Heart Rate Variability, Blood Pressure and Cognitive Function: Assessing Age Effects

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Abstract

Increasing age is the most significant risk factor for dementia. Aging populations see cognitive disorders becoming increasingly prevalent, unfortunately paired with high economic and social consequences. Mild cognitive impairment (MCI) is the earliest detectable stage preceding dementia. This study aimed to identify early links between heart rate variability (HRV) and blood pressure (BP) to cognitive performance. Three blood pressure readings were taken pre and post study. Electrocardiogram was recorded during both resting (baseline) and cognitive interventions (active). HRV was extrapolated using a fast Fourier transform algorithm to produce low and high frequency bandwidths. Two psychometric tools were administered to assess cognitive domains such as memory, reasoning and visual construction ability. In the youngest age group, 18–35 years, higher blood pressure was detrimental to judgment and orientation but beneficial to calculation and memory skills. Higher sympathetic drive (low frequency) impaired language, recall and attention ability. In the middle age group (36–50 years) higher blood pressure predicted decline in comprehension, orientation and attention domains. Higher sympathetic activity (low frequency) was linked to decreases in various domains such as similarity and construction. The oldest group (51–65 years) showed higher blood pressure precipitated declines in recall ability and high sympathetic activity (low frequency) impaired orientation func-

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tion. These various associations suggest autonomic activity biomarkers for cognitive impairment vary according to age. Few studies confirm specific autonomic implications on cognition from young to older age. The cognitive associations reported highlight the potential importance of autonomic activity as a predictive tool for cognitive decline. Early detection of cognitive impairment allows for intervention methods to be applied sooner to slow or cease cognitive decline progression.

Keywords: Aging, cognition, heart rate variability.

1 Introduction

Although aging naturally involves a degree of cognitive decline, mild to severe cognitive impairment is not considered a healthy progression of aging. Increasing age is the most significant risk factor for dementia. As global populations age, dementia prevalence is predicted to increase four-fold to 115 million people by 2050 [1]. As Alzheimer's disease (the most common form of dementia) has no known cure, early detection and prevention is crucial.

Mild cognitive impairment (MCI) is the earliest detectable stage preceding dementia onset. MCI may impede (not prevent) daily life functioning and may manifest by symptoms of memory loss and subtle difficulties performing complex cognitive tasks in domains such as attention and language. Transition rates of MCI into dementia have shown that almost 50% of MCI patients develop dementia within five years [17]. This suggests that persons with MCI may also have preclinical dementia. Early detection of this vulnerable stage would allow for earlier application of preventative treatments. The present study investigated heart rate variability (HRV) analysis as a novel physiological marker to identify those at higher risk of MCI.

In contrast to MCI, dementia impairs daily life functioning. It has extensive effects, both socially and economically [25]. Many risk factors have been established which contribute to Alzheimer's type dementia, the most prominent being increasing age. Other risk factors include female sex; presence of apolipoprotein E $\varepsilon 4$ allele; low education level and cardiovascular disease [5].

The aging process involves a gradual 'undoing' of the body, resulting in various chemical and physical alterations which contribute to cognitive decline, although there remains a difference between natural cognitive decline and cognitive impairment [8]. In an autonomic sense, aging is accompanied by a degree of parasympathetic withdrawal [32] which can lead

to hypertension due to resultant sympathetic dominance. High BP is hypothesised to contribute to cognitive impairment through subtle disturbances in cerebral perfusion, thereby altering the neuron's biochemical environment and optimal functioning. Neuroimaging studies of hypertensive patients have shown decreased cerebral oxygen metabolism, enlarged ventricles (cerebral atrophy) and increased white matter lesions [45]. These factors often occur unbeknownst to the individual until more severe cognitive symptoms develop (potentially years later), as a cumulative manifestation of neuroanatomical changes.

There remains contention in the area as many studies report variations in the relationships between BP and cognition. Most studies suggest high BP is a major risk factor (especially midlife) [4, 47], whereas others suggest low BP is more detrimental (particularly in older age) [19, 33]. Waldstein et al. [51] found links between both high and low BP impairing cognitive function (inverted U-shaped hypothesis) or no associations existing at all [10]. Most studies reinforce the importance of early BP control to reduce the development of cognitive symptoms in later life.

