

Cognitive function is associated with impaired heart rate variability in ageing adults: the Irish longitudinal study on ageing wave one results

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Abstract

Objective To examine the independent association between heart rate variability (HRV) and cognitive performance, in a nationally representative population study of older adults.

Methods Cross-sectional analysis of wave 1 data from the Irish longitudinal study on ageing (TILDA) was performed. A subset of 4,763 participants who underwent ECG recording during resting and paced breathing periods were used for the analysis. HRV indices were divided into quintiles for comparison of values and cognitive performance was defined using the Montreal cognitive assessment (MOCA) score. Multivariate linear regression was used to model the association between cognition and different quintiles of each HRV index, after adjustment for covariates.

Results The mean age was 61.7 ± 8.3 years and 2,618 (55 %) were female. Lower quintiles of SDNN ($P = 0.01$ -paced), LF ($P = 0.001$ -paced), and LF:HF ratio ($P = 0.049$ -paced) were significantly associated with

lower MOCA scores (during both recording periods), independent of confounders. Sub-domains of MOCA responsible for the relationship were predominantly memory recall and language.

Interpretation Reduced HRV is significantly associated with lower cognitive performance at a population level in people aged 50 and older. This further strengthens the relationship between autonomic dysfunction and cognitive disorders.

Keywords Autonomic function · Heart rate variability · Cognitive impairment · Paced breathing · Population studies

Introduction

Ageing is associated with a reduction in cognitive performance. The average incidence rate of mild cognitive impairment (MCI) is 12–15 per 1,000 person years in persons aged 65 and older [2]. The conversion rate from MCI to dementia is 14 % annually [30]. Predictors of conversion from MCI to dementia currently include cerebrospinal fluid biomarkers, neuropsychological tests and structural magnetic resonance imaging (MRI) morphometry [8, 11, 42].

The ageing demographic shift will likely increase the global burden of cognitive disorders in the coming years. In light of this, there is an urgent need for interventional strategies targeting modifiable determinants of MCI, dementia and conversion from MCI to dementia. Factors associated with cognitive decline include age, lower education, lifestyle (lower physical activity, smoking and high alcohol consumption), genetic predisposition, metabolic dysregulation (obesity, impaired glucose tolerance,

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diabetes), cardiovascular disease (hypertension, atherosclerosis, stroke) and inflammatory markers, many of which are evidently modifiable [13, 16, 36, 39, 45].

Many of these factors are also precursors to reduced heart rate variability (HRV), including smoking, high alcohol intake, obesity, diabetes, hypertension, and inflammation, [5, 12, 31]. This suggests that HRV and cognition have common risk factors. HRV is a marker of cardiac autonomic function, and involves the interaction of activity from the sympathetic (SNS) and parasympathetic nervous systems (PNS). Emerging evidence suggests an association between cognitive impairment and autonomic dysfunction. This relationship may be bidirectional with autonomic dysfunction causing systemic hypotension that leads to cognitive impairment [27], while neurodegenerative processes influence autonomic pathways, causing autonomic dysfunction [19].

Studies investigating the association between HRV and cognitive function have to date reported conflicting results [3, 15], however, none have been conducted in large population based samples. The aim of this study was to investigate the independent association between HRV and global cognitive function, in a nationally representative sample of older adults. HRV acquired during two breathing protocols was applied, in order to limit respiratory bias. The role of sub-domains assessed within global cognition on the association was also examined.

Methods

Study design

Data from the first wave of The Irish Longitudinal Study on Ageing (TILDA) were analyzed. TILDA is a large prospective cohort study of ageing, comprised of community dwelling people aged 50 and over resident in the Republic of Ireland. A nationally representative sample was selected using the regularly updated RANSAM sampling technique [43]. Further detail of the study design is published elsewhere [14]. Data collected within TILDA are composed of three parts: (1) computer-assisted personal interviewing (CAPI), (2) self-completion questionnaire, and (3) a physical health assessment. Participants unwilling to undergo centre-based health assessment were offered an in-home health assessment, where a sub-group of measures was recorded. Electrocardiograms were conducted in the health centre assessment but not the home assessment. Ethical approval was obtained from Trinity College Dublin Ethics committee and all participants provided signed informed consent prior to the study. All experimental procedures adhered to the Declaration of Helsinki. This study uses data from the

first wave of TILDA, collected between July 2009 and June 2011.

