

Effects of heart rate variability and blood pressure on cognition in healthy and clinical cohorts

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Declaration

Certificate of original authorship

I certify that the work in this thesis has not been previously submitted for a degree nor has it been submitted as part of requirements for a degree except as fully acknowledged within the text.

I also certify that the thesis has been written by me. Any help that I have received in my research work and the preparation of the thesis itself has been acknowledged. In addition, I certify that all information sources and literature used are indicated in the thesis.

Signature:

Date: 22/05/2016

Louisa Giblin

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List of abbreviations

AD = Alzheimer's disease	MANCOVA = Multiple analysis of covariance
ANCOVA = Analysis of covariance	MCI = Mild cognitive impairment
ANOVA = Analysis of variance	mm = Millimetres
ANS = Autonomic nervous system	mmHg = Millimetres of mercury
APOE ϵ 4 allele = Epsilon 4 allele of apolipoprotein E	MMSE = Mini-Mental State Examination
BMI = Body mass index	ms = Milliseconds
BP = Blood pressure	ms ² = Milliseconds squared
bpm = Beats per minute	mV = Millivolts
CR = Cardiac reactivity	n = Sample size
DBP = Diastolic blood pressure	NSAIDs = Non-steroidal anti-inflammatory drugs
df = Degrees of freedom	p = p value
DM = Diabetes mellitus	PFC = Prefrontal cortex
ECG = Electrocardiogram	pNN50 = Percentage of NN intervals >50ms apart ⁰¹
F = F statistic	PNS = Parasympathetic nervous system
HF = High frequency	RMSSD = Root mean square of successive differences
HPA = Hypothalamic-pituitary-adrenal	RSA = Respiratory sinus arrhythmia
HR = Heart rate	SBP = Systolic blood pressure
HREC = Human Research Ethics Committee	SD = Standard deviation
HRT = Hormone replacement therapy	SDNN = Standard deviation of NN interval
HRV = Heart rate variability	sec = Second
IQ = Intelligence quotient	SNS = Sympathetic nervous system
IQR = Interquartile range	t = t statistic
LAQ = Lifestyle Appraisal Questionnaire	U = U statistic
LF = Low frequency	ULF = Ultra low frequency
LF/HF = Low frequency to high frequency ratio (sympathovagal balance)	UTS = University of Technology
LSD = Least significant difference	

Sydney

VaD = Vascular dementia

VLF = Very low frequency

χ^2 = Chi square statistic

Z = Z score

↓ = Decrease

> = Greater than

≥ = Greater than or equal to

↑ = Increase

< = Less than

≤ = Less than or equal to

% = Percentage

± = Plus or minus

* = Regression analyses performed

List of publications and presentations

List of publications

GIBLIN, L. B., DE LEON, L., SMITH, L., SZTYNDA, T. & LAL, S. 2013. Heart Rate Variability, Blood Pressure and Cognitive Function: Assessing Age Effects. *Journal of Green Engineering*, 3, 347-361

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GIBLIN, L. B., DE LEON, L., SMITH, L., ZASLAWSKI, C., CLIFTON-BLIGH, R., & LAL, S. Heart Rate Variability and Cognitive Performance. Oral presentation: The XX World Congress on Parkinson's and Related Disorders. 8-11th December 2013. Geneva, Switzerland.

GIBLIN, L., DE LEON, L., SMITH, L., SZTYNDA, T., LAL, S. Heart Rate Variability, Blood Pressure and Cognitive Function: Assessing Age Effects. Oral presentation: 7th International Conference on Broadband and Biomedical Communications. 5-6th November 2012. Sydney, Australia.

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Abstract

Australia's aging population has heightened demand for earlier detection and prevention methods for dementia. Studies have shown that autonomic dysfunction precedes mild cognitive impairment, a precursor to dementia (Collins et al., 2012). The present study explores the links between heart rate variability (HRV) (reflecting autonomic activity), blood pressure (BP), and cognitive function in non-clinical and clinical cohorts (depression, diabetes (type 1 and 2), and hypertension).