Heart rate variability is a physiological measurement reflecting the autonomic balance of the heart [38]. HRV is derived by the spectral analysis of millisecond time variations between consecutive heart beats. These variations reflect the interplay between the parasympathetic (high frequency (HF)) and sympathetic (low frequency (LF)) branches. The sinus node of the heart acts as a pacemaker, regulating contractions to accommodate metabolic demand. It is densely innervated by both the parasympathetic and sympathetic divisions of the ANS [38]. Sympathetic innervation from the stellate ganglia is mediated by noradrenalin release at the sinus node, which is metabolised relatively slowly, as opposed to parasympathetic activation of the heart, which is moderated by the vagus nerve via acetylcholine release and quickly metabolised [38]. The distinct turnover rates of the two chemical transmitters result in variations between frequencies and fluctuations of heart rate producing a complex variability characterised by HRV analysis. These variations have been identified and quantified to establish different bandwidth frequency standards at which the two autonomic subsystems function [48]. Baseline heart rate is driven by parasympathetic activity, known as tonic inhibitory control.

Clinical applications of HRV include detection of autonomic neurodegeneration in diabetic patients [15] and clinical risk assessments of cardiac related mortalities [49]. This highlights the application of HRV as a predictive clinical tool. Studies show that changes in autonomic activity in early adult-

hood and midlife increase the risk of cognitive impairment developing later in life. In particular, low HRV has been linked with poor cognition, where the autonomic system is less reactive to changes in the external environment and is therefore less adaptable [37]. Low HRV has also been proposed as a marker of disease in many studies [11, 14, 23, 50]. Few studies, however, assess autonomic nervous system activities as predictive risk factors for the development of cognitive impairment. The present study aimed to address this gap in the literature by identifying the relationships between cognitive function and cardiac autonomic activity (HRV and BP) over a range of ages: young (18–35 years), middle (36–50 years) and older age (51–65 years). A focus on detection of the early stages of MCI is integral, before progression to a less treatable and functional state.

2 Methods

A total of 51 participants were recruited from the community adding to an existing database of 100 [9, 46] to produce a cumulative total of $n = 151$. Firstly three blood pressure (BP) measurements were taken (pre-study average) followed by a three-lead electrocardiogram. The participant underwent two interventions during which electrocardiogram was measured with eyes open; resting (baseline) state and during a cognitive task (active neutral conversation [34]). The electrocardiogram data was used to extrapolate HRV by spectral analysis of the time variations between consecutive R waves of the QRS complex. The electrocardiogram is first applied with the Butterworths filter, a band pass filter to diminish frequencies below 2 Hz and above 40 Hz, to reduce movement artefacts, T-wave interference and electrocardiogram baseline drift from influencing the data [36]. The data is then applied with a non-linear squaring function in preparation for application of the fast Fourier transform (non-parametric) [36]. The fast Fourier transform produces a spectrogram that models the power densities of the R-R intervals from the electrocardiogram (Figure 1).

Heart rate variability data reflects sympathetic (LF: 0.04–0.15 Hz) and parasympathetic (HF: 0.15–0.5 Hz) branches of the autonomic nervous system [27]. Sympathovagal balance, a measure of the sympathetic and parasympathetic equilibrium, was also determined (LF:HF) [12]. Total power (TP) reflects the total area under the spectrogram curve.

Cognitive function was assessed using two psychometric evaluation tools: the Mini-Mental State Examination [16] and the Cognistat [13]. These validated and reliable cognitive tests were administered in conjunction with one

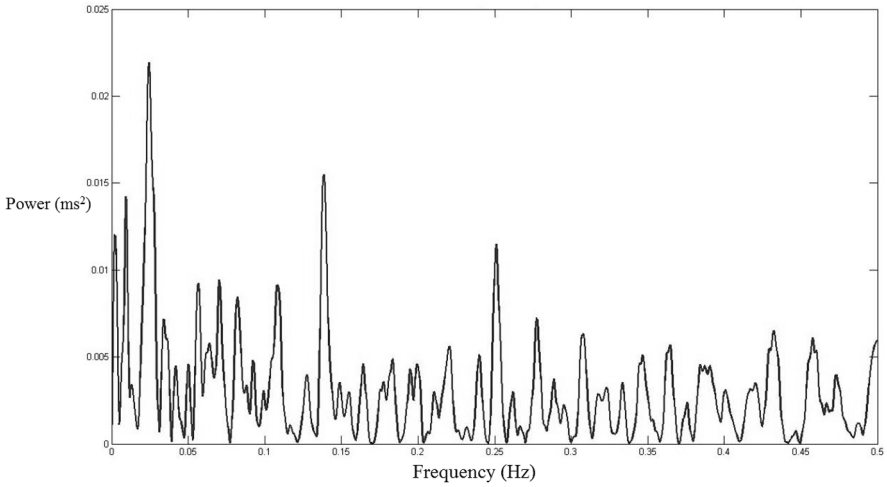

Figure 1 Heart rate variability power spectrogram of a participant during the cognitive task (active).

