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Research paper

The moderating role of depressive symptoms in the association between heart rate variability and cognitive performance in cardiac patients

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ABSTRACT

Introduction: Coronary heart disease (CHD) is strongly associated with cognitive impairment, which is a core feature of depression, highly prevalent in patients with CHD. Interestingly, patients with CHD and individuals with depression display reduced heart rate variability (HRV), which proxies a complex network integrating autonomic and attentional systems. This study investigated the moderating role of depressive symptoms in the relation between reduced HRV and cognitive performance in patients with CHD.

Method: The sample included 274 patients with CHD (mean [standard deviation] age = 62 [9.5] years; 13 % women) admitted to cardiac rehabilitation units. Visual attention and task switching were assessed through the Trail Making Test (TMT). Depressive symptoms were assessed with the Beck Depression Inventory-II (BDI-II). Resting electrocardiographic recordings were collected to compute HRV indices.

Results: Patients with more severe depressive symptoms displayed an inverse association between HRV and cognitive performance (TMT-A: $b = -0.08$, $p = .022$; TMT—B: $b = -0.07$, $p = .042$), whereas patients with milder depressive symptoms showed no significant association (TMT-A: $b = -0.00$, $p = .90$; TMT—B: b = −0.02, $p = .44$).

Conclusions: Depressive symptoms may strengthen the relation between reduced HRV and poorer cognitive performance in cardiac patients. The presence of depressive symptoms may signal the dysfunction of a network subserving autonomic and cognitive function.

1. Introduction

Research has provided consistent evidence supporting an association between coronary heart disease (CHD) and cognitive impairment (Deckers et al., 2017; Eggermont et al., 2012; Gure et al., 2012; Lutski et al., 2018; Stefanidis et al., 2018), also showing that they share common risk factors such as age, obesity, physical inactivity, smoking, high blood pressure, and elevated cholesterol (Alonso et al., 2009; Anstey et al., 2011). A systematic review (Deckers et al., 2017) has shown that patients with CHD have a 45 % increased risk of cognitive impairment and dementia, and several longitudinal studies have shown that myocardial infarction (MI) is followed by an accelerated physiological decline in global cognition and processing speed compared to age-related cognitive decline (Hammond et al., 2018; Schievink et al., 2022; Xie et al., 2019). Patients suffering from CHD display poorer performance in different cognitive domains, including executive function, attention, and psychomotor speed (Pressler et al., 2010; Silbert et al., 2007; Waldstein et al., 2003). Cognitive impairment in patients with CHD is a relevant issue, because it may interfere with the patient's ability to manage a complex chronic condition and treatment.

Intriguingly, depression is strongly intertwined with CHD and has also been consistently associated with cognitive impairment. Depression has an estimated prevalence of 5 % in the general population (American Psychiatric Association, 1994), reaching 30 % among cardiac patients

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(Karami et al., 2023; Thombs et al., 2006) and approximately 45 % in patients after a myocardial infarction (MI) (Schleifer et al., 1989). Several studies have also shown that major depressive disorder (MDD) is a predictor of poor prognosis following a cardiac event (Barth et al., 2004; Burg et al., 2003; Connerney et al., 2001; Kim et al., 2020; Penninx et al., 2001), as well as of mortality risk in MI patients (Larsen, 2013). Research has provided growing evidence supporting a direct association between CHD and depression, which has been recognized as an independent risk factor for CHD onset, development, and outcome (Ariyo et al., 2000; Carney et al., 2005; O'Neil et al., 2016; Rugulies, 2002; Wulsin and Singal, 2003). Moreover, individuals who suffer from depressive symptoms have a 60 % greater likelihood of exhibiting CHD (Wulsin and Singal, 2003).

Depression has been also associated with deficits in various cognitive domains, including attention, psychomotor speed, and working memory (Goodall et al., 2018; Å. Hammar and Årdal, 2009; Ås. Hammar et al., 2010). Consistent evidence points toward a particular impairment of executive functions in depressed individuals (Dotson et al., 2020; Nuño et al., 2021; Snyder, 2013), and switching ability has been proposed as the most prominent cognitive impairment in depression (Austin et al., 2001). Supporting the hypothesis that depression-related cognitive impairment may reflect altered patterns of activity in a specific brain region, both structural and functional abnormalities in the prefrontal cortex (PFC) have been reported in MDD patients (Levin et al., 2007; Rogers et al., 2004). Nonetheless, physiological mechanisms underlying the association between depressive symptoms and cognitive impairment are yet to be understood.

One of the mechanisms that have been proposed as the underlying link between depression and CHD is altered cardiac vagal tone. Researchers have shown increasing interest in the analysis of variations in the time between adjacent heartbeats (Heart Rate Variability, HRV) because it represents a valuable measure of autonomic modulation of cardiac activity (Task Force of the European Society of Cardiology the North American Society of Pacing Electrophysiology, 1996), and specifically cardiac vagal tone as indexed by vagally-mediated HRV indexes (vmHRV) (Laborde et al., 2017). A growing body of literature supports the role of autonomic nervous system (ANS) dysfunction in a wide range of somatic and psychopathological diseases (Beauchaine and Thayer, 2015; Shaffer et al., 2014; Thayer et al., 2010, 2012), including depression. Furthermore, consistent evidence shows that patients with CHD display reduced vmHRV (Thayer et al., 2010; Thayer and Lane, 2007; Tsuji et al., 1996), which has been linked with higher cardiac risk (Bigger et al., 1993; Kleiger et al., 1987; la Rovere et al., 1998) as well as with the negative impact of cardiac disease (Grippo and Johnson, 2009; Penninx et al., 2001).