Participants were added to an existing database (De Leon, 2009, Smith, 2010) (n=100) to produce a cumulative sample of n=297. The experimental protocol commenced with three baseline BP measurements, the Lifestyle Appraisal Questionnaire (Craig et al., 1996) and the Disease State Questionnaire (Giblin, 2013). The participant underwent two electrocardiogram recordings for HRV analysis (10 minutes of baseline and 10 minutes of a cognitive task). Two psychometric tests were then administered: the Mini-Mental State Examination (Folstein et al., 1975) and the Cognistat (Kiernan et al., 1987). Finally, three additional BP measurements completed the study protocol.

Higher baseline parasympathetic activity was significantly correlated ($p < 0.05$) to better cognitive performance (e.g. memory) in females 18-50 years and males 51-65 years however this was also correlated to poorer cognitive scores (e.g. judgment) in females 36-65 years and males 36-50 years. HRV reactivity (cognitive task minus baseline) was mostly positively correlated to cognition (e.g. comprehension) in females 18-35 and 51-65 years.

Higher vagal activity was linked to higher cognitive scores (e.g. attention) in all clinical groups yet also linked to poorer cognitive scores (e.g. orientation) in the type 1 diabetes and hypertension groups. HRV reactivity was mostly positively correlated to cognition (e.g. naming) in the hypertension sample yet inversely linked to cognition in the other clinical groups.

Both clinical and non-clinical groups had positive correlations between BP reactivity and cognitive performance (e.g. attention), suggesting low BP reactivity may be a predictor for cognitive decline.

These initial findings contribute new knowledge to the field of HRV and cognition, particularly in clinical groups and the less-studied HRV and BP reactivity in clinical and non-clinical groups. By gaining a better understanding of early autonomic risk factors for cognitive impairment, preventative countermeasures (e.g. anti-hypertensive use and autonomic biofeedback) may be considered to slow or cease dementia progression. Delaying or stopping the development of dementia has the potential to reduce expected rises in government expenditure, lower the burden on carers and nursing homes, lengthen lifespans, and ultimately improve the quality of life in elderly populations.

1. Introduction

1.1 Cognitive function

A combination of advances in medicine and technology over the past century have led to better diagnostics, pharmacotherapies, and risk factor reduction; all of which contribute to lower mortality rates and longer life spans. From 1990 to 2013, average global life expectancy increased by approximately 6 years (Global Burden of Disease Study 2013: Mortality and Causes of Death Collaborators, 2014). A longer life span, however, has not been accompanied by improved health in old age; it is one of the *'failures of success'* that has revealed itself through declining cognitive function in aging populations (Ritchie, 2004). By 2050, Australia's aging population will increase to over seven million people over the age of 65, more than double the current figure (Figure 1.1).

Figure 1.1 Number of Australians aged 65 years and over, by age group, 2012-2047

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Figure 1.1 shows a projection of Australia's population over the age of 65 from 2012 to 2047. Note that by 2047, the total number of people over the age of 65 is expected to more than double the current figure. Adapted from the Australian Department of Health and Aging (2012).

Cognitive function is a broad term used to describe the way the brain works and how effectively thought processes are organised and integrated throughout various cognitive domains. Cognitive domains are specialised areas of the brain which operate to perform different thought processes such as visual construction, naming, calculation, phonological memory and higher order reasoning. Certain areas of the brain have been mapped as both specific and crucial for particular cognitive processes (such as the occipital lobe for processing visual stimuli (Figure 1.2)).

Figure 1.2 Functions of the brain stem, cerebellum, and brain lobes

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Figure 1.2 identifies the brain stem, cerebellum, and brain lobes (shaded in varying colours) and lists the associated cognitive processes. These anatomical correlates perform both broad and specific cognitive functions integral to daily life functioning. Image adapted and modified from page 8 Bear et al. (2007).

A wide variety of aetiologies may disrupt and impair cognitive function including infection, poor cardiovascular health, hormonal change, genetics, prolonged stress and head trauma. Cognitive impairment currently affects well over 300,000 Australians, costing the Australian government greater than \$6.6 billion per annum (Alzheimer's Australia, 2011). Cognitive impairment is often difficult to diagnose; manifesting progressively with subtle early symptoms (for example, personality changes and mood alterations) (Alzheimer's Australia, 2012). The earliest recognisable and identifiable stage of cognitive impairment is known as mild cognitive impairment (MCI).

