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Heart rate variability and cognitive performance in adults with cardiovascular risk

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ABSTRACT

Background: Heart rate variability (HRV), a measure of autonomic function, has been associated with both cardiovascular disease and cognitive dysfunction. In turn, cardiovascular risk has been linked to an increased risk of dementia onset. However, whether autonomic dysfunction may represent an early marker of cognitive decline in individuals with high cardiovascular risk is still an open issue.

Methods: We performed a complete 24-hour HRV analysis in 50 middle-aged and elderly subjects with cardiovascular risk as assessed with the European Society of Cardiology Systematic Coronary Risk Evaluation (ESC SCORE). Cognitive performance was evaluated by Montreal Cognitive Assessment (MoCA), Free and Cued Selective Reminding Test (FCSRT) and Stroop Color and Word Test. Stepwise regression was used to identify significant associations between 24-hour ambulatory ECGs parameters and cognitive performances.

Results: There were 30 women and 20 men with mean age of 64.9 years (range 51-77) and the mean ESC SCORE was 6%. Four subjects were diagnosed with mild cognitive impairment. Associations were found between measures of HRV and measures of cognition. Ultra-low frequency (ULF) band power of HRV significantly correlated with MoCA ($r = 0.424$, $p = 0.003$), also after adjustment for demographics and education. A significant association was also found between the ESC SCORE and ULF band power ($r = -0.470$, $p = 0.0009$).

Conclusions: Ultra-low frequency band power of HRV is associated with cognitive performance of middle-aged and elderly subjects with cardiovascular risk. This finding may indicate that autonomic nervous system dysregulation plays a role in developing cardiovascular risk and cognitive decline.

1. Introduction

Cognitive decline is a common aspect of aging and can range from mild cognitive impairment (MCI) to dementia. Alzheimer disease (AD) is the most common form of dementia. The sporadic form of the disease is characterized by a long preclinical phase with age as the leading risk factor, and the apolipoprotein E (ApoE) polymorphic alleles as the main genetic determinants of the disease risk. The AD brain is histologically characterized by a progressive deposition of extra-neuronal plaques, mainly composed of β-amyloid, and by the formation of neurofibrillary tangles, formed of hyper-phosphorylated tau. No disease-modifying therapies are available and only recently, aducanumab, a monoclonal antibody that lowers brain Aβ plaques, has been approved the by Food & Drug Administration. However, its limited clinical efficacy and poor tolerability have raised strong criticism [1]. Thus, preventive policies based on the control and reduction of identified risk factors of dementia represent an important approach to limit the future incidence and prevalence of the diseased [2].

Growing and solid evidence suggests a close relationship between midlife cardiovascular risk factors and the future risk of AD onset [3]. Several studies have shown the importance of vascular pathology in AD. Arterial hypertension, elevated blood pressure variability, diabetes, dyslipidemia, smoke, overweight, non-adherence to the Mediterranean diet, low levels of physical activity as well as target organ damage

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(intima media thickness, carotid plaques, left ventricular hypertrophy, arterial stiffness, lacunae and white matter lesions and retinal vascular changes) are considered as potential vascular factors involved in AD [4].

The autonomic nervous system (ANS) is composed of two major branches: the sympathetic system, associated with energy mobilization, and the parasympathetic system, associated with vegetative and restorative functions. Normally, the two branches act in a dynamic balance, and can be rapidly modulated in response to changing environmental demands. On the contrary, autonomic imbalance, characterized by hyperactive sympathetic system and/or blunted vagal tone, is associated with increased morbidity and mortality from a host of conditions and diseases, including cardiovascular disease [5].

