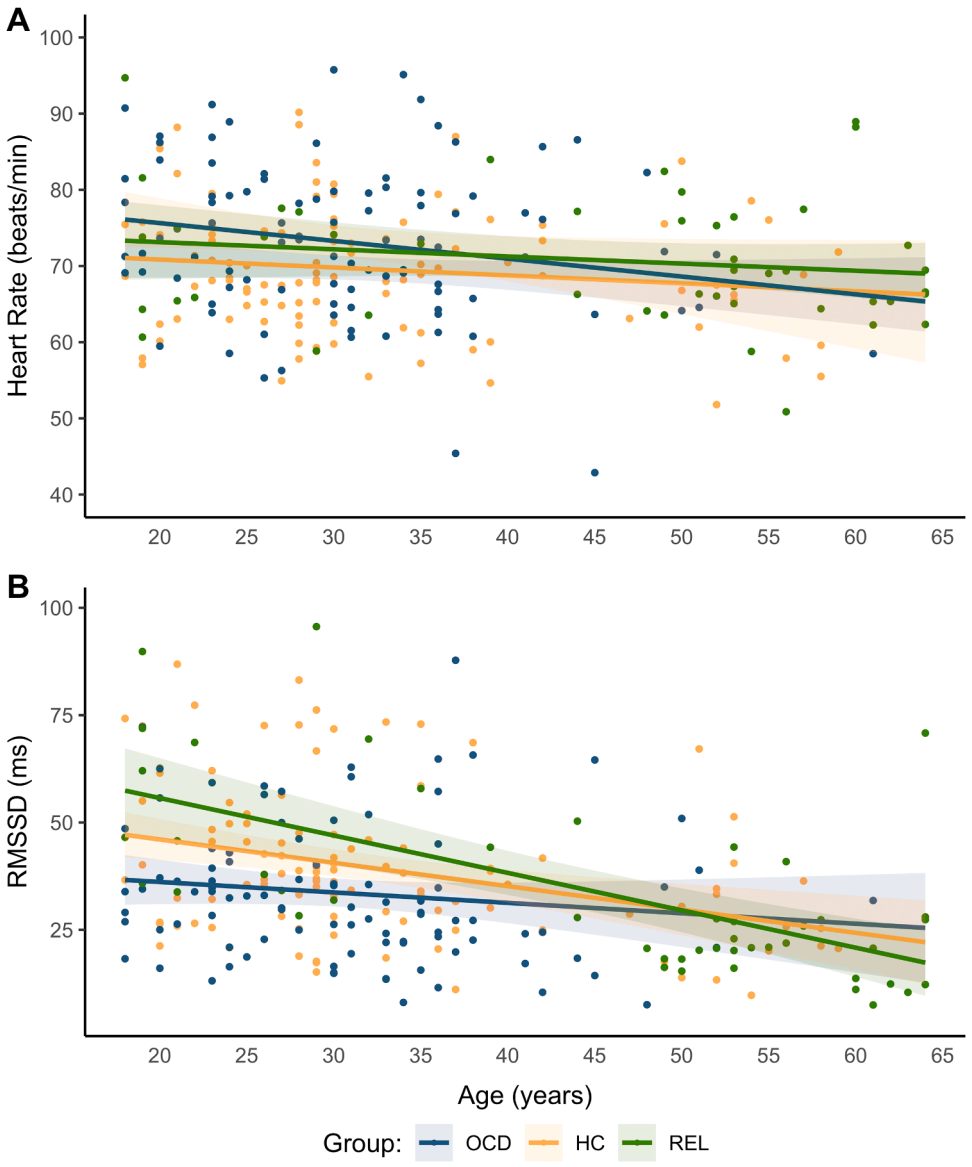

Fig. 1. Relation Between Cardiac Activity and Age Within the Groups of Patients With Obsessive-Compulsive Disorder (OCD), Healthy Control Participants (HC), and Unaffected First-Degree Relatives (REL)

Note. **(A)** Scatterplot and linear regression line of heart rate and age in each participant group. **(B)** Scatterplot and linear regression line of heart rate variability (RMSSD) and age in each participant group. Note that RMSSD was log-transformed for correlational analyses but was back-transformed to ms to facilitate data visualization. **(A – B)** The 95% confidence intervals are represented in shaded bands. RMSSD = root mean square of successive RR interval differences.

was no difference in HRV (RMSSD) between healthy participants and unaffected relatives ($p > .99$). Further HRV indices, namely SDNN, PNN50 and RSA, corroborate these age-adjusted findings, that is patients with OCD exhibited smaller HRV compared to the other two healthy participant groups (see Table 2).

Importantly, no main effects of gender or smoking on RMSSD were observed when included as covariates (all *ps* > .085; see Supplemental Material, page 3). Even though body mass index had a significant effect on group differences in HRV (RMSSD), accounting for it did not change the observed pattern in groups. Hence, group differences in HRV remained the same as reported above after accounting for gender, smoking, and body mass index (see Supplemental Material, page 3).

2.4.2. *Group classification with age as a moderator*

Results of all binary logistic regression models of HRV as classifier of group status are presented in Table 3. The logistic regression model investigating HRV, age, and the interaction term between age and HRV as predictors for group status in patients with OCD and healthy participants was significant ($p = .003$, overall classification accuracy of 64.4%), but yielded no significant interaction between HRV and age ($p = .108$; see Table 3 for all model coefficients). In the analogous logistic regression predicting group status in healthy participants and unaffected first-degree relatives, a significant model emerged ($p < .001$, overall classification accuracy of 78.6%), with a significant interaction between age and HRV as indicator of relative versus control status ($p = .002$; see Table 3). To further resolve this interaction, Johnson-Neyman analysis was performed (see Fig. 3). For a logistic regression model, Johnson-Neyman analysis evaluates the probability of group status (unaffected relatives of patients vs. healthy participants) in relation to the predictor (i.e., RMSSD) at each level of the moderator (i.e., age) and establishes a region of significance where the simple slope of the focal predictor (i.e., RMSSD) is significantly different from zero while adjusted for the value of the continuous moderator (i.e., age; Bauer & Curran, 2005; Johnson & Neyman, 1936). Johnson-Neyman