1.1.1 Mild cognitive impairment (MCI)

MCI describes a condition that emerges during the transitional stage between normal cognitive function and dementia (Simon et al., 2012). The condition commonly manifests by symptoms of memory loss (amnesia) which impedes daily life functioning, for example, through increased difficulty with household activities – using a telephone, dressing, and maintaining dental health (Ritchie, 2004). Criteria used by health practitioners to diagnose MCI are shown Table 1.1.

According to a meta-analysis of population-based epidemiological studies ($n =$ (sample size) 12212), 3-19% of adults over 65 years have MCI (Ritchie, 2004). Once diagnosed with MCI, one may either regain cognitive function, stay at a stable (but impaired) level, or progress further toward a dementia state (Petersen et al., 1999). Research on transition rates of MCI has shown that almost 50% of patients develop dementia within five years (Geslani et al., 2005, Gauthier et al., 2006). Since those with MCI are at higher risk for progressing into a dementia state, it has been suggested that persons with MCI may also have preclinical dementia (Gauthier et al., 2006) and that MCI may be classified as a

prodromal risk state for dementia (Levey et al., 2006). Early detection of this vulnerable stage of impairment could allow for earlier application of preventative treatments to delay or cease progression into a clinical dementia state.

Table 1.1 Clinical criteria used to diagnose mild cognitive impairment

1. Memory complaints, preferably corroborated by an informant
2. Objective memory impairment for age and education
3. Largely intact general cognitive function
4. Essentially preserved activities of daily living
5. Does not meet dementia criteria

Table 1.1 lists criteria used by clinicians to diagnose mild cognitive impairment. Early identification is essential as mild cognitive impairment can progress into dementia. Adapted and modified from Petersen (2003).

1.1.2 Dementia

Dementia is an umbrella term used to classify a *significant* degree of cognitive impairment. Dementia is diagnosed by health practitioners when a patient exhibits significant memory impairment together with other cognitive domain dysfunctions (Frances et al., 2010) (see diagnostic criteria in Table 1.2). To distinguish dementia from MCI, cognitive impairment must be severe enough to prevent daily life functioning, such as household activities (Levey et al., 2006). Dementia, however, is not a disease unto itself; it is a symptom of an underlying pathology such as cardiovascular disease, head trauma, infection or more commonly, Alzheimer’s disease (AD).

There are currently approximately 46 million people worldwide living with dementia, a statistic expected to nearly double every 20 years, rising to an estimated 131 million cases in 2050 (Alzheimer's Disease International, 2015). Many studies have shown that the most significant risk factor for dementia is increasing age (Chen et al., 2009). As such, and given Australia’s aging population, national prevalence of dementia is predicted to almost quadruple from 257,000 people in 2010 to nearly 1 million by 2050 (Figure 1.3). According to Alzheimer’s Australia, dementia will be the leading cause of disability in Australia by 2016 (Alzheimer's Australia, 2012).

Table 1.2 Clinical criteria used to diagnose dementia

Significant decline in memory ability and decline in one or more of the following:	
•	Generating of coherent speech or understanding spoken or written language
•	Recognising or identifying objects, assuming intact sensory function
•	Executing motor activities, assuming intact motor abilities, sensory function and comprehending the required task
•	Thinking abstractly, making sound judgments and planning and carrying out complex tasks

Table 1.2 lists criteria used to diagnose dementia, according to guidelines set by the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (4th edition). Memory decline must be accompanied by one or more of the cognitive impairments listed and together must significantly disrupt daily life functioning. Adapted and modified from Frances et al., (2010).

Figure 1.3 Expected dementia prevalence in Australia (2012-2050)

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Figure 1.3 shows a projected increase in the number of Australian dementia cases from 257,000 in 2012 to 981,000 in 2050. This almost fourfold increase is attributed to both an aging population and improvements in diagnostic techniques (allowing for earlier and more accurate detection). Adapted and modified from Alzheimer's Australia (2011).

1.1.2.1 Alzheimer's disease (AD)

AD is the most common form of dementia, contributing to approximately 62% of total dementia cases (U.S. Department of Health and Human Services, 2012). Globally, 33.9 million people currently suffer from AD with its prevalence expected to triple over the next 40 years due to aging populations (together with advancements in diagnostic techniques and longer life expectancies) (Barnes and Yaffe, 2011).

AD is irreversible, progressive, and ultimately fatal. It is characterised by changes in neuronal structure that lead cognitive impairment; primarily the build-up of beta-amyloid plaques and neurofibrillary tangles (Vernooij and Smits, 2012). Both beta-amyloid plaques and neurofibrillary tangles are diagnosed during post-mortem inspection (Mosconi et al., 2007).