Heart rate variability (HRV) is a non-invasive index of the cardiac autonomic nervous system control and it can be used to assess autonomic dysfunction. Indeed, HRV is a measure of fluctuations in beat-to-beat intervals of the sinus node, arising from the interaction between the sympathetic and parasympathetic divisions of the ANS. Although HRV gradually declines with age, reduction in HRV indicates an autonomic dysfunction [6]. Substantial evidence supports the notion that decreased HRV precedes the development of cardiovascular events and lowering cardiovascular disease risk factors is associated with increased HRV [5]. Lower mid-life HRV is independently associated with future cardiovascular diseases and mortality, as well as other morbidities, including cognitive decline. Indeed, autonomic dysfunction is common in patients with dementia, and it may precede the onset of clinical symptoms [7]. Various central nervous system structures affected in AD (hypothalamus, locus coeruleus, insular cortex, and brainstem) are also invoved in ANS regulation, and it has been hypothesized that the deficit in central cholinergic function observed in AD, a crucial regulator of the cardiovascular and autonomic functions, may lead to autonomic dysfunction [8].

Despite the well explored association of autonomic dysfunction with increased cardiovascular morbidity and mortality [9], whether autonomic dysfunction may represent an early marker of cognitive decline in individuals with high cardiovascular risk is still an open issue. Applying 24-hour HRV analysis, we investigated the relationship between ANS and cognitive performances in middle-aged and elderly subjects with moderate-to-high cardiovascular risk.

2. Methods

This cross-sectional study involved 50 consecutive patients who referred to “Don Carlo Gnocchi Foundation Cardiovascular Prevention and Rehabilitation Unit” of Parma (Italy), between October 2019 and May 2021. All subjects signed a detailed informed consent and the study was approved by the Ethics Committee of University of Parma. The study was carried out in accordance with the Helsinki ethical principles. We enrolled subjects aged between 50 and 80 years with moderate to high cardiovascular risk, undergoing primary cardiovascular prevention; subjects undergoing secondary cardiovascular prevention and subjects with cerebrovascular disease, dementia or other neurodegenerative disease were excluded.

2.1. Cardiovascular evaluation

Detailed medical history was collected to assess cardiovascular risk; family history of cardiovascular disease (CVD), hypertension, dyslipidemia, diabetes, smoking, obesity, psychosocial factors (work and family history, perceived stress, anxiety and depression) and unhealthy lifestyle (sedentary behavior, physical activity, smoking and sleep disturbances) were considered risk factors. Vascular organ damage was assessed by analysing the aorta and supra-aortic trunks using ultrasound Doppler. Cardiac organ damage was assessed by ECG, echocardiogram and cardiopulmonary exercise or ergometric testing, the latter useful for the evaluation of the chronotropic response (CR) and the heart rate recovery (HRR). CR was evaluated as a percentage of the chronotropic reserve: CR = (peak HR-rest HR) / (apm HR-rest HR) × 100. HRR was defined as the decrease in heart rate (in bpm) at 1 minute after the end of the exercise. Autonomic hemodynamics were assessed by monitoring blood pressure and heart rate over 24 hours. Ambulatory blood pressure monitoring (ABPM) was performed with a validated automated oscillometric device (Spacelabs model 90207) applying an inflatable cuff wrapped around the non-dominant arm. The device provides measurements of systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and HR every 15 minutes during the day and every 30 minutes at night. The SBP and DBP variability was quantified by the standard deviation (SD) of all measurements during the 24 hours, and by the coefficients of variation (CoV), calculated as the ratio of SD/mean and expressed as a percentage.