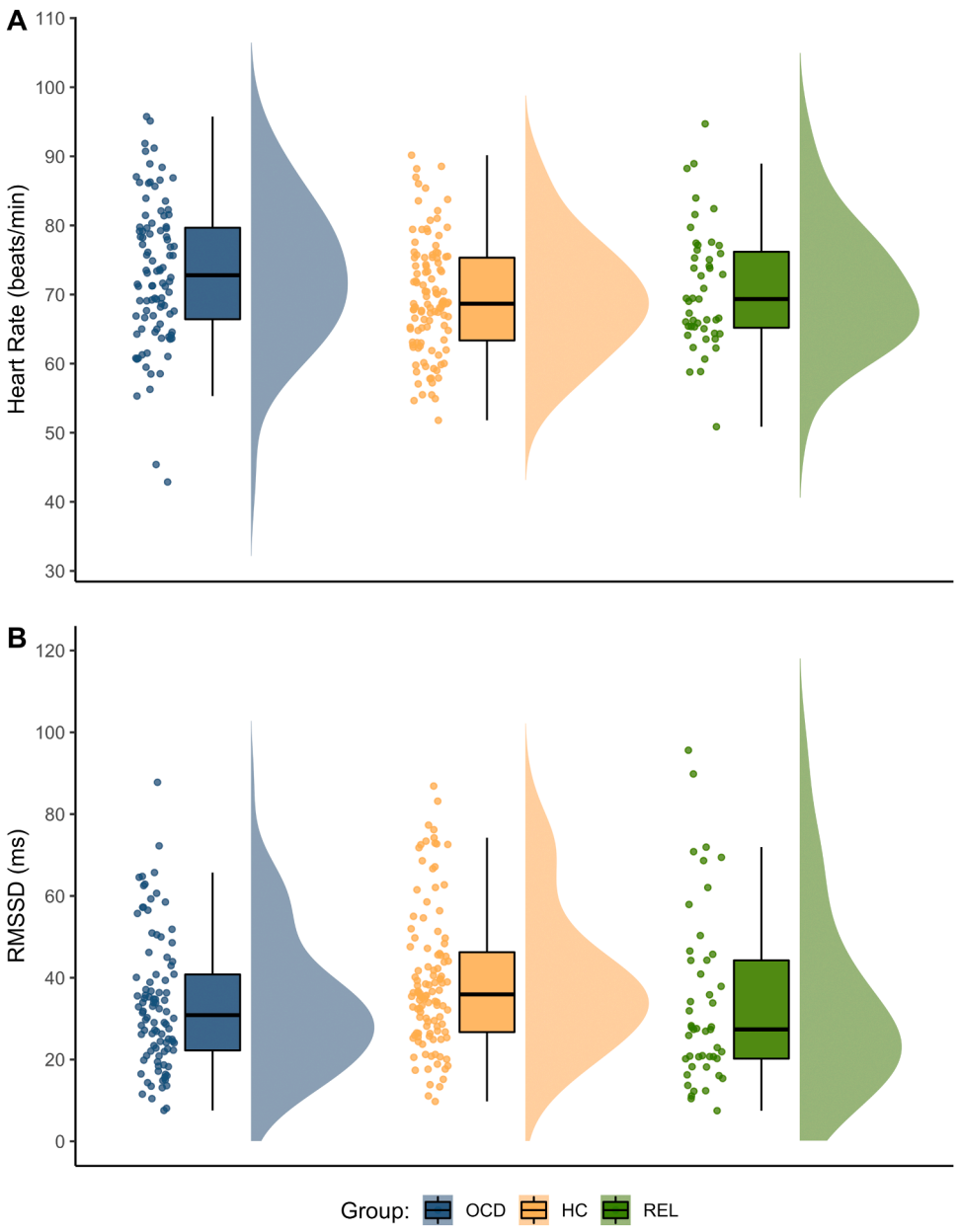

Fig. 2. Observed Heart Rate and Heart Rate Variability (RMSSD) in the Groups of Patients with Obsessive-Compulsive Disorder (OCD), Healthy Control Participants (HC), and Unaffected First-Degree Relatives (REL)

Note. **(A)** Heart rate in beats per minute per group. **(B)** Heart rate variability (RMSSD) in ms per group. **(A–B)** The plots show individual data points, boxplots, and probability density plots based on observed data that were aggregated by participant. The plots were generated in R Studio using the raincloudplots package (Version 0.2.0; Allen et al., 2021). RMSSD = root mean square of successive RR interval differences.

intervals revealed that a higher HRV was indicative of relative status only until the age of 32.6 years (i.e., the lower 53.46% of all healthy participants and unaffected relatives) and a lower HRV was indicative of relative status from the age of 58.6 years onwards (i.e., the upper 6.92% of all healthy participants and unaffected relatives).

2.4.3. *Exploratory subgroup analyses on medication effects*

See Table 4 for detailed statistics of medication effects on HRV (RMSSD). We computed exploratory subgroup analyses but did not observe HRV differences between unmedicated and medicated patients or between unmedicated patients and healthy participants. Accounting for age did not change these results. Importantly, HRV was lower in medicated patients compared to healthy individuals, before and after accounting for age.

3. Discussion

The current findings extend the existing psychophysiological profile of OCD by adding altered cardiac autonomic functioning. Results showed significant overall group differences in HR and HRV. Specifically, patients with OCD showed higher HR compared to the healthy participant group. Although HR was moderately negatively correlated with age within the OCD group, the between-groups difference was not significantly moderated by age. No significant differences in HR emerged for the relatives in comparison to any other group. Exploratory subgroup analyses showed that increases in HR were limited to unmedicated patients with OCD compared to patients on psychotropic medication and to healthy participants. With respect to HRV (RMSSD), a negative association with age was observed in both nonclinical groups, but not in patients with OCD. HRV reduction differentiated patients with

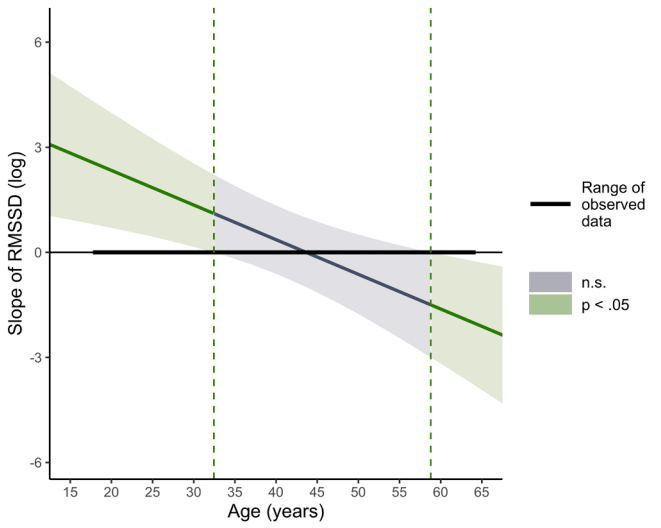

Fig. 3. Moderation Effect of Age on the Relation Between Heart Rate Variability (RMSSD) and Group Status of Healthy Participants or Unaffected First-Degree Relatives

Note. Johnson-Neyman plot showing the probability of group status (0 = healthy participant, 1 = unaffected first-degree relative) as predicted by heart rate variability (RMSSD) and moderated by age. A higher RMSSD was indicative of relative status until the age of 32.6 years (the lower 53.46% across groups) and a lower RMSSD was indicative of relative status from the age of 58.6 years onwards (upper 6.92% across groups). RMSSD was log-transformed. This plot was generated in R with the interactions package (Version 1.1.5; Long, 2019). RMSSD = root mean square of successive RR interval differences.

OCD from healthy participants, independently of age. In contrast, the significant differentiation of unaffected relatives from healthy control participants by HRV was moderated by age, in that higher HRV was only indicative of relative status in young adulthood and lower HRV in older age. Subgroup analyses on HRV (RMSSD) yielded that decreases in HRV were limited to the group of patients currently on medication while HRV in unmedicated patients did not differ from healthy participants.

The findings of HR and HRV alterations in OCD are well in line with previous studies, which reported higher HR and reduced HRV in the context of clinical anxiety (for meta-analysis, see Chalmers et al., 2014; Hsin-An et al., 2020; Kemp et al., 2014; Melzig et al., 2009) and depressive disorders (Agelink et al., 2002; Kemp et al., 2010; Koenig et al., 2016). Theoretically, our findings are in accordance with the neurovisceral theory by Thayer & Lane (2000), which posits that the described pattern of greater HR and reduced HRV indicates a diminished parasympathetic influence under conditions of rest. Previous investigations in OCD have been scarce. While two studies did not detect differences in cardiac measures of unmedicated patients with OCD compared to control groups (McCarthy et al., 1995; Slaap et al., 2004), one study did point towards analogous findings as those reported here (Pittig et al., 2013), albeit in smaller samples and unclear medication effects. The latest study by Olbrich et al. (2022) examined a larger unmedicated sample of 51 patients with OCD and reported greater HR in OCD compared to healthy participants but no group differences in HRV. The current findings are consistent with the latter study and match those by Pittig et al. (2013). They further appear to be in line with previous neuroscientific findings of altered resting state connectivity (Beucke et al., 2013) and hyperactivity in the sympathetic branch during symptom provocation (Simon et al., 2013) in OCD. Thereby, our study results corroborate in a relatively large sample that autonomic imbalance, possibly reflected in reduced cardiac vagal control, seems to be part of the pathophysiology of OCD.