Beta-amyloid plaques are effectively equivalent to scar tissue within the brain and are formed by aggregation of beta-amyloid protein fragments, degenerated neurons, and other cellular material (DaSilva et al., 2010). Up-regulated production of beta-amyloid coupled with decreased clearance results in overall higher levels of beta-amyloid, which can lead to neuronal death, neurite degeneration and synaptic disruption, contributing to cognitive symptoms such as memory dysfunction and impaired learning (Pike et al., 2009). The epsilon four allele of apolipoprotein E (APOE ϵ 4) is an important gene which increases the risk of developing AD by up-regulating amyloid precursor protein production (leading to more beta-amyloid production) (Corder et al., 1993, Gispert et al., 2015). Ongoing research aims to determine whether the beta-amyloid plaques are a result of AD or a causal factor for the disease (U.S. Department of Health and Human Services, 2012). Inflammatory mediators, such as the process of microglia activation increasing the production of beta-amyloid have also been linked to an increased risk of AD (Meda et al., 2001).

Neurofibrillary tangles are also found in those with AD. In AD, tau proteins (which help stabilise neuronal microtubules to offer structural support (Brandt et al., 2005)) become hyperphosphorylated and cause the neuron to destabilise, disintegrating the internal neuronal structure and disrupting the neuronal transport system (Maeda et al., 2006). The combination of beta-amyloid plaques and neurofibrillary tangles contribute to a loss of synaptic connections between neurons and neuronal atrophy, resulting in the insidious

onset of cognitive impairment symptoms seen in AD (Figure 1.4). Over time, widespread neuronal loss causes irreversible brain volume shrinkage, enlarging both the ventricles and sulci.

Figure 1.4 Healthy brain and neuron compared to Alzheimer's disease

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Figure 1.4 illustrates a healthy brain and neuron compared to a diseased state showing characteristic signs of Alzheimer's disease. Healthy neurons have fewer amyloid plaques and tau proteins are organised and straight yet in the diseased neuron they appear deregulated and chaotic. Neuronal atrophy results in decreased brain volume and increased ventricle size. These structural changes impact synaptic transmission and may result in cognitive dysfunction. Adapted from U.S. Department of Health and Human Services (2008).

Age is the most significant risk factor for developing AD and over 95% of cases occur sporadically with late onset (≥ 60 years). Autosomal dominant mutation leads to less than 5% of cases with early onset (≤ 59 years). A specific cause for AD remains unknown, although studies have associated an increased risk of developing AD with the presence of the APOE ϵ 4 allele (Corder et al., 1993), as well as other genes associated with earlier onset such as presenilin 1 and 2 (Richard and Amouyel, 2001).

The early stages of AD most commonly affect the entorhinal cortex and the hippocampus, both important in memory formation (Devanand et al., 2012). The disease then extends to areas such as the frontal cortex and temporal lobes, attenuating language and reasoning abilities (Figure 1.5). By the late stages of AD, patients are often unable to walk, take care of themselves or recognise close friends or family, requiring 24 hour care. Immobility also increases vulnerability to infections such as AD-related pneumonia, which is commonly fatal (Honjo et al., 2009).

The cost of carers and high demand for nursing homes places a substantial financial burden on governments, with global dementia government expenditure reaching approximately \$818 billion in 2015 (including medical care and unpaid care provided by family and other carers) (Alzheimer's Disease International, 2015). The adequate supply of such resources is recognised by the World Health Organisation, the Australian

government, and many other national governments as a health priority (Australian Institute of Health and Welfare, 2012b, World Health Organisation and Alzheimer's Disease International, 2012). AD is currently treated with acetylcholinesterase inhibitors such as donepezil which increase synaptic levels of acetylcholine and improve thought processes, memory, and speaking skills (Saify and Sultana, 2014, Gibbs et al., 2009). At present, prescribed pharmaceuticals improve cognitive and behavioural symptoms yet do not halt the underlying disease process, limiting therapeutic efficiency as the neuronal pathology becomes more prominent. It is therefore essential to identify biomarkers to detect early stages of cognitive impairment (such as MCI) so that intervention methods can occur earlier to slow or cease progression into AD and other forms of dementia.