A validated 3-channel ambulatory electrocardiographic monitoring device (Cardioline Holter ECG) with four precordial leads (C1, C4, C5 and C6) coupled with the HRVanalysis software [10] was used for the evaluation of HRV over 24 hours. Cardiac arrhythmias were deleted both automatically and manually in order to avoid biases in the analysis of HRV. The autonomous indices were calculated from HRV according to three types of analysis. The time domain analysis computed the following parameters: SDNN Index (ms), which is the mean of the 5-min standard deviation of the NN interval calculated over 24 h; RMSSD (ms) which is the square root of the mean square differences of successive NN intervals; pNN50 (%), which is the NN50 count divided by the total number of all NN intervals with NN50 being the number of differences of successive NN intervals greater than 50 ms. Both RMSSD and pNN50 are indices of vagal modulations of HR. The time domain variables were calculated during both the 24 hours and the night, while the frequency domain only during the 24 hours considering the entire recording. We also performed a frequency domain analysis which calculated the following parameters: the natural logarithm of the high frequency (lnHF); the vagal modulation index of the HR; the ratio of the natural logarithm between the low frequency (LF) and the high frequency (HF) (ln LF/HF), which is an index of cardiac sympathetic/vagal balance. The power spectra were integrated on a very low frequency band (VLF), between 0.001 and 0.04 Hz; a low frequency band (LF), between 0.04 and 0.15 Hz; a high frequency band (HF), between 0.15 and 0.50 Hz; an ultra-low frequency band (ULF), $<$ 0.003 Hz. We also applied a non-linear analysis on HRV. Both entropy and fractal analysis were performed in order to assess approximate entropy (ApEn), the entropy of the sample (Samp Entropy) and detrended fluctuation analysis (DFA). Finally, we recorded single ventricular premature complexes (VPCs), supraventricular extrasystoles (SVEs), and heart rate turbulence (HRT) onset (TO) and slope (TS).

2.2. Cardiovascular risk assessment

Cardiovascular risk was estimated with the Systematic Coronary Risk Evaluation (SCORE), a cardiovascular disease risk assessment tool developed by the European Society of Cardiology, using data from 12 European cohort studies covering a wide geographic spread of countries at different levels of cardiovascular risks [11]. The ESC SCORE estimation is based on the following risk factors: gender, age, smoking, systolic blood pressure, total cholesterol, and estimates fatal CVD events over a 10-year period.

2.3. Neuropsychological evaluation

Neuropsychological evaluation lasted about 50 min per each patient. It included the Montreal Cognitive Assessment (MoCA), the Free and

Cued Selective Reminding Test (FCSRT) and the Stroop Color and Word Test. MoCA is a neuropsychological test used as a tool for rapid screening of mild cognitive impairment [12].. The overall test score ranges from 0 to 30, with a normal performance for the Italian population indicated by a score higher than 17.5 [13]. The MoCA consists of 12 tasks exploring 6 cognitive domains (executive functions, visual-spatial skills, language, attention, space-time orientation and memory). The Free and Cued Selective Reminding Test (FCSRT) discriminates between the two main components of episodic memory, storage and retrieval, with deficits in the former burdened by a worse prognosis as they are more often related to AD [14]. The main components of the FCSRT are: Immediate Free Recall (IFR) (range 0-36), Immediate Total Recall (IRT) (range 0-36), Free Deferred Recall (DFR) (range 0-12), Total Deferred Recall (DTR) (range 0-12), Index of Sensitivity to the Semantic Suggestion (range 0-1). The Stroop Color and Word Test was originally developed from studies on the "stroop effect" that is currently used to measure selective attention, cognitive flexibility and the ability to inhibit interference. It is commonly applied in elderly subjects for the assessment of cognitive impairment related to AD or other pathologies [15]. The main parameters evaluated with this test are the effect of error interference and the effect of time interference.

2.4. CAIDE Risk Score

The Cardiovascular Risk Factors, Aging, and Incidence of Dementia (CAIDE) Risk Score is a validated tool to predict late-life dementia risk (20 years later), based on midlife vascular risk factors (age, education, gender, blood pressure, body mass index, total cholesterol, physical activity) [16].