Cognitive assessment

Cognitive function was assessed in the TILDA study using a battery of cognitive tests [14]. This included the Montreal cognitive assessment (MOCA) [21], which was administered during the health assessment and used in the present study. MOCA is a measure of global cognitive function (score range 0–30), comprised of the sub-domains (1) memory (2) visuospatial function, (3) executive function, (4) sustained attention, (5) language, and (6) orientation. It was chosen for analysis over the mini mental state examination (MMSE) due to its higher predictive value for MCI [21] and less ceiling effect in a population-representative sample.

Measurement of RR interval variability

Two 5 min supine resting surface 3-lead electrocardiograms (ECG) were recorded, during which subjects were instructed to breath spontaneously for the first period, and to control their breathing (paced) during the second period according to a pre-recorded set of auditory instructions [set at a rate of 12 cycles min^{-1} (0.2 Hz)]. This protocol controlled experimentally for the effect of respiratory rate on spectral HRV indices. Recordings were obtained in a comfortably lit, quiet room at ambient temperature (21–23 °C) using digital recorders (Medilog Darwin[®], Oxford Instruments Medical Ltd, UK).

The ECG was acquired and subsequently band-pass filtered (0.01–1,000 Hz). A proprietary algorithm was used to detect the R peak of each heart beat recorded on the ECG signal [24]. Its accuracy is described elsewhere [24]. Supra-ventricular ectopic beats and noise were excluded from the signal using linear interpolation. All recordings were screened for atrial fibrillation (AF) using criteria from the European society of cardiology (ESC) [4], and those identified with AF were subsequently excluded from analysis. Other arrhythmias were detected and excluded by the Darwin software system. Heart rate was recorded and controlled for in study analysis.

300-second epochs of RR interval data were analyzed. Statistical methods were used to derive the time domain index; the standard deviation of NN intervals (SDNN). Frequency domain (FD) features were calculated from spectral estimates derived using an autoregressive (Burg method) algorithm, with assignment of 256 discrete frequency bins. FD features were derived by integrating the power spectrum across bands using the fast Fourier transform (FFT) as recommended by the task force for HRV measurement [9]. *Low frequency power* (LF 0.04–0.15 Hz,

ms^2) and *high frequency power* (HF 0.15–0.4 Hz, ms^2) were calculated and expressed as a ratio LF:HF also.

A number of recordings ($n = 424$) were unsuitable for analysis of paced breathing data due to technical error or protocol non-compliance. These errors occurred completely at random and so were not thought to introduce a bias. Sensitivity analysis was performed to confirm this and restricted to cases with both spontaneous and paced breathing data only. Our results were not found to be sensitive to this potential bias. All subjects were therefore included in analysis of spontaneous breathing HRV data.

Measurement of covariates

Other measures acquired included age, gender, highest level of educational attainment (primary, secondary or tertiary), smoking status (never smoked, former or current), alcohol consumption (units weekly), body mass index (BMI) (kg/m^2), total blood cholesterol (mmol/L), and height (cm). Physical activity was assessed using the International Physical Activity Questionnaire (IPAQ) short form, which classifies low, medium and high levels of activity. Systolic and diastolic blood pressures (SBP and DBP, respectively) were recorded during seated rest using a digital oscillometric blood pressure (BP) monitor (OMRONTM).

The Centre for Epidemiological Studies Depression (CES-D) scale was used with a cut-off score of 16 or above, to define subjects as depressed [28]. The Hospital Anxiety and Depression (HADS) scale was used to define subjects as having anxiety, using a cut-off criteria score of 11 or above [46]. This was obtained through a self-completion questionnaire. Self-reported cardiovascular diseases were documented and included: history of angina, myocardial infarction (MI), heart failure, diabetes mellitus (DM), stroke, transient ischaemic attack (TIA), and cardiac arrhythmias.

Medication use was recorded during the home interview (CAPI) and confirmed by cross-checking the medication labels. The anatomical therapeutic classification (ATC) codes were subsequently recorded for categorisation [44]. Medication categories adjusted for analysis were alpha-blockers ('CO2CA', 'CO2LE'), beta-blockers ('C07*'), calcium channel blockers ('CO8*'), cardiac glycosides ('C01A*'), midodrine ('C01CA'), anticholinergic agents ('N04A*'), and anticholinesterase agents ('N06DA*', 'N07AA*').