Importantly, psychotropic medication might have an impact on cardiac patterns. In subgroup analyses including medicated and unmedicated patients with OCD and healthy participants, the increases in HR were limited to unmedicated patients with OCD. Moreover, in subgroup analyses on HRV (RMSSD) decreases in HRV were found exclusively in the group of patients currently on medication, while patients not receiving medication did not differ from healthy participants. Consequently, the role of medication needs to be taken into account when investigating cardiac activity alterations in OCD. The use of SSRIs and their effect on cardiac activity in psychiatric disorders has been discussed and investigated in the literature with differing results. Whereas some studies report diminishing effects of SSRIs on HRV in psychiatric disorders (Kemp, 2011; Kemp et al., 2014; Kemp, Quintana, & Malhi, 2011), others find no effects (Chalmers et al., 2014; Kemp et al., 2010; Noordam et al., 2016). In this study, 33 out of 38 medicated patients took SSRIs. Previous studies on HR and HRV in OCD were most often conducted with drug-free patients (McCarthy et al., 1995; Olbrich et al., 2022; Slaap et al., 2004). None of those studies reported lower HRV in patients with OCD and only one found greater HR (Olbrich et al., 2022). Pittig et al. (2013) reported that a lower HF-HRV in patients with OCD might be associated with psychotropic medication intake, yet, due to the small sample size the effect of medication on HRV in OCD could not be fully clarified. Interestingly, they did not find any effects of psychotropic medication on HF-HRV across groups of anxiety disorders and all anxiety disorder groups exhibited lower HF-HRV, (Pittig et al., 2013). Overall, our findings align with those by Pittig et al. (2013), such that medicated patients with OCD showed a significantly smaller resting HRV compared to healthy participants, as well as with results by Olbrich et al. (2022) of unmedicated patients having a higher resting HR compared to healthy participants. Based on a meta-analysis on resting HR in patients with OCD and on their study results, Olbrich et al. (2022) discussed higher HR as a trait marker in OCD. HR is influenced by both the sympathetic and the parasympathetic branch of the autonomous nervous system. Thus, it remains an open question whether enhanced HR in unmedicated patient with OCD predominantly stems from overactive sympathetic or diminished parasympathetic influence. Based on the observed study results, psychotropic medication might have beneficial modulatory effects on HR but detrimental effects on HRV.

It is worth noting that we did not systematically vary or control for medication status in this study. It is therefore not clear in which way medication is associated with diminished HRV and HR and no causal relation may be assumed yet. Similarly, there is still discussion on whether reductions in HRV can be exclusively ascribed to SSRIs (Kemp, 2011; Kemp et al., 2014; Kemp, Quintana, & Malhi, 2011) or whether other additional factors or confounds may play a part in the relation between medication, cardiac activity, and OCD (i.e., it is conceivable that subtle clinical differences within OCD might both be associated with alterations in HRV and with seeking or accepting medication as additional treatment). Clearly, highly controlled studies investigating medication effects on HR and HRV in OCD and other psychiatric disorders are still needed.

As mentioned above, even though HRV partially reflects vagally mediated influence on the cardiac system, the HR is both vagally and sympathetically innervated. At rest, parasympathetic inhibition is greater than sympathetic activation in a balanced, healthy autonomic nervous system, resulting in low HR. Our results demonstrate an autonomic imbalance in OCD and seem to reflect lower parasympathetic inhibition, yet, an increased sympathetic activation might also contribute to higher HR and the imbalance at rest. Patients in this study might have also responded to the experimental nature and setting of the psychophysiological assessment with elevated stress and/or anxiety levels leading to an increase of HR and small HRV. So far, we discussed HR and HRV at rest as trait markers, yet both might also encompass state aspects. To disentangle both aspects, future studies using long-term ECG or ECG applied in non-clinical settings, such as in ecological momentary assessment studies, are needed. Conceptually, effects of state or trait anxiety on HR and HRV cannot be distinguished in this study.

In addition, results of the current study elucidated age influences on changes in cardiac control in OCD. First and foremost, differences in

cardiac activity, namely HR and HRV, between patients with OCD and healthy participants remained significant after accounting for age effects. In line with previous studies (Agelink et al., 2001; Boettger et al., 2010; Fukusaki et al., 2000; Sloan et al., 2008; Voss et al., 2012), HR in healthy participants was relatively independent of age. We observed a negative correlation between age and HR at rest in patients with OCD but neither in unaffected first-degree relatives nor in healthy individuals. To resolve whether this negative relation stems from relatively high HR levels in OCD at younger age, which is also the typical time period of onset of OCD, compared to healthy individuals, prospective studies are needed to follow up on cardiac activity in patients with OCD over aging. For HRV, we observed a typical age-related reduction in both healthy groups, but no such age-related decline in patients with OCD. The absence could be due to floor effects, but this tentative explanation needs further systematic studies, as several other confounding factors might have an influence on the relation between age and cardiac activity.

Findings with regards to the unaffected first-degree relatives' group in the current investigation fail to draw a clear-cut picture. Overall, neither HR nor HRV emerged as significant risk markers in the current investigation and further studies in larger and more age-analogous samples might be necessary to come to definite conclusions in the matter. While a higher HRV in unaffected relatives could be viewed as indicative of a protective resilience mechanism (for similar findings from the same cohort, see Grützmann et al., 2021; Grützmann et al., 2017), this effect was only observed on trend level in the current investigation. Possibly, heightened control of autonomic processes would be especially distinctive during a period of age that encompasses the typical onset of OCD, as the age-moderated differentiation of relative status by HRV might suggest. Longitudinal studies are needed to solidify such a notion, but the current family study reporting an age-moderated differentiation of relative status by HRV yields an interesting starting point for further examination.

Besides the aforementioned considerations, the current investigation has several limitations worth noting. Primary, the cross-sectional design of the study prohibits conclusions regarding the direction or causality of observed associations. Longitudinal studies will be needed to determine whether the alterations observed in patients with OCD are precursors or symptoms of the disorder and whether they play a mechanistic role in the development and persistence of symptoms. Moreover, although the groups of patients and healthy participants in the current study were relatively large and spanned a rather wide age range, samples were not systematically stratified for age, thus limiting the generalizability of our current findings regarding age effects. This is especially pertinent for the much smaller sample of unaffected relatives, which could not be fully matched to the other two groups regarding age distribution. Future studies will need to include participants systematically and uniformly across the age distribution in order to get a better picture of the interactions of age and psychopathology on cardiac measures.

The current study did not include a clinical control group of patients with internalizing disorders other than OCD. Thus, although the pattern of our results, i.e., increase in HR and reduction in HRV, closely aligns with previous findings from internalizing disorders, we cannot investigate the degree of overlap regarding a transdiagnostic pattern. Furthermore, 74 out of 96 patients with OCD showed comorbidities, most prominently with affective disorders and anxiety, in line with the fairly unrestrained nature of our sample. It is conceivable, that co-occurring symptoms may influence or even amplify altered HR and HRV in OCD, given the above-mentioned findings of lower cardiac vagal tone in affective and anxiety disorder. Yet, there were no correlations between cardiac measures and depressive symptoms, as measured with the BDI-II, or anxiety, as measured with the STAI trait scale, within patients with OCD. Thus, neither affective nor anxious symptoms account for HR and HRV effects in OCD in our study. We did not include depressive or anxious symptoms in any group comparison, since healthy participants and relatives reporting psychiatric disorders were excluded and severity of symptoms would therefore be confounded with group status leading to spurious effects (Makin & Orban de Xivry, 2019). Nonetheless, we would like to acknowledge that comorbidity within the clinical sample in conjunction with the categorical groups study design represents a major limitation of the current study, since it makes it impossible to fully disentangle effects of OCD from influences of anxious and depressive symptoms on cardiac measures. Further dimensional studies will be needed that systematically incorporate variation across multiple symptom dimensions and severity levels (i.e., clinical, subclinical, and healthy) to investigate effects on biological characteristics (see Riesel, Härpfer, Thoma, Kathmann, & Klawohn, 2023, for such an approach) and to elucidate whether more fine-grained differences in HR and HRV alterations between these disorders do exist.