Moreover, according to the Neurovisceral Integration Model (Thayer and Lane, 2000), brain areas that are responsible for the modulation of cardiac vagal tone, identified as the central autonomic network (including the ventromedial prefrontal cortices, the amygdala, the periaqueductal gray matter, the ventral striatum, and autonomic motor nuclei of the brainstem), are also involved in cognitive and emotional control. Supporting evidence from neuroimaging studies shows that higher resting-state vmHRV is associated with increased activity in the prefrontal cortex (Thayer et al., 2009). Furthermore, vmHRV was found to be related to performance on tasks involving the prefrontal cortex activation, such as sustained attention and working memory (Colzato et al., 2018; Thayer et al., 2009). A recent systematic review (Forte et al., 2019) showed that the association between vmHRV and executive function survives also controlling for relevant confounding variables such as age, gender, and cardiovascular risk. However, the number of studies that investigated the relation between cognitive function and vmHRV in cardiac patients is limited (Beer et al., 2017), suggesting the need for further investigations on this issue.

In the pathway linking altered autonomic activity to impaired cognitive function in CHD patients, depression might have an important moderating role. In fact, depression is not only associated with higher cardiac risk and cognitive impairment, but also with altered cardiac vagal tone. Reduced vmHRV has been reported in depression, showing a direct association between the severity of depressive symptoms, and reduced cardiac vagal modulation (Agelink et al., 2002; Kemp et al., 2012; Koch et al., 2019). Decreased parasympathetic activity has also been proposed to account for a substantial part of the cardiac risk associated with depression in patients with CHD (Carney and Freedland, 2009; Udupa et al., 2007). Therefore, the literature suggested that an integrated assessment of psychological and biomedical risk factors might dramatically improve the identification of those patients at high risk for depression-related adverse outcomes after cardiac surgery (Patron et al., 2014, 2020).

To our knowledge, no previous studies investigated the role of depressive symptoms in the relation between vmHRV and cognitive function in cardiac patients. Thus, the present study aimed to assess the moderating role of depressive symptoms in the relationship between altered cardiac vagal tone (i.e., reduced vmHRV) and cognitive functions in patients with CHD. First, as shown by previous studies on other populations (Thayer et al., 2009), an association between reduced vmHRV and poorer cognitive performance was expected. Second, it was hypothesized that depressive symptoms would have a moderating role in this relation. Specifically, patients with more severe depressive symptoms were expected to show a stronger association between lower vmHRV and poorer cognitive performance, than those with milder depressive symptoms.

2. Materials and methods

2.1. Participants

This study was part of a larger research project conducted by the Department of General Psychology at the University of Padua, Italy. Participants were recruited from the Unit of Cardiac Rehabilitation, ULSS 6 Euganea (Padua, Italy) and the Unit of Cardiac Rehabilitation, San Marco Hospital (Venice, Italy). The project was approved by the local ethics committees (Nucleo di Ricerca Clinica - AULSS 6 Euganea, prot. No. 209498; Comitato Etico Sperimentazione Clinica Provincia di Venezia e IRCSS San Camillo (CESC), prot. No. 5137B6558BA9E00C7-BE4CBFD4FED0BFA; Comitato Etico Della Ricerca Psicologica (AREA 17), prot. No. 2229).

A total of 447 consecutive patients referring to a cardiovascular visit to the Unit of Cardiac Rehabilitation, ULSS 6 Euganea, (Padua, Italy) and the Unit of Cardiac Rehabilitation, San Marco Hospital (Venice, Italy), between December 2017 and December 2019, were approached to participate in the study. Of the 447 patients approached, 58 (20 %) were unable to take part in the study and 10 (3 %) declined participation (see Fig. 1). Exclusion criteria were inability to read or understand Italian; procedure different from percutaneous coronary intervention (PCI), heart valve, or coronary artery bypass graft (CABG) surgery; visual or auditory impairments; severe psychiatric illness (e.g., psychotic disorder) or psychiatric drugs therapy; a history of symptomatic cerebrovascular and/or neurological disease as obtained from patient's medical records and confirmed by medical staff. Three hundred and seventy-nine patients were recruited. Forty-six patients were excluded since they did not meet inclusion criteria; of those excluded, 3 patients were not able to read or understand Italian, 7 were outside the age range, 2 underwent a procedure different from PCI, heart valve or CABG surgery, 23 were prescribed psychiatric drugs, and 11 had a history of cerebrovascular disease. None of the patients included in our study received psychopharmacological therapy. Therefore, 333 patients met the inclusion criteria and underwent the evaluation protocol. Thirty-nine patients were excluded from data analysis because data collection was incomplete (for 22 patients electrocardiographic recording was missing, 17 patients were missing cognitive evaluation). Of the pre-processed data, 20 additional patients were excluded since the ECG recording presented excessive artifacts (>50 % of the recorded signal were artifacts). The