Statistical analysis

Statistical analysis was performed using Stata version 12 (StataCorp, College Station, TX, USA). Distribution of continuous variables was assessed using Q–Q plots and

histograms. Normally distributed variables were described as means and standard deviations (SD), and were compared across groups using independent t tests. Non-normally distributed variables were described as medians and percentiles and compared using Mann–Whitney tests, and categorical variables were compared using Chi squared tests. HRV indices were divided into quintiles for analysis, to investigate the non-linear association between HRV and cognition. Quintiles for time and frequency domain indices were determined equally; by splitting the sample with non-missing data into fifths according to their index value. Multivariate linear regression was used to assess the relationship between HRV indices and MOCA score (continuous scale). Indices measured during spontaneous and paced breathing periods were compared. Significance was taken as $P < 0.05$. For each quintile increase in HRV, the standardized regression coefficient (β) corresponded to the associated change in MOCA cognitive score. A core model (A) was first tested, adjusting for age, gender and education level, and a subsequent model (B) was tested, adjusting for these three variables, along with all remaining covariates described above, namely behavioral health (smoking, alcohol and physical activity), clinical profile (BMI, cholesterol, height, seated blood pressure), mental health (CES-D and HADS-A scores), cardiovascular disease (angina, MI, heart failure, DM, stroke, TIA, arrhythmias) and medications listed above. Adjusted predictive MOCA scores across quintiles of HRV indices were fitted.

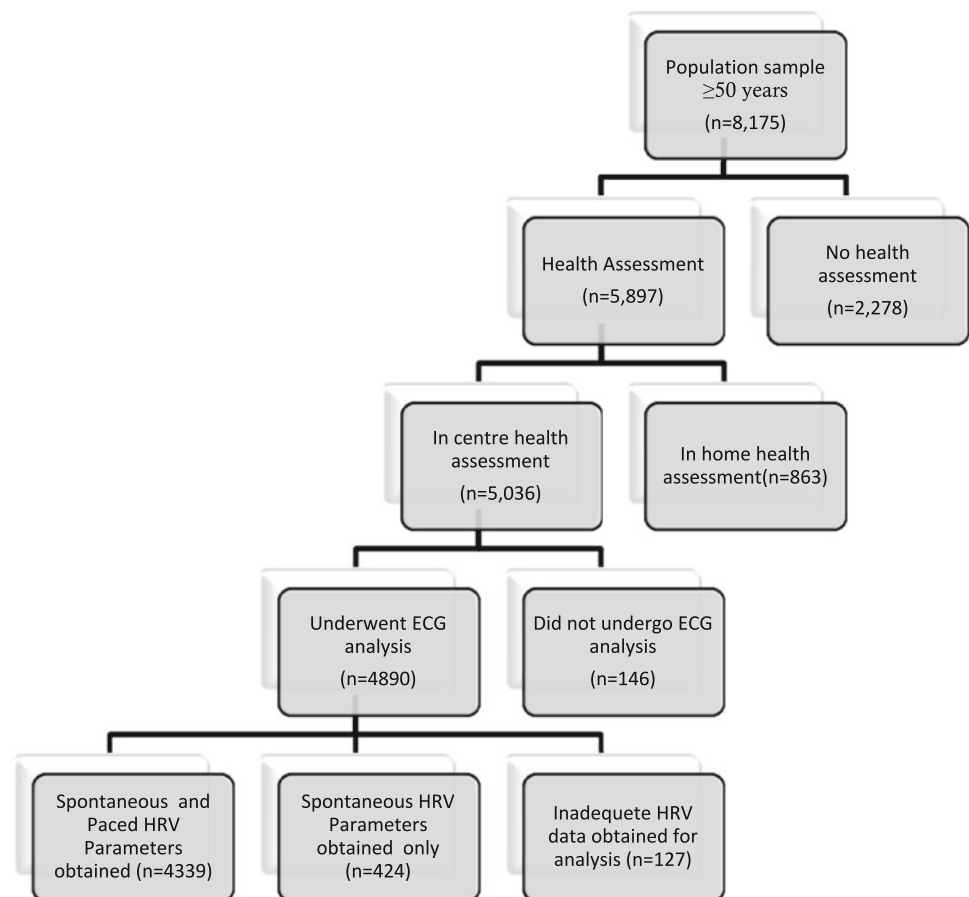
Results

A total of 8,175 participants aged 50 years and older were recruited to the TILDA study [14]. Of these 5,036 agreed to undergo an in-centre health assessment, 4,763 of whom had technically adequate data for HRV analysis (see Fig. 1). A subset of 424 subjects had spontaneous breathing HRV data only.