2.5. Sleep evaluation

Sleep evaluation included self-reported number of hours of sleep, self-reported quality of sleep (0-10 rating scale), history of sleep apnoea, history of snoring, and the Epworth Sleepiness Scale (ESS). The use of medications which can affect sleep was also collected. Subjects with history of sleep apnoea and/or subjects with ESS score higher than 9 underwent nocturnal pulse oximetry. Subjects with abnormal oxygen desaturation index (> 14) were referred to the Sleep Disorders Center at the University of Parma, for further sleep evaluation including polysomnography. Total ESS is a scale that estimates daytime sleepiness [17] and distinguishes normal subjects from patients in various diagnostic groups including obstructive sleep apnoea syndrome, narcolepsy and idiopathic hypersomnia. ESS scores correlate with sleep latency measured during the multiple sleep latency test and during overnight polysomnography. In patients with obstructive sleep apnoea syndrome, ESS scores significantly correlate with the respiratory disturbance index and the minimum arterial oxygen saturation recorded overnight. ESS scores of simple snorers did not differ from controls [18].

2.6. Statistics

Continuous variables were expressed as mean and standard deviation (SD). The Shapiro-Wilk test was used to check the normality distribution of continuous variables. Categorical variables were expressed as number (N) and percentage (%). Univariate and multivariate regression models were used to examine the association between cognitive function and cardiovascular evaluation variables. MoCA total and sub-scores, Free and Cued Selective Reminding Test sub-scores and Stroop Color-Word Test sub-scores were used as continuous outcomes. CAIDE Risk, ESC SCORE, and Log-transformed HRV measures were used as predictors. For each unit increase in Log-HRV, the β coefficient corresponded to the associated increase in cognitive function score. To assess whether the significant associations in the univariate analysis were influenced by several covariates, multivariate analysis, was performed using two different model: Model 1 including age, gender and education; Model 2 including age, gender, education and selected HRV parameters (SDANN, SDNNIDX, RMSSD, VLF, LF, HF, LF/HF, ULF, DFA, Entropy). Statistical significance was set at $p < 0.05$. All statistics were performed with SPSS version 24 for IBM (Armonk, NY).

3. Results

3.1. Baseline characteristics

The mean age of subjects was 64.9 years (range 51-77) and 60% were females; the mean education was 11.7 years and the average body mass index (BMI) was 26.6 kg/m^2. Overall, 38% of the subjects had family history of CVD, 46% hypertension, 78% dyslipidemia, 18% diabetes and 30% obesity. Twenty-two percent of the subjects were current smokers, 46% former smokers and 49% had a sedentary lifestyle (Table 1). Overall, cardiovascular risk estimation, using ESC SCORE, was found to be moderate-or-high with a mean value of 6% (Table 1). The mean number of reported hours of nocturnal sleep was 6.5 hours (range 5-8 hours). Eleven subjects (22%) reported less than 6 hours of sleep. Regarding medication which can affect sleep, 4 patients were taking benzodiazepines (2 on a regular basis and 2 as-needed) and one patient was taking trazodone. No subjects had previous history of obstructive sleep apnoea. The mean value of the ESS scale was 4.8 (range 0-14) (Table 1). Two subjects reported an ESS score above the normal range (0-9), 13 and 14, respectively. One of them showed severe nocturnal oxygen desaturation index (86) and was diagnosed with obstructive sleep apnoea. The whole cardiovascular parameters including ABPM and exercise stress testing data are shown in Tables 2. Mean nocturnal BP dipping, defined as percent nocturnal BP decline relative to daytime BP, was 5.8% and 9.0% for systolic and diastolic blood pressure, respectively (Table 2). Since a 10-20% decrease in nocturnal BP relative to daytime BP is generally considered normal [18], these data confirm the increased cardiovascular risk of our patients.