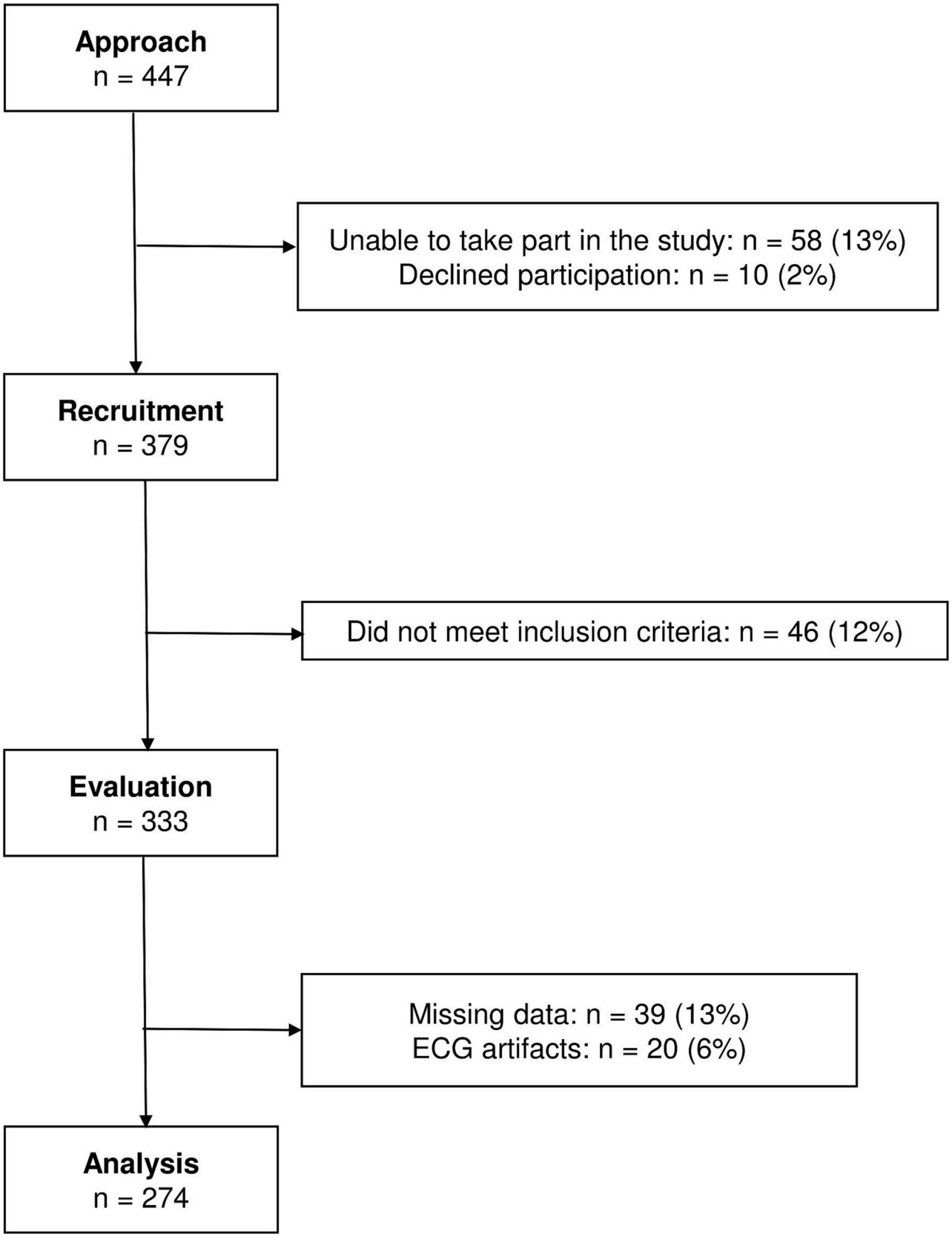

Fig. 1. *STROBE diagram.* STROBE diagram of patients' enrollment and selection through stages of analysis.

analyzed final sample included 274 patients, mostly men (n = 239, 87 %) with a mean [standard deviation (SD)] age of 62.0 (9.46) years, and a mean (SD) education of 12.1 (4.16) years of schooling. Most patients had not completed secondary education (n = 214, 75 %). The sociodemographic and biomedical characteristics of patients are reported in Table 1. The present study was conducted in accordance with the Declaration of Helsinki, and all procedures were performed with an adequate understanding and written consent of the patients.

2.2. Procedure

The assessment was performed for each patient at the Units of Cardiac Rehabilitation of ULSS 6 Euganea (Padua) and San Marco Hospital (Venice). For the purpose of the present study, an ad-hoc interview, a questionnaire, and a cognitive task were administered individually by a trained psychologist in a quiet and isolated room. First, an interview assessing sociodemographic variables (age, sex, and education), and lifestyle habits (such as smoking) was conducted. Afterward, the physiological recording took place. After the placement of electrodes and a 10-minutes adaptation to the sensors, the ECG was recorded at rest for 5 min. Participants were instructed to stay still and avoid talking during the recording. Then, the Beck Depression Inventory-II (BDI-II) and the Trail Making Test (TMT) were administered to respectively assess the severity of depressive symptoms and cognitive performance, particularly in tasks requiring the involvement of visuospatial attention and switching ability. Ultimately, patients' medical data were collected from medical records, including body mass index (BMI), type of intervention, days from intervention, history of cardiovascular events, cardiac risk factors (i.e., hypertension, dyslipidemia, diabetes, and arrhythmia), and pharmacological treatment (i.e., anticoagulants, beta-blockers, ACE-inhibitors, anti-hypertensives, antiarrhythmics, statins, and psychotropic drugs).