Furthermore, we did not assess physical activity. This is problematic in a sense that with increasing levels of physical activity, the absolute levels of HR decrease and of HRV elevate (Aubert et al., 2003; Rennie et al., 2003). Not accounting for this factor limits the interpretability of the study findings. Psychiatric disorders often go along with changes in lifestyle, which increases the risk for cardiovascular diseases (Alvares et al., 2016) and could impact cardiac regulation as of higher HR and lower HRV. Patients with OCD could have been more inactive, with the observed higher levels of depression potentially reinforcing the inactivity, which could serve as another explanation of a smaller HRV and higher HR. On another note, we accounted for other sociodemographic factors, such as gender, body mass index, or smoking status, with ANCOVAs and found no effects of those variables. Future studies on OCD should systematically control for these factors to achieve more precise results regarding possible confounds of cardiac measures.

This study did not account for respiration rate or movement, however, results on group differences in the variable RMSSD were supported by additional analyses on other HRV indices (i.e., SDNN, pNN50, logRSA), speaking for the robustness of the findings. Since some indices, such as the logRSA or the HF-HRV, are highly correlated with breathing rate and depth (Allen et al., 2007), statistically controlling for respiration, e.g., with ANCOVAs, potentially removes variance in the dependent HRV or HR variable and might result in misleading or spurious effects. Laborde et al. (2017) as well as Allen et al. (2007) recommend to not routinely correct for spontaneous breathing or experimentally manipulate breathing rate but to increase likelihood for steady breathing (such as in our resting paradigms with no movements) and to monitor respiration rates to be sure of no group differences in breathing rates. In sum, as we did not monitor respiration in this study, respiration could have potential effects on our findings, although this seems unlikely due to the consistency in results across different HRV variables.

Further, results on the frequency domain are not investigated here. Both the RMSSD as well as the variable logRSA utilized in this study highly correlate with HF-HRV (Allen et al., 2007; Kleiger, Stein, & Bigger, 2005). In some studies, logRSA is interchangeably used with HF-HRV (Lane et al., 2013). Frequency analyses allow for amplitude and frequency information about oscillatory activity in the HR waveform. Therefore, frequency analyses quantify autonomic dynamics, with different neurophysiological processes corresponding to the frequency bands, which time domain analyses do not measure. Time domain measures, on the other hand, quantify the variance in the IBI over time statistically, which in turn makes them comparable across data collections. Overall, future studies should expand on the current findings by explicitly investigating frequency domain variables in patients with OCD.

The nature of this study including a fairly unrestrained sample of patients (high rate of comorbidities, intake of medication, seeking psychotherapy) brings in confounding factors, as discussed above, yet the heterogenous sample in such an observational approach increases the external validity and application to clinical practice. It also increases chances of discovering clinical biomarkers which can then be further validated and tested for their mechanisms in more controlled experimental studies.

Taken together, the current findings show a pattern of alterations in cardiac measures in patients with OCD, which aligns with changes previously reported in other internalizing disorders. Medication was associated with modulations in these cardiac alterations, such that group differences in HR were limited to the unmedicated patients' subgroup, whereas patients on psychotropic medication exhibited normative HR but reduced HRV compared to healthy participants. Thus, results of this study suggest that after accounting for various variables, alterations in HR might potentially function as biological indicators that may help to classify and further psychophysiologically characterize patients with OCD compared to healthy individuals. Such classificatory utility could potentially be further increased when combined with additional measures (see Klawohn et al., 2021, for a similar approach). Results on HRV differences appear less robust with medication possibly altering HRV in patients, and further clarification is needed.

Funding

The work was supported by the Deutsche Forschungsgemeinschaft (DFG; KA815/6–1, WA731/10–1, and FOR5187 [project number 442075332]). The funding sources had no further influence on study conduction and publication.

CRediT authorship contribution statement

Rosa Grützmann: Writing – review & editing, Investigation, Data curation, Conceptualization. **Stephan Heinzel:** Writing – review & editing, Conceptualization, Investigation. **Björn Elsner:** Writing – review & editing, Resources, Data curation. **Norbert Kathmann:** Writing – review & editing, Resources, Project administration, Funding acquisition, Conceptualization. **Julia Klawohn:** Writing – review & editing, Supervision, Resources, Methodology, Investigation, Data curation, Conceptualization. **Katharina Bey:** Writing – review & editing, Conceptualization. **Michael Wagner:** Writing – review & editing, Project administration, Funding acquisition, Conceptualization. **Christian Kaufmann:** Writing – review & editing, Supervision, Resources, Data curation, Conceptualization. **Anja Riesel:** Writing – review & editing, Investigation, Data curation, Conceptualization. **Franziska Jüres:** Writing – review & editing, Writing – original draft, Visualization, Formal analysis, Data curation.

Declaration of Generative (AI) and AI-assisted technologies in the writing process

The authors did not use generative AI technologies for preparation of this work.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

Data will be made available on request.

Acknowledgements

We would like to thank Dr. Eva Kischkel and Dr. Benedikt Reuter for clinical supervision and Thomas Pinkpank and Rainer Kniesche for technical support. We thank Ulrike Bunzenthal, Sarah Dreßel, Alexandra Günther, Marvin Groh, Anna Unger-Nübel, and Verena Wüllhorst for their help in data collection. Finally, we thank all individuals who participated in the study.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.biopsycho.2024.108786.

References

Agelink, M. W., Boz, C., Ullrich, H., & Andrich, J. (2002). Relationship between major depression and heart rate variability. Clinical consequences and implications for antidepressive treatment. *Psychiatry Research, 113*(1-2), 139–149. https://doi.org/10.1016/s0165-1781(02)00225-1

Agelink, M. W., Malessa, R., Baumann, B., Majewski, T., Akila, F., Zeit, T., & Ziegler, D. (2001). Standardized tests of heart rate variability: Normal ranges obtained from 309 healthy humans, and effects of age, gender, and heart rate. *Clinical Autonomic Research, 11*(2), 99–108. https://doi.org/10.1007/bf02322053

Alkon, A., Boyce, W. T., Davis, N. V., & Eskenazi, B. (2011). Developmental changes in autonomic nervous system resting and reactivity measures in Latino children from 6 to 60 months of age. *Journal of Developmental & Behavioral Pediatrics, 32*(9), 668–677. https://doi.org/10.1097/DBP.0b013e3182331fa6

Alkon, A., Goldstein, L. H., Smider, N., Essex, M. J., Kupfer, D. J., & Boyce, W. T. (2003). Developmental and contextual influences on autonomic reactivity in young children. *Developmental Psychobiology, 42*(1), 64–78. https://doi.org/10.1002/dev.10082

Allen, J. J., Chambers, A. S., & Towers, D. N. (2007). The many metrics of cardiac chronotropy: A pragmatic primer and a brief comparison of metrics. *Biological Psychology, 74*(2), 243–262. https://doi.org/10.1016/j.biopsycho.2006.08.005

Allen, M., Poggiali, D., Whitaker, K., Marshall, T., van Langen, J., & Kievit, R. (2021). Raincloud plots: A multi-platform tool for robust data visualization. *Wellcome Open Research, 4*, 63. https://doi.org/10.12688/wellcomeopenres.15191.2

Alvares, G. A., Quintana, D. S., Hickie, I. B., & Guastella, A. J. (2016). Autonomic nervous system dysfunction in psychiatric disorders and the impact of psychotropic medications: A systematic review and meta-analysis. *Journal of Psychiatry and Neuroscience, 41*(2), 89–104. https://doi.org/10.1503/jpn.140217

American Psychiatric Association. (2020). *Diagnostic and statistical manual of mental disorders* (5 ed., Vol. 21). https://doi.org/10.1176/appi.books.9780890425787.