The mean age was 61.7 and 2,618 (55 %) were female. HRV patterns of the sample for both spontaneous and paced breathing periods are outlined in Table 1, together with subject characteristics. Men had higher levels of alcohol consumption, former smoking, physical activity, BMI, SBP, DBP, and prevalence of cardiovascular disease. Women had higher levels of cholesterol and prevalence of anxiety and depression. Minimum, mean and maximum HR values were greater during paced breathing. HRV indices LF and HF were greater during spontaneous breathing, while SDNN and LF:HF ratio were greater during paced breathing period.

The association between HRV (measured as quintiles) and MOCA score is summarized in Table 2, according to spontaneous or paced breathing. In Model A (adjusted for

Fig. 1 Flowchart of TILDA study participants eligible for ECG recording in TILDA



age, gender, and education), lower (quintiles of) LF:HF ratio during spontaneous breathing, lower HF and higher mean HR during paced breathing, and lower SDNN and LF during both periods were significantly associated with a lower MOCA score.

Following further adjustment for other confounders of cardiovascular and cognitive health (Model B), lower HRV remained significantly associated with lower MOCA score across several indices. Lower (quintiles of) SDNN, LF and LF:HF ratio during both periods were associated with a lower MOCA score. The association between higher mean HR and lower MOCA score remained significant in Model B, during paced breathing only.

There was a dose response in the multivariate adjusted effect size between HRV and MOCA score, for the indices LF and LF:HF ratio. MOCA scores were fitted across quintiles of paced LF, with adjustment for covariates, to illustrate this dose response (see Fig. 2). Subjects in the lowest LF quintile group had an adjusted estimated MOCA score of 25 (95 % CI; 24.8–25.3), whereas subjects in the highest LF quintile group scored 25.7 (95 % CI; 25.5–26).

Figure 3 illustrates the HRV changes associated with poor cognitive performance. SDNN² is shown instead of SDNN as it is indicative of total power and yielded

identical significance to SDNN in analysis. Regression analysis using a dichotomised MOCA score, according to the criteria for cognitive impairment (scores below 24) [7, 17], yielded broadly similar results (not shown). Further sub-analysis stratifying by gender yielded similar results between men and women.

Analysis of the sub-domains of MOCA score was performed to determine the component responsible for the effect of HRV on cognitive function. Confounders included in Model B above were adjusted for here (see Table 3). Domains of memory recall and language predominantly accounted for the association between HRV and MOCA score.

Discussion

HRV was independently associated with poor global cognitive performance in a large representative population sample of community dwelling, non-demented persons over 50 years. Furthermore, there was a graded association between degrees of impaired cognitive performance and spectral indices of LF and LF:HF ratio, which was independent of respiration, indicating impaired baroreflex

Table 1 Characteristics of the study population

Characteristics	Men (<i>n</i> = 2145)	Women (<i>n</i> = 2618)	<i>P</i> value
Age, mean ± SD	61.8 ± 8.3	61.5 ± 8.3	0.29
Education, % (<i>n</i>)			
Primary	23.4 (502)	19.6 (512)	
Secondary	41.5 (890)	42.2 (1,105)	0.0001
Tertiary	35.1 (753)	38.2 (999)	0.0001
MOCA score ^a	26 (23, 28)	26 (24, 28)	0.11
Smoking status, % (<i>n</i>)			
Never	38.3 (821)	52.5 (1,374)	
Former	46.5 (998)	32.4 (849)	0.0001
Current	15.2 (326)	15.1 (395)	0.0001
Standard drinks consumed weekly ^a	4.5 (0.48, 12)	1.5 (0, 6)	0.0001
Level of physical activity (IPAQ), % (<i>n</i>)			
Low	23.1 (490)	31 (804)	
Medium	32.6 (694)	39.5 (1,026)	0.0001
High	44.3 (942)	29.5 (770)	0.0001
Body mass index (kg/m ²), mean ± SD	29.1 ± 4.4	28 ± 5.2	<0.0001
Total cholesterol (mmol/L), mean ± SD	4.9 ± 1.1	5.4 ± 1	<0.0001
Systolic blood pressure (mmHg), mean ± SD	139 ± 18.3	131 ± 19.6	<0.0001
Diastolic blood pressure (mmHg), mean ± SD	83.7 ± 11	81.2 ± 11.1	<0.0001
Mental health, % (<i>n</i>)			
Anxiety (HADS-A ≥ 11)	15.3 (328)	19.1 (500)	<0.0001
Depression (CES-D ≥ 16)	7 (149)	12 (312)	<0.0001
Disease prevalence, % (<i>n</i>)			
Angina	6 (129)	2.8 (72)	<0.0001
Myocardial infarction	6.6 (142)	1.7 (44)	<0.0001
Heart failure	1.3 (27)	0.3 (8)	<0.0001
Diabetes	8.6 (185)	4.4 (115)	<0.0001
Stroke/TIA	2.8 (61)	2.5 (65)	0.44
Cardiac arrhythmia	6.2 (133)	5.5 (145)	0.33
Heart rate variability	(<i>n</i> = 4,339)		<i>P</i> value
	Spontaneous breathing period	Paced breathing period	
Minimum heart rate, mean ± SD	57.6 ± 9.6	58.1 ± 9.6	<0.0001
Mean heart rate, mean ± SD	64 ± 10.1	66.4 ± 10.6	<0.0001
Maximum heart rate, mean ± SD	75 ± 16.3	77.9 ± 15.2	<0.0001
SDNN (ms) ^a	34.6 (25.5, 47.3)	41.1 (30, 55.7)	<0.0001
LF (ms ²) ^a	164.4 (104.1, 288.8)	148.3 (74.4, 298.8)	<0.0001
HF (ms ²) ^a	215.2 (140.2, 330.8)	160.9 (72.2, 354.6)	<0.0001
LF:HF ratio ^a	0.73 (0.57, 1.13)	0.94 (0.52, 1.66)	<0.0001