Table 1
Descriptive statistics of main demographic characteristics and cardiovascular risk factors and cardiovascular risk score of the subjects. ESC SCORE: European Society of Cardiology Systematic Coronary Risk Evaluation

Demographic, Cardiovascular and Sleep variables	
Demographic data	
• Age (years, mean and SD)	64.9 (6.7)
• Male sex (n and %)	20 (40%)
• Female sex (n and %)	30 (60%)
• Body mass index (kg/m2, mean and SD)	26.6 (3.9)
• Education (years, mean and SD)	11.7 (3.8)
Cardiovascular risk factors	
• Family history of cardiovascular disease (n and %)	19 (38%)
• Hypertension (n and %)	23 (46%)
• Dyslipidemia (n and %)	39 (78%)
• Total blood cholesterol (mg/dl, mean and SD)	204.7 (48.2)
• Blood HDL (mg/dl, mean and SD)	58.5 (13.9)
• Blood LDL (mg/dl, mean and SD)	120.8 (42.6)
• Blood triglycerides (mg/dl, mean and SD)	130.9 (50.8)
• Diabetes (n and %)	9 (18%)
• Obesity (n and %)	15 (30%)
• Sedentary lifestyle (n and %)	24 (49%)
• Physical activity (n and %)	20 (40%)
• Current smoker (n and %)	11 (22%)
• Former smoker (n and %)	20 (47%)
Cardiovascular risk score	
• ESC SCORE (% and SD)	6 (5)
Sleep variables	
• Sleeping hours per night (h)	6.5 (1.0)
• Epworth Sleepiness Scale score (mean and SD)	4.8 (3.0)
• History of sleep apnoea (n and %)	0 (0%)
• Subjects with oxygen desaturation index ≥ 14 (n and %)	1 (2%)

Table 2
Descriptive statistics of ambulatory blood pressure monitoring (ABPM) and exercise testing variables.

24-hour ABPM and Exercise testing variables	
24-hour ABPM	
• Mean Systolic PB (mmHg, mean and SD)	127.6 (12.1)
• Mean Diastolic BP (mmHg, mean and SD)	75.9 (6.3)
• Daytime Systolic BP (mmHg, mean and SD)	130 (12.6)
• Daytime Diastolic BP (mmHg, mean and SD)	78.1 (6.6)
• Night-time Systolic BP (mmHg, mean and SD)	120.2 (13.9)
• Night-time Diastolic BP (mmHg, mean and SD)	69.1 (7.8)
• Systolic BP variability (mmHg, mean and SD)	14.1 (3.5)
• Coefficient of BP variability (%, mean and SD)	11 (2.7)
• Systolic BP Peak (mmHg, mean and SD)	165.4 (17.0)
• Mourning surge (mmHg, mean and SD)	27 (13.6)
• Systolic BP Night-time Dipping (%, mean and SD)	5.8 (6.0)
• Diastolic BP Night-time Dipping (%, mean and SD)	9.0 (6.6)
Exercise testing	
• Chronotropic competence (%, mean and SD)	80.3 (10)
• Systolic BP peak (mmHg, mean and SD)	184.9 (22.2)
• Diastolic BP peak (mmHg, mean and SD)	90.7 (8.7)
• Heart Rate Recovery (bpm, mean and SD)	25.4 (21.2)

Table 3
Mean and SD values of cognitive, behavioural and sleep variables. CAIDE: Cardiovascular Risk Factors, Aging, and Incidence of Dementia

Cognitive and behavioural variables	
Montreal Cognitive Assessment (raw scores)	
• Total score (range 0-30)	24.3 (2.8)
• Visuospatial abilities (range 0-4)	2.7 (1.2)
• Executive functions (range 0-4)	2.8 (1.2)
• Language (range 0-6)	5.2 (0.8)
• Orientation (range 0-6)	5.9 (0.3)
• Attention (range 0-6)	5.5 (0.6)
• Memory (range 0-5)	2.6 (1.5)
Free and Cued Selective Reminding Test (raw scores)	
• Immediate Free Recall (range 0-36)	31.04 (3)
• Immediate Total Recall (range 0-36)	35.7 (0.6)
• Delayed Free Recall (range 0-12)	10.9 (0.9)
• Delayed Total Recall (range 0-12)	12 (0.0)
• Index of Sensitivity to Cueing (range 0-1)	0.9 (0.1)
Stroop Color-Word Test (raw scores)	
• Time Interference	25.2 (11.6)
• Errors Interference	0.3 (1.0)
CAIDE risk (range 1.0-16.4%)	2.4 (1.9)
Perceived stress scale (range 0-40)	16.1 (6.6)
Generalized anxiety disorder 7 scale (range 0-21)	5.4 (4.5)
Patient Health Questionnaire-9 depression scale (0-27)	4.4 (4.6)