Appelhans, B. M., & Luecken, L. J. (2006). Heart rate variability as an index of regulated emotional responding. *Review of General Psychology, 10*(3), 229–240. https://doi.org/10.1037/1089-2680.10.3.229

Aubert, A. E., Seps, B., & Beckers, F. (2003). Heart rate variability in athletes. *Sports Medicine, 33*(12), 889–919. https://doi.org/10.2165/00007256-200333120-00003

Bar-Haim, Y., Marshall, P. J., & Fox, N. A. (2000). Developmental changes in heart period and high-frequency heart period variability from 4 months to 4 years of age. *Developmental Psychobiology, 37*(1), 44–56. https://doi.org/10.1002/1098-2302(200007)37:1<44::AID-DEV6>3.0.CO;2-7

Bauer, D. J., & Curran, P. J. (2005). Probing interactions in fixed and multilevel regression: Inferential and graphical techniques. *Multivariate Behavioral Research, 40*(3), 373–400. https://doi.org/10.1207/s15327906mbr4003_5

Beauchaine, T. P., & Thayer, J. F. (2015). Heart rate variability as a transdiagnostic biomarker of psychopathology. *International Journal of Psychophysiology, 98*(2), 338–350. https://doi.org/10.1016/j.ijpsycho.2015.08.004

Beck, A. T., Steer, R. A., & Brown, G. K. (1996). *Manual for the Beck Depression Inventory-II*. Psychological Corporation.

Beucke, J. C., Sepulcre, J., Talukdar, T., Linnman, C., Zschenderlein, K., Endrass, T., Kaufmann, C., & Kathmann, N. (2013). Abnormally high degree connectivity of the orbitofrontal cortex in obsessive-compulsive disorder. *JAMA Psychiatry, 70*(6), 619–629. https://doi.org/10.1001/jamapsychiatry.2013.173

Bey, K., Campos-Martin, R., Klawohn, J., Reuter, B., Grützmann, R., Riesel, A., Wagner, M., Ramirez, A., & Kathmann, N. (2022). Hypermethylation of the oxytocin receptor gene (OXTR) in obsessive-compulsive disorder: Further evidence for a biomarker of disease and treatment response. *Epigenetics, 17*(6), 642–652. https://doi.org/10.1080/15592294.2021.1943864

Bey, K., Kaufmann, C., Lennertz, L., Riesel, A., Klawohn, J., Heinzel, S., Grützmann, R., Kathmann, N., & Wagner, M. (2018). Impaired planning in patients with obsessive-compulsive disorder and unaffected first-degree relatives: Evidence for a cognitive endophenotype. *Journal of Anxiety Disorders, 57*, 24–30. https://doi.org/10.1016/j.janxdis.2018.05.009

Bey, K., Kloft, L., Lennertz, L., Grützmann, R., Heinzel, S., Kaufmann, C., Klawohn, J., Riesel, A., Meyhöfer, I., & Kathmann, N. (2017). Volitional saccade performance in a large sample of patients with obsessive-compulsive disorder and unaffected first-degree relatives. *Psychophysiology, 54*(9), 1284–1294. https://doi.org/10.1111/psyp.12884

Bey, K., Lennertz, L., Riesel, A., Klawohn, J., Kaufmann, C., Heinzel, S., Grützmann, R., Kathmann, N., & Wagner, M. (2017). Harm avoidance and childhood adversities in patients with obsessive–compulsive disorder and their unaffected first-degree relatives. *Acta Psychiatrica Scandinavica, 135*(4), 328–338. https://doi.org/10.1111/acps.12707

Bey, K., Meyhöfer, I., Lennertz, L., Grützmann, R., Heinzel, S., Kaufmann, C., Klawohn, J., Riesel, A., Ettinger, U., & Kathmann, N. (2019). Schizotypy and smooth pursuit eye movements as potential endophenotypes of obsessive-compulsive disorder. *European Archives of Psychiatry and Clinical Neuroscience, 269*(2), 235–243. https://doi.org/10.1007/s00406-018-0899-x

Bey, K., Weinhold, L., Grützmann, R., Heinzel, S., Kaufmann, C., Klawohn, J., Riesel, A., Lennertz, L., Schmid, M., & Ramirez, A. (2020). The polygenic risk for obsessive-compulsive disorder is associated with the personality trait harm avoidance. *Acta Psychiatrica Scandinavica, 142*(4), 326–336. https://doi.org/10.1111/acps.13226

Boettger, M. K., Schulz, S., Berger, S., Tancer, M., Yeragani, V. K., Voss, A., & Bär, K. J. (2010). Influence of age on linear and nonlinear measures of autonomic cardiovascular modulation. *Annals of Noninvasive Electrocardiology, 15*(2), 165–174. https://doi.org/10.1111/j.1542-474X.2010.00358.x

Box, G. E. P., & Cox, D. R. (1964). An analysis of transformations. *Journal of the Royal Statistical Society: Series B (Methodological), 26*(2), 211–243. https://doi.org/10.1111/j.2517-6161.1964.tb00553.x

Butler, E. A., Wilhelm, F. H., & Gross, J. J. (2006). Respiratory sinus arrhythmia, emotion, and emotion regulation during social interaction. *Psychophysiology, 43*(6), 612–622. https://doi.org/10.1111/j.1469-8986.2006.00467.x

Chalmers, J. A., Quintana, D. S., Abbott, M. J., & Kemp, A. H. (2014). Anxiety disorders are associated with reduced heart rate variability: A meta-analysis. *Frontiers in Psychiatry, 5*, 80. https://doi.org/10.3389/fpsyt.2014.00080

Chamberlain, S. R., Fineberg, N. A., Menzies, L. A., Blackwell, A. D., Bullmore, E. T., Robbins, T. W., & Sahakian, B. J. (2007). Impaired cognitive flexibility and motor inhibition in unaffected first-degree relatives of patients with obsessive-compulsive disorder. *American Journal of Psychiatry, 164*(2), 335–338. https://doi.org/10.1176/appi.ajp.164.2.335

Ciccone, A. B., Siedlik, J. A., Wecht, J. M., Deckert, J. A., Nguyen, N. D., & Weir, J. P. (2017). Reminder: RMSSD and SD1 are identical heart rate variability metrics. *Muscle & Nerve, 56*(4), 674–678. https://doi.org/10.1002/mus.25573

De Geus, E. J., Kupper, N., Boomsma, D. I., & Snieder, H. (2007). Bivariate genetic modeling of cardiovascular stress reactivity: Does stress uncover genetic variance? *Psychosomatic Medicine, 69*(4), 356–364. https://doi.org/10.1097/PSY.0b013e318049cc2d

De Rogalski Landrot, I., Roche, F., Pichot, V., Teyssier, G., Gaspoz, J. M., Barthelemy, J. C., & Patural, H. (2007). Autonomic nervous system activity in premature and full-term infants from theoretical term to 7 years. *Autonomic Neuroscience, 136*(1-2), 105–109. https://doi.org/10.1016/j.autneu.2007.04.008

Eckberg, D. L., & Eckberg, M. J. (1982). Human sinus node responses to repetitive, ramped carotid baroreceptor stimuli. *American Journal of Physiology-Heart and Circulatory Physiology, 242*(4), H638–644. https://doi.org/10.1152/ajpheart.1982.242.4.H638

Fernandes, R. A., Vaz Ronque, E. R., Venturini, D., Barbosa, D. S., Silva, D. P., Cogo, C. T., Carnelossi, M. S., Batista, M. B., Coelho, E. S. M. J., Sardinha, L. B., & Cyrino, E. S. (2013). Resting heart rate: Its correlations and potential for screening metabolic dysfunctions in adolescents. *BMC Pediatrics, 13*, 48. https://doi.org/10.1186/1471-2431-13-48

Fineberg, N. A., Hengartner, M. P., Bergbaum, C., Gale, T., Rössler, W., & Angst, J. (2013). Lifetime comorbidity of obsessive-compulsive disorder and sub-threshold obsessive-compulsive symptomatology in the community: Impact, prevalence, socio-demographic and clinical characteristics. *International Journal of Psychiatry in Clinical Practice, 17*(3), 188–196. https://doi.org/10.3109/13651501.2013.777745

Foa, E. B., Huppert, J. D., Leiberg, S., Langner, R., Kichic, R., Hajcak, G., & Salkovskis, P. M. (2002). The Obsessive-Compulsive Inventory: Development and validation of a short version. *Psychological Assessment, 14*(4), 485–496. https://doi.org/10.1037/1040-3590.14.4.485