SD standard deviation

^a Summarized as median (25th percentile, 75th percentile), because of skewed distribution

function and sympathovagal homeostasis in early cognitive ageing. This is the first such study in a population sample of both men and women detailed with information on co-medications and co-morbidities. Memory recall and language were most strongly associated with lower HRV

values, suggesting implication of a common neuro-anatomical pathway, possibly the fornix, which is the predominant outflow tract of the hippocampus and functions in autonomic control [6]. The direction of causality will be explored in futures waves of this longitudinal study.

Table 2 Adjusted regression coefficients and 95 % confidence intervals of cognitive performance comparing quintiles of HRV indices during spontaneous and paced breathing

HRV variable and model number	Range of values within each quintile	Quintile	MCA score					
			Spontaneous breathing (<i>n</i> = 4763)			Paced breathing (<i>n</i> = 4339)		
			β	95 % CI	<i>P</i>	β	95 % CI	<i>P</i>
Mean HR	40.78–55.52	Q ₁	–	–	–	–	–	–
Model A	55.65–60.69	Q ₂	–0.017	–0.28, 0.25	0.06	–0.274	–0.55, 0.01	<0.001
	60.78–65.56	Q ₃	–0.129	–0.4, 0.14		–0.301	–0.58, –0.02	
	65.68–72.1	Q ₄	–0.182	–0.45, 0.09		–0.434	–0.72, –0.15	
	72.25–102.2	Q ₅	–0.363	–0.64, 0.09		–0.631	–0.91, –0.35	
	Model B	42.04–57.6	Q ₁	–	–	–	–	–
Model B	57.75–63.1	Q ₂	–0.067	–35, 0.22	0.3	–0.362	–0.66, –0.06	<0.001
	63.18–68.17	Q ₃	–0.119	–0.41, –0.17		–0.316	–0.62, –0.01	
	68.28–74.82	Q ₄	–0.220	–0.52, 0.08		–0.582	–0.89, –0.27	
	74.96–104.3	Q ₅	–0.306	–0.61, –0.01		–0.646	–0.97, –0.34	
	SDNN	6.5–24	Q ₁	–	–	–	–	–
Model A	24.2–31.2	Q ₂	0.237	–0.03, 0.5	<0.001	0.525	0.25, 0.8	<0.001
	31.5–40	Q ₃	0.455	0.19, 0.72		0.654	0.37, 0.93	
	40.2–52.9	Q ₄	0.485	0.22, 0.76		0.439	0.16, 0.72	
	53.4–157.7	Q ₅	0.728	0.45, 1		0.574	0.28, 0.87	
	Model B	8.2–28.1	Q ₁	–	–	–	–	–
Model B	28.3–37.3	Q ₂	0.019	–0.27, 0.31	0.001	0.465	0.16, 0.77	0.01
	37.5–47.3	Q ₃	0.334	0.04, 0.63		0.506	0.19, 0.82	
	47.5–62.1	Q ₄	0.283	–0.03, 0.56		0.276	–0.05, 0.6	
	62.5–162.6	Q ₅	0.599	0.27, 0.93		0.435	0.08, 0.79	
	LF	10.7–94.5	Q ₁	–	–	–	–	–
Model A	95.4–141	Q ₂	0.238	–0.03, 0.5	<0.001	0.430	0.15, 0.71	<0.001
	142–208.7	Q ₃	0.467	0.2, 0.73		0.687	0.41, 0.97	
	210.9–363.7	Q ₄	0.455	0.19, 0.72		0.575	0.92, 0.86	
	369.2–4712.2	Q ₅	0.861	0.58, 1.14		0.78	0.49, 1.1	
	Model B	2.1–64.5	Q ₁	–	–	–	–	–
Model B	65.1–119.8	Q ₂	0.197	–0.1, 0.49	<0.001	0.324	0.02, 0.63	0.001
	121–205.4	Q ₃	0.411	0.11, 0.71		0.507	0.2, 0.82	
	207.5–381.6	Q ₄	0.455	0.15, 0.76		0.470	0.15, 0.79	
	385.4–5013.2	Q ₅	0.846	0.52, 1.2		0.697	0.36, 1	
	HF	5.9–123.3	Q ₁	–	–	–	–	–
Model A	125–189.9	Q ₂	–0.001	–0.27, 0.26	0.2	0.351	0.08, 0.63	0.003
	191.3–260.1	Q ₃	0.045	–0.22, 0.31		0.402	0.13, 0.68	
	261.6–389.3	Q ₄	0.115	–0.15, 0.38		0.438	0.16, 0.72	
	392.1–3129.2	Q ₅	0.309	0.03, 0.59		0.554	0.26, 0.85	
	Model B	2.7–61.3	Q ₁	–	–	–	–	–
Model B	62.4–127.7	Q ₂	–0.095	–0.38, 0.19	0.6	0.067	–0.23, 0.37	0.7
	129–237.3	Q ₃	–0.007	–0.3, 0.28		0.106	–0.21, 0.42	
	240–473.6	Q ₄	0.023	–0.28, 0.33		0.151	–0.17, 0.48	
	486–4395.7	Q ₅	0.165	–0.2, 0.49		0.239	–0.1, 0.58	
	LF:HF	0.17–0.54	Q ₁	–	–	–	–	–
Ratio	0.54–0.66	Q ₂	0.171	–0.1, 0.44	<0.001	0.055	–0.23, 0.34	0.2
	0.67–0.84	Q ₃	0.212	–0.06, 0.48		0.159	–0.13, 0.44	
	0.84–1.44	Q ₄	0.454	0.18, 0.73		0.319	0.03, 0.61	
	1.49–11.58	Q ₅	0.566	0.3, 0.84		0.186	–0.1, 0.48	