another to increase sensitivity and specificity of the cognitive outcomes [43]. The tests assess cognitive function in domains such as memory, language, judgement and calculation. A final three BP readings were taken (post-study average), completing the study protocol. Differences between age groups were assessed by Analysis of Variance with post-hoc least significant difference Fisher analysis. Relationships between cognitive function and other variables (BP and HRV) were assessed using Pearson's correlations. Where a cognitive domain was significantly linked to three or more other variables, a regression analysis was performed to determine the most significant predictor. All significant findings were reported at p values of < 0.05.

3 Results

Blood pressure increased significantly with increasing age yet affected cognitive domains differently over the life span. Results suggest aging and age-related BP levels are significant predictors for cognitive impairment, with performance in domains of language ($p = 0.0002$), orientation ($p = 0.002$), construction ($p = 0.03$) and total score ($p = 0.01$) declining with aging. Significant findings between BP and cognitive function for the three age groups are shown in Table 1. Heart rate variability effects on cognition during baseline were assessed among the three age groups, significant findings are

Table 1 Comparison between blood pressure and cognitive domain performance in three age groups.

Age group	Blood pressure	Cognitive domain	r	p
18-35 years	Systolic	Memory	0.3	0.02
		Recall	0.29	0.03
		Repetition	0.39	0.002
	Diastolic	Calculation	0.25	0.048
		Orientation	-0.32	0.01
		Judgment	-0.3	0.02
36-50 years	Systolic	Comprehension	-0.37	0.01
		Similarity	0.31	0.03
	Diastolic	Comprehension	-0.29	0.05
		Orientation	-0.35	0.02
		Attention	-0.29	0.04
		Calculation	0.28	0.049
51-65 years	Systolic	Recall	-0.39	0.01
	Diastolic	Recall	-0.34	0.03

presented in Table 2. A regression analysis performed found 13% of the variance of the total MMSE scores (36–50 years) were predicted by LF, HF and TP collectively ($F = 1.95$, $df = (3, 39)$, $p < 0.14$, $R = 0.36$, $R^2 = 0.13$, adjusted $R^2 = 0.64$). The multiple regression for the similarity domain for 36–50 years had an overall significance of $p < 0.004$. The regression identified significance for three HRV variables (LF, HF and TP) which together explained 28% of the variance in the similarity domain ($F = 5.14$, $df = (3, 39)$, $p < 0.004$, $R = 0.53$, $R^2 = 0.28$, adjusted $R^2 = 0.23$). However, individually two HRV factors, LF ($p < 0.02$) and TP ($p < 0.02$) were the strongest significant predictors The 36–50 year group also showed 10% of the variability of the total Cognistat score was explained by LF, HF and TP ($F = 1.2$, $df = (3, 31)$, $p < 0.33$, $R = 0.32$, $R^2 = 0.1$, adjusted $R^2 = 0.02$). Cognitive performance and HRV associations were also identified during the active cognitive task (Table 3).

Table 2 Comparison between heart rate variability (baseline) and cognitive domain performance in three age groups.

Age group	Baseline HRV parameter	Cognitive domain	r	p
18-35 years	HF	Construction	-0.36	0.01
		Naming	-0.45	0.001
	LF	Recall	-0.4	0.003
	TP	Construction	-0.3	0.03
		Recall	-0.32	0.02
36-50 years	HF	Judgment	-0.32	0.046
		Similarity	-0.43	0.01
		Total score (Cognistat)	-0.34	0.03
		Total score (MMSE)	-0.33	0.04
	LF	Attention	-0.38	0.02
		Construction	-0.33	0.04
		Repetition	-0.36	0.02
		Similarity	-0.32	0.04
		Total score (Cognistat)	-0.32	0.04
		Total score (MMSE)	-0.37	0.02
	TP	Attention	-0.39	0.01
		Construction	-0.34	0.03
		Judgement	-0.32	0.046
		Repetition	-0.41	0.01
		Repetition	-0.41	0.01
		Similarity	-0.44	0.01
		Total score (Cognistat)	-0.41	0.01
		Total score (MMSE)	-0.39	0.01
51-65	LF	Orientation	-0.53	0.001