Friedman, B. H., & Thayer, J. F. (1998). Anxiety and autonomic flexibility: A cardiovascular approach. *Biological Psychology, 49*(3), 303–323. https://doi.org/10.1016/s0301-0511(98)00051-9

Fukusaki, C., Kawakubo, K., & Yamamoto, Y. (2000). Assessment of the primary effect of aging on heart rate variability in humans. *Clinical Autonomic Research, 10*(3), 123–130. https://doi.org/10.1007/bf02278016

Galeev, A., Igisheva, L., & Kazin, E. (2002). Heart rate variability in healthy six- to sixteen-year-old children. *Human Physiology, 28*(4), 428–432. https://doi.org/10.1023/A:1016529931519

Gentzler, A. L., Rottenberg, J., Kovacs, M., George, C. J., & Morey, J. N. (2012). Atypical development of resting respiratory sinus arrhythmia in children at high risk for depression. *Developmental Psychobiology, 54*(5), 556–567. https://doi.org/10.1002/dev.20614

Goedhart, A. D., van der Sluis, S., Houtveen, J. H., Willemsen, G., & de Geus, E. J. (2007). Comparison of time and frequency domain measures of RSA in ambulatory recordings. *Psychophysiology, 44*(2), 203–215. https://doi.org/10.1111/j.1469-8986.2006.00490.x

Golosheykin, S., Grant, J. D., Novak, O. V., Heath, A. C., & Anokhin, A. P. (2017). Genetic influences on heart rate variability. *International Journal of Psychophysiology, 115*, 65–73. https://doi.org/10.1016/j.ijpsycho.2016.04.008

Gönner, S., Leonhart, R., & Ecker, W. (2008). The Obsessive–Compulsive Inventory-Revised (OCI-R): Validation of the German version in a sample of patients with OCD, anxiety disorders, and depressive disorders. *Journal of Anxiety Disorders, 22*(4), 734–749. https://doi.org/10.1016/j.janxdis.2007.07.007

Goodman, W. K., Price, L. H., Rasmussen, S. A., Mazure, C., Fleischmann, R. L., Hill, C. L., … Charney, D. S. (1989). The Yale-Brown Obsessive Compulsive Scale: I. Development, use, and reliability. *Archives of General Psychiatry, 46*(11), 1006–1011. https://doi.org/10.1001/archpsyc.1989.01810110048007

Grossman, P., Wilhelm, F. H., & Spoerle, M. (2004). Respiratory sinus arrhythmia, cardiac vagal control, and daily activity. *American Journal of Physiology-Heart and Circulatory Physiology, 287*(2), H728–734. https://doi.org/10.1152/ajpheart.00825.2003

Grützmann, R., Kaufmann, C., Wudarczyk, O. A., Balzus, L., Klawohn, J., Riesel, A., Bey, K., Wagner, M., Heinzel, S., & Kathmann, N. (2021). Error-related brain activity in patients with obsessive-compulsive disorder and unaffected first-degree relatives: Evidence for protective patterns. *Biological Psychiatry Global Open Science, 2*(1), 79–87. https://doi.org/10.1016/j.bpsgos.2021.07.001

Grützmann, R., Riesel, A., Klawohn, J., Heinzel, S., Kaufmann, C., Bey, K., Lennertz, L., Wagner, M., & Kathmann, N. (2017). Frontal alpha asymmetry in OCD patients and unaffected first-degree relatives. *Journal of Abnormal Psychology, 126*(6), 750. https://doi.org/10.1037/abn0000283

Hand, I., & Büttner-Westphal, H. (1991). Die Yale-Brown Obsessive Compulsive Scale (Y-BOCS): Ein halbstrukturiertes Interview zur Beurteilung des Schweregrades von Denk- und Handlungszwängen. *Verhaltenstherapie, 1*(3), 223–225. https://doi.org/10.1159/000257972

Hansen, A. L., Johnsen, B. H., & Thayer, J. F. (2003). Vagal influence on working memory and attention. *International Journal of Psychophysiology, 48*(3), 263–274. https://doi.org/10.1016/S0167-8760(03)00073-4

Hautzinger, M., Keller, F., & Kühner, C. (2006). *Beck Depressions-Inventar (BDI-II). Revision.* Harcourt Test Services.

Hayes, A. F. (2017). *Introduction to mediation, moderation, and conditional process analysis: A regression-based approach.* Guilford publications.

Heinzel, S., Bey, K., Grützmann, R., Klawohn, J., Kaufmann, C., Lennertz, L., Wagner, M., Kathmann, N., & Riesel, A. (2021). Spatial working memory performance in people with obsessive–compulsive disorder, their unaffected first-degree relatives and healthy controls. *BJPsych Open, 7*(6). https://doi.org/10.1192/bjo.2021.1052

Heinzel, S., Kaufmann, C., Grützmann, R., Hummel, R., Klawohn, J., Riesel, A., Bey, K., Lennertz, L., Wagner, M., & Kathmann, N. (2018). Neural correlates of working memory deficits and associations to response inhibition in obsessive compulsive disorder. *NeuroImage: Clinical, 17*, 426–434. https://doi.org/10.1016/j.nicl.2017.10.039

Heinzel, S., Kaufmann, C., Grützmann, R., Klawohn, J., Riesel, A., Bey, K., Heilmann-Heimbach, S., Weinhold, L., Ramirez, A., & Wagner, M. (2021). Polygenic risk for obsessive-compulsive disorder (OCD) predicts brain response during working memory task in OCD, unaffected relatives, and healthy controls. *Scientific Reports, 11*(1), 1–11. https://doi.org/10.1038/s41598-021-98333-w

Hsin-An, C., Wen-Hui, F., Fang-Jung, W., Tzeng, N.-S., Liu, Y.-P., Shyu, J.-F., Chang, T.-C., San-Yuan, H., & Chuan-Chia, C. (2020). Attenuated vagally-mediated heart rate variability at rest and in response to postural maneuvers in patients with generalized anxiety disorder. *Psychological Medicine, 50*(9), 1433–1441. https://doi.org/10.1017/S0033291719001302

Huikuri, H. V., Perkiömäki, J. S., Maestri, R., & Pinna, G. D. (2009). Clinical impact of evaluation of cardiovascular control by novel methods of heart rate dynamics. *Philosophical Transactions of the Royal Society A: Mathematical, Physical and Engineering Sciences, 367*(1892), 1223–1238. https://doi.org/10.1098/rsta.2008.0294

Jacobsen, D., Kloss, M., Fricke, S., Hand, I., & Moritz, S. (2003). Reliabilität der deutschen Version der Yale-Brown Obsessive Compulsive Scale [Reliability of the German version of the Yale-Brown Obsessive Compulsive Scale]. *Verhaltenstherapie, 13*(2), 111–113. https://doi.org/10.1159/000072184

Jandackova, V. K., Britton, A., Malik, M., & Steptoe, A. (2016). Heart rate variability and depressive symptoms: A cross-lagged analysis over a 10-year period in the Whitehall II study. *Psychological Medicine, 46*(10), 2121–2131. https://doi.org/10.1017/S003329171600060X

Johnson, P. O., & Neyman, J. (1936). Tests of certain linear hypotheses and their application to some educational problems. *Statistical Research Memoirs, 1*, 57–93.