Table 2 continued

HRV variable and model number	Range of values within each quintile	Quintile	MCA score					
			Spontaneous breathing (<i>n</i> = 4763)			Paced breathing (<i>n</i> = 4339)		
			β	95 % CI	<i>P</i>	β	95 % CI	<i>P</i>
Model B	0.07–0.45	Q ₁	–	–	–	–	–	–
	0.45–0.74	Q ₂	0.213	–0.07, 0.5	<0.001	0.035	–0.27, 0.34	0.049
	0.75–1.17	Q ₃	0.229	–0.06, 0.52		0.186	–0.12, 0.49	
	1.18–1.92	Q ₄	0.533	0.24, 0.83		0.314	0.01, 0.62	
	1.94–12.67	Q ₅	0.583	0.29, 0.87		0.404	0.09, 0.72	

Model A included age, gender and education

Model B included age (both linear and non-linear effects), gender, education, smoking status, alcohol consumption, exercise level, body mass index, total cholesterol level, height, systolic blood pressure, diastolic blood pressure, CES-D depression score, HADS-A anxiety score, angina, myocardial infarction, heart failure, diabetes mellitus, stroke/transient ischaemic attack, cardiac arrhythmias, mean heart rate, and the following medications: alpha-blockers, beta-blockers, calcium channel blockers, midodrine, anti-cholinergics, and anti-cholinesterases

Statistically significant relationships are in boldface

HR heart rate, SDNN standard deviation of NN intervals, LF low frequency, HF high frequency, β standardized regression coefficients