Key: HF=High frequency; LF=Low frequency; MMSE=Mini Mental State Examination; TP=Total power

4 Discussion

4.1 Blood Pressure and Cognitive Function

Many studies report that autonomic cardiovascular factors may affect cognitive function, particularly BP levels [44, 52]. The majority of research is confined to assessing BP effects on cognition on those aged 50 and over, with little attention paid to its effects in healthy younger populations. The present research identified that increased BP may be beneficial to certain cognitive domains, while detrimental to others. In the young cohort (18–35 years), calculation skill showed a positive relationship with increasing diastolic blood

Table 3 Comparison between heart rate variability (active) and cognitive domain performance in three age groups.

Age group	Active HRV parameter	Cognitive domain	r	p
18-35 years	LF	Attention	-0.3	0.03
		Language	-0.31	0.03
36-50 years	HF	Naming	-0.35	0.03
		Repetition	-0.33	0.03
		Similarity	-0.37	0.02
	TP	Similarity	-0.32	0.04
51-65 years	LF	Orientation	-0.36	0.04
	LF:HF	Total score (Cognistat)	0.39	0.02
	TP	Orientation	-0.37	0.03

Key: HF=High frequency; LF=Low frequency; LF:HF=Sympathovagal balance; TP=Total power

pressure (DBP), seemingly contradicting findings from a retrospective cross-sectional study ($n = 5{,}077$) [28]. Judgement ability, on the other hand, a sub-skill of the reasoning domain [13], was shown to diminish with increasing DBP, agreeing with other current findings [28]. Increased systolic blood pressure (SBP) was found to improve performance in the memory, repetition and recall domains. This conflicts with a 2006 study by Wharton's laboratory that assessed BP and cognitive function in 18–21 year olds ($n = 105$) [52]. The group also reported a positive relationship between BP and visual search and spatial orientation tasks, whilst the present study showed increasing DBP impaired orientation performance.

The literature suggests that midlife hypertension increases the risk of dementia more than late-life hypertension [2]. Pathological changes (such as white matter lesions) noted in the brain during hypertensive states midlife reflect similar pathological changes seen in the early stages of Alzheimer's disease [40]. Current findings showed higher SBP and DBP were associated with better performance in similarity and calculation domains, but impaired comprehension, orientation, and attention domains. This is supported by the findings of a retrospective study ($n = 5{,}838$) [45]. Although, the recent Bogalusa Heart Study [21] presented results inconsistent with this association, reporting an inverse relationship between SBP and 63% of the cognitive

domains of the neuropsychological assessments ($n = 351$). The vast majority of BP and cognition studies demonstrate SBP and DBP as predictors for cognitive impairment in older age. The present study found increased SBP and DBP linked to impaired recall ability in the older age group (51–65 years). This is supported by various studies, recall being a sub-skill of short-term memory [18]. The current study identified recall domain performance with high BP as a strong predictor for cognitive impairment. Increasing awareness of the importance of BP control in older age is a vital step towards manipulating modifiable risk factors to preserve cognitive function.