3.2. Neuropsychological evaluation

Main descriptive statistics of the neuropsychological test are shown in Table 3. The mean MoCA total score was 24.3 (range 18-29). None of the subjects obtained pathological scores on MoCA according to the Italian normative values [13]. Based on Stroop and FCSRT scores, 4 subjects were diagnosed with MCI (3 amnestic and one non-amnestic) according to the Petersen criteria [19]. Tables 3 reports main descriptive statistics of cognitive tests and standardized questionnaires on perceived stress, generalized anxiety disorder, depression.

3.3. Relationship between dementia risk and cognitive variables

The mean CAIDE risk score was 2.9% (n = 49). The CAIDE risk score was found to be inversely associated with both the MoCA test score (r = -0.412, p = 0.003, Figure 1) and the Immediate Free Recall score of the FCSRT (r = -0.311, p = 0.032). The CAIDE risk score was also found to be directly correlated with the Time (r = 0.399, p = 0.005) and Errors (r = 0.283, p = 0.044) Interference subgroups of the Stroop Color-Word test.

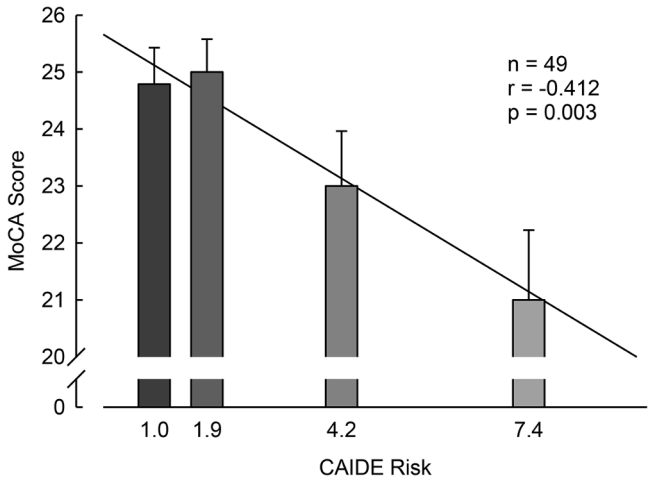

Figure 1. Relationship between CAIDE (Cardiovascular Risk Factors, Aging, and Incidence of Dementia) risk score and MoCA (Montreal Cognitive Assessment) score.

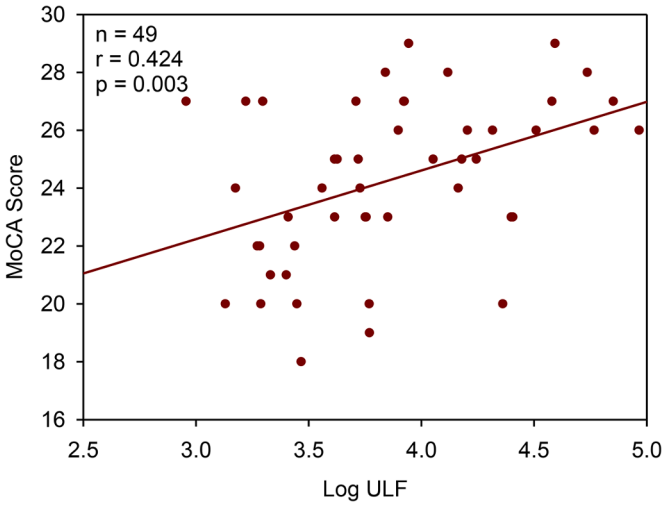

Figure 2. Relationship between 24-hour ultra-low frequency (ULF) band power of heart rate variability and MoCA (Montreal Cognitive Assessment) score.