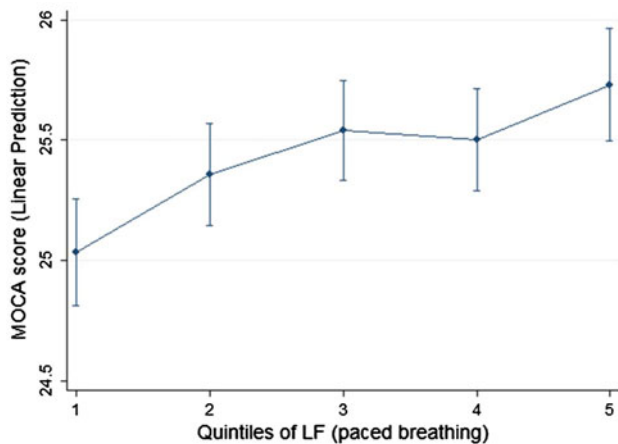


Fig. 2 Fitted MOCA scores across quintiles of Low Frequency HRV with 95 % CIs. Analysis adjusted for age (both linear and non-linear effects), gender, education, smoking status, alcohol consumption, exercise level, body mass index, total cholesterol level, height, systolic blood pressure, diastolic blood pressure, CES-D depression score, HADS-A anxiety score, angina, myocardial infarction, heart failure, diabetes mellitus, stroke/transient ischaemic attack, cardiac arrhythmias, mean heart rate, and the following medications: alpha-blockers, beta-blockers, calcium channel blockers, midodrine, anti-cholinergics, and anti-cholinesterases. MOCA montreal cognitive assessment, HRV heart rate variability, LF low frequency

The interpretation of LF as an index of sympathetic function is debated, with recent evidence suggesting LF to be more reflective of baroreflex function than sympathetic function [1, 20]. LF:HF ratio is considered a measure of sympathovagal balance, however, it may be more closely associated with cardiac autonomic modulation, a term more inclusive of complexities of the autonomic system [22]. In light of this, findings from this study suggest that reduced overall HRV (SDNN), baroreflex function (LF),

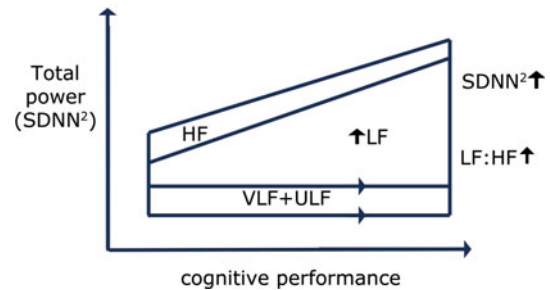


Fig. 3 Schema explaining the HRV changes independently associated with cognitive decline. SDNN standard deviation of NN intervals, ULF ultra low frequency, VLF very low frequency, LF low frequency, HF high frequency

and cardiac autonomic modulation (LF:HF) are all associated with poor cognitive performance in the community dwelling population. The methods and details applied in TILDA differ from previous studies which have examined this association. Kim et al. [15] reported an association between low LF and HF and poor global cognition in a convenience sample of 311 female participants. In the Whitehall study, which was a younger cohort of civil servants, no association was noted either cross-sectionally or longitudinally [3]. A possible explanation for this difference is social class.

The MOCA sub-domains of memory recall and language were most strongly associated with lower HRV values. This is in accordance with previous studies reporting significant associations between HRV and verbal memory recall [35]. The integrity of the fornix, which is the predominant outflow tract of the hippocampus, is predictive of memory performance and progression from MCI to AD [19]. This region is also implicated in autonomic

Table 3 Model B regression coefficients and standard errors of MOCA sub-domains, comparing 1st to 5th quintiles of HRV indices

MOCA subdomain	Breathing period	Mean HR		SDNN		LF		HF		LF:HF	
		Q ₅		Q ₅		Q ₅		Q ₅		Q ₅	
		β	SE	β	SE	β	SE	β	SE	β	SE
Memory recall	Spont ^a	-0.086	0.078	0.249	0.084	0.435	0.084	0.155	0.082	0.224	0.074
	Paced	-0.154	0.082	0.273	0.09	0.335	0.085	0.066	0.088	0.169	0.08
Visuospatial function	Spont ^a	-0.064	0.039	0.108	0.043	0.085	0.043	0.007	0.042	0.05	0.038
	Paced	-0.125	0.042	-0.02	0.046	0.073	0.043	0.062	0.045	0.013	0.041
Executive function	Spont ^a	-0.035	0.048	0.057	0.052	0.051	0.052	-0.027	0.051	0.097	0.046
	Paced	-0.139	0.051	0.026	0.056	0.041	0.053	0.058	0.055	0.031	0.05
Sustained attention	Spont ^a	-0.071	0.043	0.079	0.047	0.102	0.047	-0.022	0.046	0.122	0.041
	Paced	-0.097	0.046	0.058	0.05	0.103	0.048	0.069	0.049	0.033	0.045
Language	Spont ^a	-0.026	0.059	0.166	0.063	0.184	0.063	0.008	0.062	0.174	0.056
	Paced	-0.163	0.062	0.153	0.068	0.167	0.065	0.011	0.067	0.153	0.061
Orientation	Spont ^a	-0.019	0.015	0.02	0.016	0.012	0.016	-0.027	0.016	0.027	0.014
	Paced	-0.016	0.016	0.019	0.018	0.017	0.017	0.007	0.018	-0.005	0.016