4.2 HRV and Cognitive Function (Baseline)

The current study showed LF was inversely linked to recall performance in the 18–35 year old group during baseline. Higher LF reflects sympathetic dominance, which is associated with increased BP, stress, cardiovascular disease and heightened mortality risk [7]. Construction skill decreased as HF and TP increased (baseline), reflecting parasympathetic dominance. This relationship may be influenced by unrefined construction abilities as visuospatial construction skills are still forming during adolescence and young adulthood [42]. Higher HF was linked with decreased ability in the naming domain. Prior to young adulthood there is a sharp improvement in the naming domain, as the frontal lobe is maturing, whereas only a gradual increase thereafter as one progresses towards midlife [6]. In older age, naming ability declines, not caused by a loss of vernacular, but rather increased difficulty in accessing existing knowledge stores, learning, and integrating new information. These associations reinforce that cardiovascular and neurocognitive systems do not operate in isolation from one another. Assessing the effects of autonomic activity over the lifetime may prompt adjustment of maintenance methods for autonomic control to prevent future onset of cognitive decline. Higher cardiac activity during middle age for LF and TP was associated with lower scores in the attention, construction, and repetition domains. Catecholamine exposure produced during the sympathetic (LF) response (particularly dopamine and norepinephrine) attenuates working memory function, as well as other higher order skills [39]. Research shows that imbalanced HRV during resting state heightens the risk of cognitive impairment, cardiovascular disease, vascular dementia and Alzheimer's disease [33]. Low HRV was linked to lowered orientation skill in older age (51–65 years) (baseline). Clinically, diminishing orientation function is one of the earliest predictors of cognitive decline seen in Alzheimer's disease [30]. Sympathetic dominance accompanying reduced

cognitive function in old age has been supported by many studies [31, 41] and has been linked to other diseased states including hypertension and anxiety disorders [3, 26].

4.3 HRV and Cognitive Function (Active)

Measuring HRV changes during an active cognitive task is crucial as reactivity to a stimulus is an essential mechanism reflecting the body's ability to adapt to the surroundings and supply metabolic needs. Although there are few literature comparisons, findings from the present study showed that in the youngest age group higher LF was linked to lower language and attention ability during performance of the cognitive task. In contrast, increasing parasympathetic activity (HF and TP) diminished similarity, repetition and naming skill during midlife (36–50 years). Increased parasympathetic drive has been associated with lowered cerebral perfusion, potentially causing ischemic injury and impairing cognition which may progress into dementia [24]. Higher LF was inversely correlated to orientation ability yet positively linked to total Cognistat score in older age participants (51–65 years). Heightened sympathovagal balance was linked to better total Cognistat score in the older sample which suggests sympathetic drive benefits overall cognitive function in the 51–65 year group. This has also been supported by several other studies [20, 22, 29, 35].

5 Conclusion

This research highlighted the prospective use of autonomic markers such as HRV (LF, HF, TP and LF:HF) and BP in relation to physiological aging to be utilised as early biomarkers of cognitive impairment. Future studies within the Neuroscience Research Unit, University of Technology, Sydney see to analysing sex effects, increasing sample size and assessing a clinical sample. This will help identify when cognitive function is most susceptible to autonomic changes. Early detection of those at higher risk of cognitive impairment would allow for preventative measures (such as anti- hypertensive use and autonomic biofeedback) to be applied earlier in life, to prevent or delay abnormal cognitive decline and progression into dementia. This would not only result in economic and social benefits, but also reduce the burden on carers and ultimately and most importantly preserve cognition in our aging population.

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Biographies

Louisa Giblin obtained her Bachelor's degree in Medical Science with first class honours at the University of Technology, Sydney. Louisa is currently completing a PhD within the Neuroscience Research Unit, School of Medical and Molecular Biosciences under the principal supervision of Professor Sara Lal. Louisa's research is focused on the links between heart rate variability and cognitive function.

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Lisa Smith obtained a Bachelor's degree in Medical Science with first class honours at the University of Technology, Sydney. Lisa currently studies dentistry at Griffith University, Queensland.

Tamara Sztynda completed a Bachelor of Science, Master of Science and PhD (Medicine) at the University of Melbourne. Dr. Sztynda is a Senior Lecturer at UTS within the School of Medical and Molecular Biosciences and the Program Director for the Bachelor of Forensic Biology in Biomedical Science. Dr. Sztynda is an Associate within the National Institute of Forensic Science, a member of the Australian and New Zealand Forensic Science Society and the NSW Histotechnology Group. Dr. Sztynda's research interests are in histopathology and forensic biology and currently she has research students who she is co-supervising with Professor Sara Lal in the forensic application of optical flow analysis for detection of facial emotions.

Sara Lal (PhD, MAppSc, BSc, GCHE, DipLaw) is a neuroscientist in the School of Medical and Molecular Biosciences at the University of Technology, Sydney. Professor Lal is the principal supervisor on this research publication. Professor Lal has supervised multiple research students and published widely in medical, scientific and engineering journals in areas of neuroscience, fatigue, algorithms, cognitive sciences, countermeasures and in cardiovascular research. She has attracted multiple competitive grants.