Kathmann, N., Endrass, T., Klawohn, J., Grützmann, R., & Riesel, A. (2016). Error-related brain activity as an endophenotype of obsessive-compulsive disorder. *European Neuropsychopharmacology, 26*(5), 894–895. https://doi.org/10.1016/j.euroneuro.2015.06.028

Kemp, A. (2011). Depression, antidepressant treatment and the cardiovascular system. *Acta Neuropsychiatrica, 23*(2), 82–83. https://doi.org/10.1111/j.1601-5215.2011.00535.x

Kemp, A. H., Brunoni, A. R., Santos, I. S., Nunes, M. A., Dantas, E. M., Carvalho de Figueiredo, R., Pereira, A. C., Ribeiro, A. L., Mill, J. G., Andreao, R. V., Thayer, J. F., Bensenor, I. M., & Lotufo, P. A. (2014). Effects of depression, anxiety, comorbidity, and antidepressants on resting-state heart rate and its variability: An ELSA-Brasil cohort baseline study. *The American Journal of Psychiatry, 171*(12), 1328–1334. https://doi.org/10.1176/appi.ajp.2014.13121605

Kemp, A. H., Quintana, D. S., & Malhi, G. S. (2011). Effects of serotonin reuptake inhibitors on heart rate variability: Methodological issues, medical comorbidity, and clinical relevance. *Biological Psychiatry, 69*(8), e25–26. https://doi.org/10.1016/j.biopsych.2010.10.035

Kemp, A. H., Quintana, D. S., Felmingham, K. L., Matthews, S., & Jelinek, H. F. (2012). Depression, comorbid anxiety disorders, and heart rate variability in physically healthy, unmedicated patients: Implications for cardiovascular risk. *PLoS One, 7*(2), Article e30777. https://doi.org/10.1371/journal.pone.0030777

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. *Biological Psychiatry, 67*(11), 1067–1074. https://doi.org/10.1016/j.biopsych.2009.12.012

Kim, S., Zemon, V., Cavallo, M. M., Rath, J. F., McCraty, R., & Foley, F. W. (2013). Heart rate variability biofeedback, executive functioning and chronic brain injury. *Brain Injury, 27*(2), 209–222. https://doi.org/10.3109/02699052.2012.729292

Klawohn, J., Burani, K., Bruchnak, A., Santopetro, N., & Hajcak, G. (2021). Reduced neural response to reward and pleasant pictures independently relate to depression. *Psychological Medicine, 51*(5), 741–749. https://doi.org/10.1017/S0033291719003659

Kleiger, R. E., Stein, P. K., & Bigger, J. T., Jr. (2005). Heart rate variability: Measurement and clinical utility. *Annals of Noninvasive Electrocardiology, 10*(1), 88–101. https://doi.org/10.1111/j.1542-474X.2005.10101.x

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. *Clinical Psychology Review, 46*, 136–150. https://doi.org/10.1016/j.cpr.2016.04.013

Kupper, N. H., Willemsen, G., van den Berg, M., de Boer, D., Posthuma, D., Boomsma, D. I., & de Geus, E. J. (2004). Heritability of ambulatory heart rate variability. *Circulation, 110*(18), 2792–2796. https://doi.org/10.1161/01.CIR.0000146334.96820.6E

Laborde, S., Mosley, E., & Thayer, J. F. (2017). Heart rate variability and cardiac vagal tone in psychophysiological research–recommendations for experiment planning, data analysis, and data reporting. *Frontiers in Psychology, 8*, 213. https://doi.org/10.3389/fpsyg.2017.00213

Lane, R. D., Weidenbacher, H., Smith, R., Fort, C., Thayer, J. F., & Allen, J. J. (2013, Sep 5). Subgenual anterior cingulate cortex activity covariation with cardiac vagal control is altered in depression. *Journal of Affective Disorders, 150*(2), 565–570. https://doi.org/10.1016/j.jad.2013.02.005

Latvala, A., Kuja-Halkola, R., Rück, C., D'Onofrio, B. M., Jernberg, T., Almqvist, C., Mataix-Cols, D., Larsson, H., & Lichtenstein, P. (2016). Association of resting heart rate and blood pressure in late adolescence with subsequent mental disorders: A longitudinal population study of more than 1 million men in Sweden. *JAMA Psychiatry, 73*(12), 1268–1275. https://doi.org/10.1001/jamapsychiatry.2016.2717

Laux, L., Glanzmann, P. G., Schaffner, P., & Spielberger, C. D. (1981). *Das State-Trait-Angstinventar (STAI): Theoretische Grundlagen und Handanweisung*. Beltz.

Long, J.A. (2019). *interactions: Comprehensive, User-Friendly Toolkit for Probing Interactions*. (Version 1.1.5) [Computer software]. ⟨https://cran.r-project.org/package=interactions⟩.

Makin, T. R., & Orban de Xivry, J. J. (2019). Ten common statistical mistakes to watch out for when writing or reviewing a manuscript. *Elife, 8*. https://doi.org/10.7554/eLife.48175

Malik, M. (1996). Heart rate variability: Standards of measurement, physiological interpretation, and clinical use: Task force of the European Society of Cardiology and the North American Society for Pacing and Electrophysiology. *Annals of Noninvasive Electrocardiology, 1*(2), 151–181. https://doi.org/10.1111/j.1542-474X.1996.tb00275.x

McCarthy, P. R., Ray, W. J., & Foa, E. B. (1995). Cognitive influences on electrocortical and heart rate activity in obsessive-compulsive disorder. *International Journal of Psychophysiology, 19*(3), 215–222. https://doi.org/10.1016/0167-8760(95)00009-H

McLaughlin, K. A., Rith-Najarian, L., Dirks, M. A., & Sheridan, M. A. (2015). Low vagal tone magnifies the association between psychosocial stress exposure and internalizing psychopathology in adolescents. *Journal of Clinical Child & Adolescent Psychology, 44*(2), 314–328. https://doi.org/10.1080/15374416.2013.843464

Melzig, C. A., Weike, A. I., Hamm, A. O., & Thayer, J. F. (2009). Individual differences in fear-potentiated startle as a function of resting heart rate variability: Implications for panic disorder. *International Journal of Psychophysiology, 71*(2), 109–117. https://doi.org/10.1016/j.ijpsycho.2008.07.013

Michels, N., Clays, E., De Buyzere, M., Huybrechts, I., Marild, S., Vanaelst, B., De Henauw, S., & Sioen, I. (2013). Determinants and reference values of short-term heart rate variability in children. *European Journal of Applied Physiology, 113*(6), 1477–1488. https://doi.org/10.1007/s00421-012-2572-9

Montgomery, S. A., & Asberg, M. (1979). A new depression scale designed to be sensitive to change. *British Journal of Psychiatry, 134*, 382–389. https://doi.org/10.1192/bjp.134.4.382

Nashiro, K., Yoo, H. J., Cho, C., Min, J., Feng, T., Nasseri, P., Bachman, S. L., Lehrer, P., Thayer, J. F., & Mather, M. (2022). Effects of a randomised trial of 5-Week heart rate variability biofeedback intervention on cognitive function: Possible benefits for inhibitory control. *Applied Psychophysiology and Biofeedback, 14*(1). https://doi.org/10.1007/s10484-022-09558-y

Neumann, N., & Schulte, R. (1989). *MADR-Skala zur psychometrischen Beurteilung depressiver Symptome (MADRS) [MADR scale for psychometric assessment of depressive symptoms (MADRS)]*. Perimed.

Noordam, R., van den Berg, M. E., Niemeijer, M. N., Aarts, N., Hofman, A., Tiemeier, H., Kors, J. A., Stricker, B. H., Eijgelsheim, M., Visser, L. E., & Rijnbeek, P. R. (2016). Antidepressants and heart-rate variability in older adults: A population-based study. *Psychological Medicine, 46*(6), 1239–1247. https://doi.org/10.1017/s0033291715002779

Olbrich, H., Jahn, I., Stengler, K., Seifritz, E., & Colla, M. (2022). Heart rate variability in obsessive compulsive disorder in comparison to healthy controls and as predictor of treatment response. *Clinical Neurophysiology, 138*, 123–131. https://doi.org/10.1016/j.clinph.2022.02.029

Paniccia, M., Paniccia, D., Thomas, S., Taha, T., & Reed, N. (2017). Clinical and non-clinical depression and anxiety in young people: A scoping review on heart rate variability. *Autonomic Neuroscience, 208*, 1–14. https://doi.org/10.1016/j.autneu.2017.08.008

Pittig, A., Arch, J. J., Lam, C. W., & Craske, M. G. (2013). Heart rate and heart rate variability in panic, social anxiety, obsessive–compulsive, and generalized anxiety disorders at baseline and in response to relaxation and hyperventilation. *International Journal of Psychophysiology, 87*(1), 19–27. https://doi.org/10.1016/j.ijpsycho.2012.10.012

R Core Team. (2021). *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing. https://www.R-project.org/.