Model included age (both linear and non-linear effects), gender, education, smoking status, alcohol consumption, exercise level, body mass index, total cholesterol level, height, systolic blood pressure, diastolic blood pressure, CES-D depression score, HADS-A anxiety score, angina, myocardial infarction, heart failure, diabetes mellitus, stroke/transient ischaemic attack, cardiac murmurs, cardiac arrhythmias, mean heart rate, and the following medications: alpha-blockers, beta-blockers, calcium channel blockers, midodrine, anti-cholinergics, and anti-cholinesterases. Paced $n = 4,339$

Statistically significant relationships are in boldface (ANOVA across all quintiles)

β standardized regression coefficients

^a Spont = spontaneous ($n = 4,863$)

control [6], suggesting that the fornix may form the anatomical location underlying the relationship between HRV and cognition.

The cholinergic anti-inflammatory pathway may also explain the association between reduced HRV and cognitive decline. Efferent vagal nerve activity inhibits pro-inflammatory cytokine release, protecting against systemic inflammation [25]. Reduced LF, HF, and SDNN along with increased HR are associated with higher levels of C-reactive protein (CRP) [18, 31, 38] and IL-6 [38], both of which are associated with cognitive decline, thus inflammation may mediate the relationship between reduced HRV and cognitive performance [34, 40, 41].

Another hypothesis implicates Noradrenaline (NAd). Up-regulation of NAd is proposed to optimize function of the key elements of cognitive reserve—namely educational level, IQ, mental and social engagement—which together lengthen the period between onset of pathological changes consistent with AD and symptoms of the disease (Robertson [30]). Reduction in NAd and acetylcholine (ACh) function (neurotransmitters of the SNS) results in lower HRV values.

Hypertension is an established predictor of cognitive decline [10], and is also associated with reduced HRV [37], indicating a possible role in the relationship of HRV and cognition. We controlled for resting blood pressure,

however, demonstrating that hypertension does not account for our findings.

Our analysis adjusted for both linear and non-linear effects of chronological age; however, the role of unidentified biological ageing processes cannot be excluded. Hence, such factors may account for decline in both HRV and cognitive function, without the two systems being causally related.

A standardized protocol for recording HRV describing the optimal duration, environment, and respiratory rate for recording has yet to be established. Adherence to procedure recommendations [9] remains sub-standard, limiting the interpretive value of absolute HRV data between studies [23]. Re-test reliability of HRV measures is poor [33], however, paced breathing data collection protocol improves reliability and so its use is encouraged [26, 32]. For this reason, a paced breathing protocol was implemented here. The association between HRV and cognitive function, adjusted for respiration, indicates that a stronger relationship possibly exists than previously reported, as studies to date have recorded HRV during spontaneous breathing only. Given the practicality of delivering comprehensive assessments to participants nationwide it was not possible to ask participants to fast or to standardize The time of the day that health assessments were performed. The time of the day, however, was recorded and

subsequently analyzed to determine its effect on HRV. It was not independently associated with HRV indices.

The similarity of results when re-analysis was performed using dichotomous MOCA score (<24) serves to further validate our findings of an association between reduced HRV and cognitive decline (not shown).

The study sample is nationally representative of the community dwelling population aged 50 years and older living in Ireland. For this reason, our results reflect all members of the community and sub-group analyses are valid. TILDA uniquely measures HRV, global and specific cognitive function assessments, and is coupled with specific details on medications. This allows for correction of possible medication confounding effects on HRV.

Conclusion

In light of the ageing population demographic predicted in the coming years, interventional strategies to combat the associated rise in burden of cognitive disorders is imperative. This study has for the first time reported an association between HRV (as a measure of cardiac autonomic function) and global cognitive performance at a population level. Reduced overall HRV (SDNN), baroreflex function (LF), and cardiac autonomic modulation (LF:HF) are all independently associated with reduced cognitive performance. This may reflect shared anatomical pathways or mechanistic pathways such as inflammation or depletion of NAd reserves. Longitudinal follow-up will help to explain our observations.

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Conflict of interest None declared.

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