3.4. Relationship between autonomic, cardiovascular and cognitive evaluation

Considering the association between neuropsychological and autonomic evaluations, several HRV parameters derived from the 24-hour ECG Holter monitoring were analysed. The patient diagnosed with sleep apnoea was excluded from statistical analysis. The most significant unadjusted association was found between the ULF band power of HRV and MoCA (r = 0.424, p = 0.003, Figure 2). The association between MoCA and ULF band power persisted after multiple adjustments for HRV variables (Model 1: time domain, frequency domain, complexity analysis, β= 0.505, p = 0.021) and main demographic characteristics (Model 2: time domain, frequency domain, complexity analysis, age, gender, education, β = 0.464, p = 0.034). ULF band power was also significantly associated with executive functions (r = 0.307, p = 0.034), language (r = 0.311, p = 0.031), and memory (r = 0.332, p = 0.021) scores of the MoCA test. Moreover, ULF band power was significantly correlated with both IFR (r = 0.329, p = 0.022) ITR (r = 0.315, p = 0.029) scores of the FCSRT. Interestingly, ULF band power was significantly associated with vagal markers of HRV (SDNNINDEX and VLF). Duration of sleep and ESS score were not significantly associated with either 24-hour ULF band power nor nocturnal ULF band power (r = -0.260, p = 0.157; r = 0. 257,

p = 0.125, respectively). Finally, a significant association was found between the ESC SCORE and ULF band power (r = -0.470, p = 0.001).

Table S1 shows descriptive statistics of single ventricular premature complexes (VPCs), supraventricular extrasystoles (SVEs), and heart rate turbulence (HRT) onset (TO) and slope (TS). Table S2 shows correlation coefficients between ULF and all HRV parameters. Table S3 details correlation coefficients (r) between MoCA score and all HRV parameters.

4. Discussion

We investigated the association between autonomic dysfunction and cognitive performances in subjects with CVD risk through a comprehensive neuropsychological investigation (MoCA test, FCSRT, Stroop Color-Word test), an integrated cardiovascular risk assessment and complete 24-hour HRV analysis. The results showed that ULF band power of HRV was significantly associated with MoCA test and with cardiovascular risk scores. This association may indicate that autonomic dysregulation plays a role in developing cardiovascular risk and cognitive decline. Whether a direct relation exists between cardiac autonomic function and cognitive performance has received increased attention and yet remains not completely understood. Previous cross-sectional studies have generally reported positive associations between indices of HRV and cognitive functions, as demonstrated by higher HRV linked to better cognitive performance and a lower HRV associated with cognitive impairment [20]. This association was also confirmed in the Multi-Ethnic Study of Atherosclerosis (MESA), a large and ongoing prospective, population-based cohort study [21]. However, it must be pointed out that most of these studies used short-term ECG recordings to assess HRV, which do not allow the evaluation of more sensitive frequency domain measures of HRV. In the present study, we used a 24-hour ambulatory ECG recording that allowed the opportunity to better capture autonomic function in real-world settings. Among the variables derived from the 24 hours HRV analysis, the ULF band power was found to be strongly associated with both global cognitive performances (assessed with the MoCA test) and specific cognitive domains, such as executive functions, language and memory. ULF power was also related to episodic memory performance as assessed by the FCSRT, a test specifically recommended by the International Working Group for the diagnosis of AD [22] and useful for identifying individuals with cognitive impairment and AD pathology [23]. Our results are in agreement with those obtained by Shah and colleagues [24] who found that VLF and ULF of the 24-hour HRV analysis were associated with verbal memory.