Figure 1.5 Typical progressive stages of Alzheimer’s disease

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Figure 1.5 illustrates areas of the brain affected by different stages of Alzheimer’s disease (in blue shading); preclinical, mild/moderate, and severe. Image adapted and modified from page 211 Bear et al. (2007) and U.S. Department of Health and Human Services (2008).

1.1.2.2 Vascular dementia (VaD)

Vascular dementia (VaD) is the second most common form of dementia (after AD), and is caused by cardiovascular diseases such as stroke, heart failure and hypertension (Ligthart et al., 2010). Risk factors for cardiovascular disease (and therefore VaD) include increasing age, high levels of circulating cortisol, diabetes mellitus (DM), and lifestyle factors such as smoking, poor diet, lack of physical activity and alcoholism (Hajifathalian et al., 2015). In contrast to the gradual onset typical of AD, VaD is often characterised by an acute onset of cognitive symptoms that fluctuate in intensity depending on the origin of the cardiovascular disease (Mathias and Burke, 2009). Cognitive decline progresses more severely after each additional cardiovascular event (Mathias and Burke, 2009). Cardiovascular pathologies often result in cerebral hypoperfusion, which can lead to ischemic injury, impairing neuronal function and presenting as cognitive impairment (Figure 1.6). A study conducted by Dolan’s laboratory (2010) calculated the risk of dementia from intracranial atherosclerosis, that is, the build-up of fatty tissue hardening along the inner arterial wall, effectively narrowing lumen diameter and reducing cerebral blood flow (Roher et al., 2011). The study showed that those with intracranial atherosclerosis were 34% more likely to develop dementia (n=200, mean age 88 ± 7 years, 67% male), highlighting the important relationship between cardiovascular health and preservation of cognitive function (Dolan et al., 2010).

Figure 1.6 Ischemic injury as a result of cerebral artery blockage

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Figure 1.6 illustrates reduced cerebral blood flow resulting in ischemic injury (grey area) due to a combination of atherosclerosis and a blood clot (ischaemic stroke) impairing circulation through the artery. Image adapted and modified from Yale Medical Group (2012) (online).

1.1.2.3 Other types of dementia

Other diseases such as Parkinson's disease, Creutzfeldt-Jakobs disease, and Wernicke-Korsakoff syndrome, are less common forms of dementia. Each condition has different pathological mechanisms that lead to cognitive impairment. The most common of these dementia-causing diseases are outlined in Table 1.3.

Table 1.3 Common types of dementia

Type of dementia	Pathological mechanisms affecting cognition	Total % of dementia cases
Alzheimer's disease (AD)	Beta-amyloid plaques and neurofibrillary tangles in the brain and significant neuronal atrophy	62%
Vascular dementia (VaD)	Cardiovascular disease such as stroke, chronic heart failure, hypertension and atherosclerosis which reduce cerebral perfusion	17%
Mixed dementia	Beta-amyloid plaques and neurofibrillary tangles in the brain (typical of AD) together with cardiovascular disease (typical of VaD) and/or cerebral Lewy bodies (see below)	10%
Dementia with Lewy bodies	Cerebral Lewy bodies (alpha-synuclein plaques) thought to contribute to neuronal atrophy	4%
Fronto-temporal lobe dementia	Glial tau positive inclusions and lobe specific neuronal atrophy	2%
Parkinson's disease	Decreased cerebral dopamine levels particularly in the substantia nigra	2%
Huntington's disease	Protein aggregations forming inclusion bodies in the neuronal nuclei and cytoplasm	2%
Creutzfeldt-Jakob's disease	Prion disease causing neuronal swelling and abnormal cerebral prion protein deposits which result in plaque accumulations	1%
Wernicke-Korsakoff syndrome	Thiamine deficiency disrupting glucose metabolism, leading to significant atrophy of the dorsomedial thalamus and mammillary bodies	1%

Table 1.3 outlines common types of dementia and their clinical manifestations. Note that the majority of pathological mechanisms alter neuronal structure and impair synaptic transmission resulting in cell atrophy and ultimately, cognitive impairment. Other, rarer forms of dementia, such as corticobasal degeneration, Niemann Pick disease type C and Binswanger's disease, are excluded from this outline. Adapted and modified from p11 Alzheimer's Disease International (2010), p1 Alzheimer's Society (2012) and p1 Bayer and Metzler-Baddeley (2012).