Table 1
Sociodemographic, biomedical and pharmacological data.

	Mean (SD) or N (%)
Age (years)	61.95 (9.46)
Education (years)	12.14 (4.16)
BMI (kg/m^2)	26.41 (3.55)
Male, N (%)	239 (87)
Smoking	
Actual, N (%)	67 (25)
Past, N (%)	106 (39)
Hypertension, N (%)	194 (71)
Dyslipidemia, N (%)	164 (60)
Diabetes, N (%)	48 (17)
Myocardial infarction, N (%)	42 (15)
Days from intervention	28.59 (27.57)
Intervention	
PCI, N (%)	173 (63)
Surgery, N (%)	59 (21)
Pharmacological therapy	
Anticoagulants, N (%)	268 (98)
Beta-blockers, N (%)	221 (81)
ACE inhibitors, N (%)	113 (41)
Antiarrhythmics, N (%)	24 (9)
Anti-hypertensives, N (%)	69 (25)
BDI-II score	8.22 (6.23)
lnHF	4.89 (1.45)
TMT-A time	42.54 (25)
TMT-B time	130.60 (89.51)

The table shows the mean (SD) for continuous variables and frequency (%) for categorical variables. BMI = Body Mass Index; PCI = Percutaneous Coronary Intervention; BDI-II = Beck Depression Inventory (2nd edition); lnHF = natural logarithm of high-frequency heart rate variability in ms^2; TMT-A = Trail Making Test (Part A); TMT-B = Trail Making Test (Part B).

2.3. Materials

2.3.1. Psychological and cognitive assessment

Cognitive performance and depressive symptoms were assessed by employing the following standardized questionnaires and tests:

- The Trail Making Test (Reitan, 1956; Giovagnoli et al., 1996) requires connecting numbered circles in numerical sequence (Part A), and alternatively connecting numbered and alphabetic circles in ascending sequence (Part B) by drawing a line with a pencil. The TMT-A allows the evaluation of visuospatial attention, while the TMT-B is a measure of switching ability. Scores correspond to the time for tests' completion (in seconds) and lower scores indicate better performances (i.e., shorter completion times). Importantly, the use of the Trail Making Test has been recommended by the Consensus on Neurobehavioral Assessment (Murkin et al., 1995) for the evaluation of neurobehavioral outcomes after cardiac surgery. The consensus statement highlights the importance of assessing specific cognitive domains, including attention and concentration in patients with cardiovascular diseases, recommending the TMT-A and TMT-B as core tests. Research studies have consistently demonstrated a significant association between TMT performance and different key cognitive functions, including executive functioning, working memory, and processing speed (Arbuthnott and Frank, 2000; Salthouse, 2011). This suggests that the TMT goes beyond a single cognitive domain, providing valuable insights into multiple aspects of cognitive functioning that are specifically compromised in cardiac patients (Messerotti Benvenuti et al., 2012; Moser et al., 1999; Singh-Manoux et al., 2003; Gayda et al., 2017; Messerotti Benvenuti et al., 2014; Patron et al., 2013b).
- The Beck Depression Inventory-II (Sica and Ghisi, 2007; Beck et al., 1996) is a reliable and valid 21 items self-report questionnaire that evaluates the severity of depressive symptoms in the previous two weeks. Each item is composed of a group of statements that refer to a specific symptom of depression according to the Diagnostic and Statistical Manual of Mental Disorders-IV (American Psychiatric Association, 1994). Each item is scored on a scale from 0 to 3 (total score ranges from 0 to 63) depending on its level of severity. Scores below 13 reflect minimal depression, scores from 14 to 19 indicate mild depressive symptoms, scores from 20 to 28 reflect moderate depressive symptoms, and scores from 29 to 63 suggest severe depression.

2.3.2. Electrocardiographic recording

The electrocardiographic (ECG) recording was performed using three disposable Ag/AgCl electrodes that were positioned according to the lead II Einthoven's configuration. The ECG signal was acquired at rest for 5 min and sampled at 256 Hz, then a band-pass filter (1–100 Hz) was applied. All ECG recordings were visually inspected, and artifacts (e.g., ectopic beats) were corrected with a piecewise cubic spline interpolation method to generate missing or corrupted values into the normal-to-normal (NN) intervals. Inter-beat interval series were obtained using R-peak detection and mean HR was calculated. Frequency-domain HRV indices were computed through autoregressive spectral analysis using Kubios HRV Analysis software 2.2 (Matlab, Kupio, Finland). HF power (ms^2) of HRV is considered a reliable index of parasympathetic tone in short-term resting recordings (Shaffer et al., 2014). Therefore it was calculated as an index of vagally mediated HRV (vmHRV). HF power was natural log-transformed to fit the assumptions for linear analyses (Malik et al., 1996).