HRV arises from the complex interplay of sympathetic and parasympathetic autonomic regulation of heart rate. The $\leq$ 0.003 Hz ULF derives from the frequency domain measurements and requires a recording period of at least 24 hours [25]; physiological bases of ULF are still unclear, but probably very slow acting biological processes, such as circadian rhythms, may be involved; low frequency bands may also vary with physical activity [26] and temperature regulation. In the present study we confirmed the association between ULF and vagal markers, in particular SDNN time-domain index [27] and VLF, suggesting that the vagal tone could be a contributor in the genesis of ULF. Interestingly, ULF band power has been associated with mortality in patients with myocardial infarction [27].

Several mechanisms may link HRV to cognitive performances. The ANS regulates important cardiovascular functions, including the maintenance of blood pressure and cerebral perfusion [28]. Considering that reduced HRV is associated with poor baroreflex sensitivity, increased blood pressure variability and orthostatic hypotension [29], it is plausible that reduced HRV may impair cognitive functions through mechanisms related to blood pressure dysregulation. Several studies have shown that hypoperfusion and hypoxia caused by atherosclerosis of cerebral vessels may enhance the production of Aβ while flow-limiting large-artery stenosis, arterial stiffening and microvascular dysfunction could contribute to AD pathophysiology by impairing Aβ clearance [30]. In the early stages of AD, dysregulation of the autonomic nervous system can contribute to the maintenance of chronic hypoperfusion, also affecting brain self-regulation and neurovascular unit functioning [31]. On the other hand, neurodegenerative changes during dementia may also influence autonomic functions and HRV, via derangement of vegetative networks in the insular cortex and brainstem [32]. Disruption to central autonomic nuclei occurring in preclinical AD pathology, which in fact exhibits a hierarchical progression that includes the insular cortex and brainstem, is therefore a possible explanation for reduced cardiac autonomic function in non-demented elderly individuals, suggesting that autonomic dysfunction may be an additional manifestation of early dementia-related neurodegenerative changes [8].

Mid-life risk factors for cardiovascular disease such as hypertension and type 2 diabetes mellitus, are known to be important precipitants of cognitive decline [33] and are associated with reduced HRV [34]. Substantial evidence suggests that reduced HRV may precede these risk factors [5] establishing clinical utility for low HRV as a potential non-invasive preclinical marker for cardiovascular disease and cognitive decline. Interestingly, a recent longitudinal study involving 2147 older subjects free of dementia found an elevated resting heart rate associated with an increased risk for dementia and global cognitive decline, an association independent of cardiovascular risk factors and CVDs [35].

This study has several limitations. First, the study is cross-sectional and involved a low number of participants. Secondly, brain magnetic resonance imaging (MRI) was not performed so we were unable to explore any potential relationship between possible signs of cerebrovascular damage and ANS abnormalities. Furthermore, assessment of AD biomarkers was not carried out to better characterize the nature of MCI in 4 participants. Finally, nocturnal sleep was not measured by polysomnography; therefore, sleep disturbances which may affect ANS function and cognitive outcomes could not be objectively excluded.

Future longitudinal studies in cognitively healthy subjects, in subjects with mild cognitive impairment and in subjects with AD will confirm the promising associations observed in the present study between heart rate parameters and cognitive performances. Since emerging evidence has shown that circadian function may play an important role in the progression of AD [36], the possible link between circadian disorders and HRV abnormalities in subjects with impaired cognitive function and cardiovascular risk needs also to be evaluated.

5. Conclusion

The results of our study revealed that ULF band power of HRV is associated with cognitive performance in middle-aged and elderly subjects with cardiovascular risk. This association may indicate that ANS dysregulation plays a role in the development of cardiovascular risk and cognitive decline and that autonomic dysfunction may be an early indicator of cognitive impairment in individuals at high cardiovascular risk. The identification of early correlates of cognitive performances offers the opportunity to improve targeted strategies to prevent or attenuate cognitive decline during the middle and late age period.

Declaration of Competing Interest

None of the authors have any conflicts of interest to declare.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cccb.2022.100136.

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