Rabbia, F., Grosso, T., Cat Genova, G., Conterno, A., De Vito, B., Mulatero, P., Chiandussi, L., & Veglio, F. (2002). Assessing resting heart rate in adolescents: Determinants and correlates. *Journal of Human Hypertension, 16*(5), 327–332. https://doi.org/10.1038/sj.jhh.1001398

Rennie, K. L., Hemingway, H., Kumari, M., Brunner, E., Malik, M., & Marmot, M. (2003). Effects of moderate and vigorous physical activity on heart rate variability in a British study of civil servants. *American Journal of Epidemiology, 158*(2), 135–143. https://doi.org/10.1093/aje/kwg120

Riesel, A. (2019). The erring brain: Error-related negativity as an endophenotype for OCD-A review and meta-analysis. *Psychophysiology, 56*(4), Article e13348. https://doi.org/10.1111/psyp.13348

Riesel, A., Härpfer, K., Thoma, L., Kathmann, N., & Klawohn, J. (2023). Associations of neural error-processing with symptoms and traits in a dimensional sample recruited across the obsessive–compulsive spectrum. *Psychophysiology, 60*(2), Article e14164. https://doi.org/10.1111/psyp.14164

Riesel, A., Kathmann, N., & Klawohn, J. (2019). Flexibility of error-monitoring in obsessive–compulsive disorder under speed and accuracy instructions. *Journal of Abnormal Psychology, 128*(7), 671. https://doi.org/10.1037/abn0000463

Ruscio, A. M., Stein, D. J., Chiu, W. T., & Kessler, R. C. (2010). The epidemiology of obsessive-compulsive disorder in the National Comorbidity Survey Replication. *Molecular Psychiatry, 15*(1), 53–63. https://doi.org/10.1038/mp.2008.94

Schmidt, K.-H., & Metzler, P. (1992). *Wortschatztest (WST)*. Beltz.

Sharma, R. K., Balhara, Y. P., Sagar, R., Deepak, K. K., & Mehta, M. (2011). Heart rate variability study of childhood anxiety disorders. *Journal of Cardiovascular Disease Research, 2*(2), 115–122. https://doi.org/10.4103/0975-3583.83040

Silvetti, M. S., Drago, F., & Ragonese, P. (2001). Heart rate variability in healthy children and adolescents is partially related to age and gender. *International Journal of Cardiology, 81*(2–3), 169–174. https://doi.org/10.1016/S0167-5273(01)00537-X

Simon, D., Kaufmann, C., Kniesche, R., Kischkel, E., & Kathmann, N. (2013). Autonomic responses and neural-cardiac coupling during individually tailored symptom provocation in obsessive-compulsive disorder. *Journal of Anxiety Disorders, 27*(7), 635–644. https://doi.org/10.1016/j.janxdis.2013.08.005

Slaap, B., Nielen, M., Boshuisen, M., Van Roon, A., & Den Boer, J. (2004). Five-minute recordings of heart rate variability in obsessive–compulsive disorder, panic disorder and healthy volunteers. *Journal of Affective Disorders, 78*(2), 141–148. https://doi.org/10.1016/S0165-0327(02)00240-9

Sloan, R. P., Huang, M. H., McCreath, H., Sidney, S., Liu, K., Dale Williams, O., & Seeman, T. (2008, May 30). Cardiac autonomic control and the effects of age, race, and sex: The CARDIA study. *Autonomic Neuroscience, 139*(1-2), 78–85. https://doi.org/10.1016/j.autneu.2008.01.006

Smith, R., Thayer, J. F., Khalsa, S. S., & Lane, R. D. (2017). The hierarchical basis of neurovisceral integration. *Neuroscience & Biobehavioral Reviews, 75*, 274–296. https://doi.org/10.1016/j.neubiorev.2017.02.003

Snieder, H., Harshfield, G. A., & Treiber, F. A. (2003). Heritability of blood pressure and hemodynamics in African- and European-American youth. *Hypertension, 41*(6), 1196–1201. https://doi.org/10.1161/01.HYP.0000072269.19820.0D

Spielberger, C., Gorsuch, R., Lushene, R., Vagg, P., & Jacobs, G. (1983). *Manual for the State-Trait Anxiety Inventory*. Consulting Psychologists Press.

Srinivasan, K. (2006). Childhood anxiety disorder and heart rate variability. In A. Sanfelippo (Ed.), *Panic disorders: New research* (pp. 65–81). Nova Science Publishers.

Thayer, J. F., & Brosschot, J. F. (2005). Psychosomatics and psychopathology: Looking up and down from the brain. *Psychoneuroendocrinology, 30*(10), 1050–1058. https://doi.org/10.1016/j.psyneuen.2005.04.014

Thayer, J. F., Hansen, A. L., Saus-Rose, E., & Johnsen, B. H. (2009). Heart rate variability, prefrontal neural function, and cognitive performance: The neurovisceral integration perspective on self-regulation, adaptation, and health. *Annals of Behavioral Medicine, 37*(2), 141–153. https://doi.org/10.1007/s12160-009-9101-z

Thayer, J. F., & Lane, R. D. (2000). A model of neurovisceral integration in emotion regulation and dysregulation. *Journal of Affective Disorders, 61*(3), 201–216. https://doi.org/10.1016/s0165-0327(00)00338-4

Umetani, K., Singer, D. H., McCraty, R., & Atkinson, M. (1998). Twenty-four hour time domain heart rate variability and heart rate: Relations to age and gender over nine decades. *Journal of the American College of Cardiology, 31*(3), 593–601. https://doi.org/10.1016/s0735-1097(97)00554-8

Uusitalo, A. L., Vanninen, E., Levalahti, E., Battié, M. C., Videman, T., & Kaprio, J. (2007). Role of genetic and environmental influences on heart rate variability in middle-aged men. *American Journal of Physiology-Heart and Circulatory Physiology, 293*(2), H1013–H1022. https://doi.org/10.1152/ajpheart.00475.2006

Voss, A., Heitmann, A., Schroeder, R., Peters, A., & Perz, S. (2012). Short-term heart rate variability—age dependence in healthy subjects. *Physiological Measurement, 33*(8), 1289. https://doi.org/10.1088/0967-3334/33/8/1289

Voss, A., Schroeder, R., Heitmann, A., Peters, A., & Perz, S. (2015). Short-term heart rate variability—influence of gender and age in healthy subjects. *PLoS One, 10*(3), Article e0118308. https://doi.org/10.1371/journal.pone.0118308

Wang, B., Liao, C., Zhou, B., Cao, W., Lv, J., Yu, C., Gao, W., & Li, L. (2015). Genetic contribution to the variance of blood pressure and heart rate: A systematic review and meta-regression of twin studies. *Twin Research and Human Genetics, 18*(2), 158–170. https://doi.org/10.1017/thg.2015.8

Williams, D. P., Cash, C., Rankin, C., Bernardi, A., Koenig, J., & Thayer, J. F. (2015). Resting heart rate variability predicts self-reported difficulties in emotion regulation: A focus on different facets of emotion regulation. *Frontiers in Psychology, 6*, 261. https://doi.org/10.3389/fpsyg.2015.00261

Williams, D. P., Thayer, J. F., & Koenig, J. (2016). Resting cardiac vagal tone predicts intraindividual reaction time variability during an attention task in a sample of young and healthy adults. *Psychophysiology, 53*(12), 1843–1851. https://doi.org/10.1111/psyp.12739

Wittchen, H., Zaudig, M., Fydrich, T. (1997). *Strukturiertes klinisches Interview für DSM-IV (SKID)*. Hogrefe.