2.4. Statistical analysis

All analyses were performed using RStudio Version 1.4.1717. In order to evaluate the role of depressive symptoms as a possible moderator of the relation between lnHF and cognitive performance at the TMT,

two hierarchical regression analyses exploring main and interaction effects were performed. TMT-A and TMT-B were the designated outcome variables of the models. The lnHF was the predictor, while the BDI-II continuous score was the moderator. Indeed, using the continuous BDI-II scores provides a more comprehensive and nuanced understanding of the relationship between depressive symptoms and our study variables, since it allows to capture the full spectrum of symptom severity and avoid potential oversimplification that comes with applying rigid cut-off values. Concerning TMT-A and —B time of completion in seconds, both variables were natural log-transformed to fit the assumptions for linear analyses (Malik et al., 1996). Both the moderator and predictor variables were mean centered and scaled. In the first block of the hierarchical regression models, control variables (i.e., age, level of education, type of cardiovascular intervention, days from surgery, hypertension and pharmacological therapy with anti-hypertensives and β-blockers) were inserted. In the second block, lnHF and BDI-II score and the interaction lnHF × BDI-II were added. To assess the presence of multicollinearity between the variables entered in the models, the *mctest* package (Imdad and Aslam, 2020; Imdadullah et al., 2016) was used, showing acceptable levels of collinearity (variance inflation factor <4, tolerance >0.03, and condition index <30). To explore interaction effects, the Johnson-Neyman interval was computed using the *interactions* package (Long, 2022). Using G*Power (Faul et al., 2007), a sensitivity power analysis for multiple regression model including a sample size of 274 and 10 predictors was performed. Results from the sensitivity analysis show that the present study had adequate statistical power (i.e., power = 0.80) to detect a small effect size ($d = 0.12$).

The statistical type I two-sided (alpha) level was fixed at $\alpha < 0.05$.

3. Results

3.1. Characteristics of the sample

Regarding cognitive performance, the mean (SD) time for the completion of the TMT-A was 41.34 (25.56) seconds, with observations ranging from 15 to 282 s, whereas time for the completion of the TMT-B was 122.47 (81.96) seconds, with observations ranging from 34 to 420 s. Mean (SD) BDI-II total score was 7.56 (6.20), with observations ranging from 0 to 43. Thirty-six (13 %) patients showed depressive symptoms (BDI-II scores ≥ 14), while the remaining 228 (87 %) patients displayed no depressive symptoms (BDI-II scores <14). The mean (SD) HR was 63.04 (11.09) beats/min, ranging from 41.17 to 108.37 beats/min. Mean (SD) lnHF was 4.83 (1.49) with observations ranging from 0.61 to 8.63 ms^2. Since slow-paced breathing can alter HF power, we have conducted additional analyses[1] to assess the influence of patients' respiratory rate (see Supplementary Material 1).

3.2. The moderating role of depressive symptoms on the relation between cardiac vagal tone and visuospatial attention

Block 1 of the regression model on TMT-*A* (see Table 2) showed a significant association between age and TMT-A ($p < .001$). Younger patients were faster in the completion of the TMT-A. No other control variables (i.e., education, type of intervention, days from surgery, hypertension, anti-hypertensive and beta-blocking therapy) were significantly associated with TMT-A completion time (all *ps* > .05). Consistent with results observed in block 1, a significant association between age and TMT-A ($p < .001$) emerged in block 2. Also, a significant relation between BDI-II scores and TMT-A was found ($p = .017$). Patients with higher depressive symptoms were slower at TMT-A completion. No association between lnHF and TMT-A emerged ($p = .68$). A significant interaction lnHF × BDI-II emerged ($p = .024$). This interaction was better specified through the Johnson-Neyman calculation (see Fig. 2). Results showed that the lnHF slope was significant for BDI-II scores outside the interval i = [−23.04, 13.43]. Specifically, a negative relation between lnHF and TMT-A completion time emerged in patients with a BDI-II scores equal to or higher than 14 ($b = -0.08$, $p = .022$). Conversely, in patients with a BDI-II score lower than 14 no association emerged ($b = -0.00$, $p = .90$).

The hierarchical multiple regression revealed that the addition of BDI-II score, lnHF and their interaction significantly contributed to the regression model ($F_{(3,\ 262)} = 4.74$, $p = .003$). Together, the ten dependent variables accounted for 24 % of the variance in TMT-A completion time. The overall model fit was $R^2 = 0.24$ with an effect size of $f^2 = 0.32$, hence the power of this study was more than adequate to detect the effect of the model, being $(1\text{-}\beta) = 1$.

3.3. The moderating role of depressive symptoms on the relation between cardiac vagal tone and switching ability

Block 1 of the regression analysis performed on TMT-B (see Table 2), showed significant linear associations between the TMT-B and age ($p < .001$), education ($p = .007$), and PCI ($p = .007$). In particular, younger patients, with higher education level and who underwent PCI, compared to those who did not undergo an intervention, were faster in TMT-B completion. No other control variable (i.e., surgery, days from surgery, hypertension, anti-hypertensive and beta-blocking therapy) resulted associated with TMT-B completion time (all *ps* > .05). Consistent with results observed in block 1, significant associations between TMT-B and age, education level and PCI emerged in block 2. Also, a significant relation between BDI-II scores and TMT-B completion time was found ($p = .028$). Specifically, patients with higher depressive symptoms were slower in completing the TMT—B. No significant association was found between lnHF and TMT-B time ($p = .39$). Ultimately, a significant lnHF × BDI-II interaction effect was found ($p = .010$). This interaction was better specified by the Johnson-Neyman calculation, showing that the slope of the lnHF was significant ($p < .05$) for values of the BDI-II outside the interval i = [−13.90, 11.02]. Moreover, results from the simple slope analysis showed a significant association between lnHF and TMT-B time in patients with BDI-II equal to or higher than 12 ($b = -0.07$, $p = .042$), while patients with a BDI-II score lower than 12 showed no significant association ($b = -0.02$, $p = .45$).

The hierarchical multiple regression revealed that BDI-II scores, lnHF and their interaction significantly contributed to the regression model ($F_{(3,\ 262)} = 5.50$, $p = .001$). The overall model fit was $R^2 = 0.31$ accounting for 31 % of the variance in TMT-B with an effect size of $f^2 = 0.45$, hence the power of this study was more than adequate to detect the effect of the model, being $(1\text{-}\beta) = 1$.

4. Discussion

The present study aimed to investigate the moderating role of depressive symptoms on the relation between cognitive performance and cardiac vagal tone in patients with CHD. Specifically, a significant association between reduced cardiac vagal tone (indexed by lnHF) and poorer visuospatial attention, as well as poorer task switching ability (indexed by TMT completion time), was expected. Moreover, it was hypothesized that patients with higher depressive symptoms would display a stronger association between cardiac vagal tone and cognitive performance compared to individuals with lower depressive symptoms.

Results showed significant associations between the severity of

[1] During electrocardiographic recording, respiratory rate was detected with a strain gauges/tube filled with conduction fluid worn abdominally. Out of the 274 patients included in our study, only seven exhibited a respiratory rate below 9 breaths per minute. The mean (SD) respiratory frequency was 14.7 (2.8) breaths per minute, while the observed range of respiratory frequencies was 7.1 to 18.8 breaths per minute. Since slow-paced breathing can alter high frequency power, sensitivity analyses were conducted excluding those with a respiratory rate below 9 breaths per minute, showing that results remained unaltered (see Supplementary Material 1).

Table 2
Moderation role of depressive symptoms on cognitive performance.

		TMT-A							TMT-B						
Block	Predictor	*b*	Std. Err.	t value	*p*		R^2	ΔR^2	*b*	Std. Err.	t value	*p*		R^2	ΔR^2
1							0.21	0.21						0.27	0.27
	(Intercept)	2.39	0.18	13.57	<0.001	***			3.05	0.20	15.37	<0.001	***		
	Age	0.02	0.00	8.62	<0.001	***			0.03	0.00	9.15	<0.001	***		
	Education (0 = High; 1 = Low)	0.05	0.05	0.88	0.38				0.17	0.06	2.72	0.007	**		
	PCI (0 = MI; 1 = PCI)	−0.11	0.07	−1.61	0.11				−0.20	0.07	−2.74	0.007	**		
	Surgery (0 = MI; 1 = Surgery)	−0.09	0.08	−1.20	0.23				−0.16	0.09	−1.88	0.061			
	Days from surgery	−0.00	0.00	−1.63	0.11				−0.00	0.00	−0.31	0.76			
	Beta-Blockers	0.03	0.06	0.50	0.62				0.02	0.07	0.35	0.73			
	Anti-hypertensives (0 = No; 1 = Yes)	−0.01	0.06	−0.21	0.84				−0.01	0.06	0.14	0.89			
	Hypertension	−0.04	0.05	−0.84	0.41				−0.04	0.06	0.74	0.46			
2							0.24	0.03						0.31	0.04
	(Intercept)	2.40	0.17	13.87	<0.001	***			3.08	0.19	15.83	<0.001	***		
	Age	0.02	0.00	8.43	<0.001	***			0.02	0.00	8.96	<0.001	***		
	Education (0 = High; 1 = Low)	0.06	0.06	1.08	0.28				0.18	0.06	2.84	0.005	**		
	PCI (0 = IM; 1 = PCI)	−0.09	0.06	−1.39	0.17				−0.19	0.07	−2.58	0.010	*		
	Surgery (0 = IM; 1 = Surgery)	−0.08	0.08	−1.06	0.29				−0.16	0.09	−1.87	0.063			
	Days from surgery	−0.00	0.00	−1.53	0.13				−0.00	0.00	−0.16	0.87			
	Beta-Blockers	0.04	0.06	0.64	0.52				0.04	0.07	0.53	0.60			
	Anti-hypertensives (0 = No; 1 = Yes)	−0.00	0.05	−0.02	0.98				0.02	0.06	0.33	0.74			
	Hypertension	−0.05	0.05	−0.92	0.36				0.04	0.06	0.73	0.47			
	lnHF	−0.01	0.02	−0.41	0.68				−0.02	0.02	−0.86	0.39			
	BDI-II	0.01	0.00	2.41	0.017	*			0.01	0.00	2.21	0.028	*		
	lnHF × BDI-II	−0.00	0.00	−2.26	0.024	*			−0.01	0.00	−2.60	0.010	**		

Note: TMT-A = Trail Making Test (Part A); TMT-B = Trail Making Test (Part B); PCI = Percutaneous Coronary Intervention; BDI-II = Beck Depression Inventory (2nd edition); lnHF = natural logarithm of high-frequency heart rate variability in ms2.
*** $p < .001$.
** $p < .01$.
* $p < .05$.

depressive symptoms and cognitive performance. Specifically, patients with higher depressive symptoms showed longer TMT-A and -B completion times. This result is in line with previous findings showing that depression severity is associated with more pronounced cognitive impairment (Austin et al., 2001; McClintock et al., 2010; McDermott and Ebmeier, 2009). However, no association between cardiac vagal tone and cognitive performance was found.

Moreover, a significant interaction between the severity of depressive symptoms and vmHRV emerged. In particular, reduced vmHRV was associated with poorer cognitive performance in patients with higher depressive symptoms. In contrast, no significant association emerged in patients with lower depressive symptoms. The present results suggest that depressive symptoms have a role in the negative effect of reduced vmHRV on cognitive functions that are required for the completion of the TMT, including visuospatial attention and switching ability.

Concerning the role of covariates, a significant relationship between patients' age and TMT completion time was found for both parts of the TMT, consistently with previous evidence. Consistent with previous evidence, older patients took longer to complete both the TMT-A and the TMT-B (Amodio et al., 2002; Giovagnoli et al., 1996; Salthouse, 2011). Furthermore, patients with a lower education level were slower in completing the TMT—B, but not the TMT-A. The different influence of education level on the two parts of the TMT was already reported, underliyng a greater variance explained by education level in the TMT-B score, compared to the TMT-A (Llinàs-Reglà et al., 2017). The type of cardiac intervention and specifically PCI was found to be inversely related to cognitive performance. Specifically, patients who underwent PCI were faster in completing the TMT-B compared to those who underwent no intervention. In contrast, no effect of CABG surgery on cognitive performance was found. These results could be interpreted considering the different impacts of postoperative cognitive decline in patients undergoing PCI and CABG, particularly in favor of those who receive PCI. Indeed, patients who underwent PCI usually have a better prognosis and experience faster recovery compared to other cardiac patients. Furthermore, this is in line with evidence suggesting that PCI may decrease the likelihood of dementia, compared with medical treatment alone (Mutch et al., 2011).

Importantly, we found that 13 % of the participants exhibited clinically relevant depressive symptoms, defined as a BDI-II score of 14 or higher. While acknowledging the imbalanced presence of clinically relevant depressive symptoms in our study, this prevalence aligns with findings from previous research investigating depressive symptoms in patients with coronary heart disease (CHD) after cardiac surgery, utilizing the BDI-II with the same cut-off (Goyal et al., 2005; Kala et al., 2016; Patron et al., 2020). Additionally, it is important to note that our moderation analyses were conducted using BDI-II scores as a continuous variable. This allowed us to observe the distinction between patients with high depressive symptoms and those with low depressive symptoms with a data-driven approach, rather than by applying a standard cut-off, by means of the Johnson Neyman interval calculation (D'Alonzo, 2004).

Altogether, the present results suggest that depressive symptoms may strengthen the link between reduced vmHRV and poorer cognitive performance. It may be speculated that depressive symptoms signal the dysfunction of a complex network of neural structures, defined as the central autonomic network, subserving central-periphery neural feedback mechanisms (Thayer and Lane, 2000). Alterations in the central autonomic network would be expected to affect cognitive abilities linked to the prefrontal cortex, including visuospatial attention and switching (Alvarez and Emory, 2006; Hovland et al., 2012; Thayer et al., 2009). Integrated psychophysiological interventions targeting autonomic imbalance which have been shown to be effective in reducing depressive symptomatology (such as HRV-biofeedback) could reduce the risk of cognitive impairment in patients with CHD undergoing medical treatment and cardiac surgery. Indeed, previous studies showed that HRV-biofeedback is an effective tool in increasing psychological

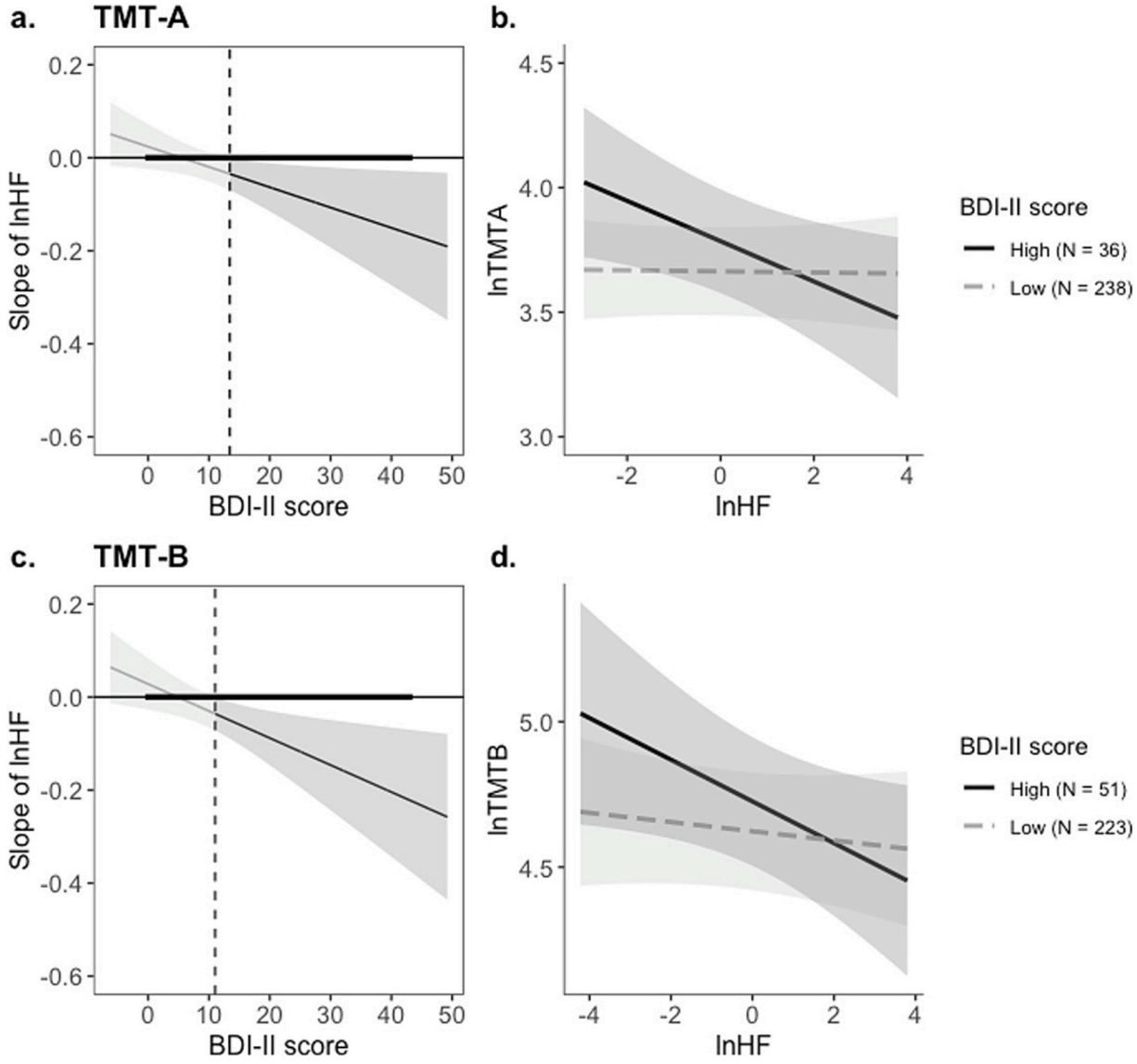

Fig. 2. *Johnson-Neyman interval plots.* The figure displays Johnson-Neyman interval plots for the TMT-A (panel a) and TMT-B (panel c). The dark grey part of the curve represents the values of the BDI-II scores for which the slope of lnHF is significant at a fixed $\alpha = 0.05$. Conversely, the light grey part of the curve represents the values of the BDI-II scores for which the slope of lnHF is not statistically significant. *Interaction plots.* The figure shows the moderation effect of depressive symptoms (BDI-II scores) on the association between lnHF and cognitive performance at the TMT-A (panel b) and TMT-B (panel d). The dark grey lines represent the significant negative association between lnHF and cognitive performance in patients with higher depressive symptoms, whereas the dashed light grey line represents no significant association in patients with lower depressive symptoms.
Note: lnHF = natural logarithm of high-frequency power; lnTMTA = natural logarithm of time for completion of the Trail Making Test (part A); lnTMTB = natural logarithm of time for completion of the Trail Making Test (part B); BDI-II = Beck Depression Inventory (2nd edition).

adjustment to CHD (Nolan et al., 2005), reducing depressive symptoms in surgical patients (Patron et al., 2013a), and improving cognitive function (Jester et al., 2018). Also, it was suggested that screening for depression in patients with CHD may be useful to identify those that are more subjected to a higher risk of adverse cardiovascular events, and eventually improve health outcomes by means of a collaborative care programme to treat depressive symptoms (Celano and Huffman, 2011; Jha et al., 2019).

The present study has some limitations that should be considered. First, our sample mainly involved male patients, therefore it is not possible to generalize the present results to the female population. The majority of studies that investigated the role of socio-demographic variables in TMT performance reported a worse performance in women, in respect to men, likely due to lower education level in women of the considered cohorts (Amodio et al., 2002; Llinàs-Reglà et al., 2017). Second, depressive symptoms were assessed using the BDI-II, which is a self-report questionnaire. Self-report measures are knowingly subjected to biases and methodological caveats (Althubaiti, 2016) that could limit the reliability of the present study. Nevertheless, the BDI-II was shown to have high reliability and capacity to discriminate between depressed and non-depressed individuals (Wang and Gorenstein, 2013). Third, this is a cross-sectional study design, therefore it is not possible to draw conclusions concerning the causal relations among the considered variables.

Overall, the current study examined the moderating role of depressive symptoms in the relation between vmHRV and cognitive performance in cardiac patients who underwent PCI. The present results show that patients with depressive symptoms display a negative association between reduced vmHRV (as indexed by lnHF) and cognitive performance at the TMT. This evidence is of considerable importance in light

of the consistent link between depression and CHD. Indeed, it suggests that the presence of depressive symptoms might strengthen the link between reduced vmHRV and poorer cognitive performance. It may be speculated that depressive symptoms signal a dysfunction of the central autonomic network, serving both autonomic and cognitive function. We suggest that the inclusion of an integrated psychophysiological intervention aimed at targeting depressive symptomatology and vmHRV in cardiovascular rehabilitation programmes could reduce the risk of cognitive impairment, and diminish the impact of depression-related cardiac risk in patients with CHD.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2023.08.022.

CRediT authorship contribution statement

EP, SMB, CG, AP and DP conceived and designed the study; FM, AP and FDP gathered the data; FM and EP analyzed the data; FM, EP, and SMB wrote the paper, and all authors reviewed and approved the final manuscript.

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Declaration of competing interest

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