1.2 Risk factors for cognitive impairment

Both MCI and dementia have multifactorial origins. Many studies have shown they are linked to various modifiable (e.g. lifestyle) and non-modifiable risk factors (e.g. genetics and age) (Reitz and Mayeux, 2014, Campbell et al., 2013). Although the effect of removing singular risk factors is not entirely known, some studies have determined that certain risk factors are more likely to result in cognitive impairment (cerebrovascular disease) than others (smoking) (Reitz and Mayeux, 2014). Some risk factors often coexist, as seen in metabolic syndrome (hypertension, type 2 diabetes, hyperlipidaemia, and obesity) and may be effectively reduced by interventions targeting common causal origins such as diet and exercise (Yaffe et al., 2004, Barnes and Yaffe, 2011). Strategies for intervention ought to target multiple risk factors to most effectively lower the risk of cognitive impairment.

The following section discusses a number of known risk factors for cognitive impairment: age, sex and hormones, genetics and ethnicity, disease states (hypertension, diabetes (type 1 and 2), and depression), and lifestyle.

1.2.1 Age

Increasing age is accompanied by a normal progressive decline in biological function and is the most significant risk factor for cognitive impairment and dementia. It must be stressed, however, that there is a difference between a state of cognitive impairment and natural cognitive decline.

The natural aging process involves a gradual ‘undoing’ of the body, resulting in various chemical and physical changes which contribute to cognitive decline (de Carli, 2003). Cognitive decline typically manifests in difficulty accessing semantic memory (naming) (Birren and Schaie, 2001), reduced attention span (Braver and Barch, 2002, Birren and Schaie, 2001), weaker working memory (a task that requires simultaneous acquisition and processing of information involving the dorsolateral prefrontal cortex), and poorer source memory (remembering the context of learned information involving the hippocampus) (Kensinger, 2009). There are several existing hypotheses explaining cerebral changes that occur with aging.

The ‘dopaminergic hypothesis’ describes a correlative triad between increasing age, decreasing dopamine levels, and cognitive decline (Bäckman et al., 2010). Various studies have shown aging is accompanied by a decline in dopamine and tyrosine hydroxylase levels (dopamine precursor enzyme), the number of dopamine receptors on the post-synaptic terminal (D₁ (Wang et al., 1998) and D₂ (Volkow et al., 1998, Bäckman et al., 2000)), as well as a decline in the binding potential for the dopamine transporter (pre-synaptic terminal) (Wang et al., 1998). This natural decline in dopamine predominantly impacts the dopamine projection areas such as the nigro-striatal dopaminergic tract and the frontal cortex, affecting executive functioning, episodic memory, and processing speed (Kensinger, 2009, Esiri, 2007).

The ‘cholinergic hypothesis’ proposes cognitive decline in aging is, in part, a result of decreased choline acetyltransferase levels (acetylcholine precursor enzyme) (Dumas and Newhouse, 2011). The resultant decline in cerebral acetylcholine in the basal forebrain complex has been linked to both short-term memory loss and attention dysfunction (Sarter and Bruno, 2004). Medications that enhance synaptic acetylcholine improve short-term memory (such as physostigmine), highlighting the importance of a balanced level of this neurotransmitter for optimal cognitive performance (Creasey and Rapoport, 1985). Some have hypothesised that the sum of the dopaminergic and cholinergic imbalance in the aging brain contributes to Parkinsonian-like symptoms such as gait disturbances, short-term memory loss, excessive fatigue, and difficulties in movement initiation, all commonly seen in the healthy elderly population (Creasey and Rapoport, 1985, Esiri, 2007).

The ‘oxidative stress hypothesis’ is yet another widely accepted theory explaining cerebral change accompanying increasing age. It involves a complex process of increased reactive oxygen species, calcium ion imbalance, mitochondrial dysfunction (leaking reactive oxygen species from the electron transport chain) and molecular inflammatory pathways (up-regulation of pro-inflammatory mediators) (Kregel and Zhang, 2007) (Figure 1.7). These processes accumulate and damage proteins, lipids, and macromolecules, causing faulty deoxyribonucleic acid replication and neuronal apoptosis, ultimately resulting in cognitive decline (Kregel and Zhang, 2007).

Figure 1.7 Oxidative stress hypothesis of aging

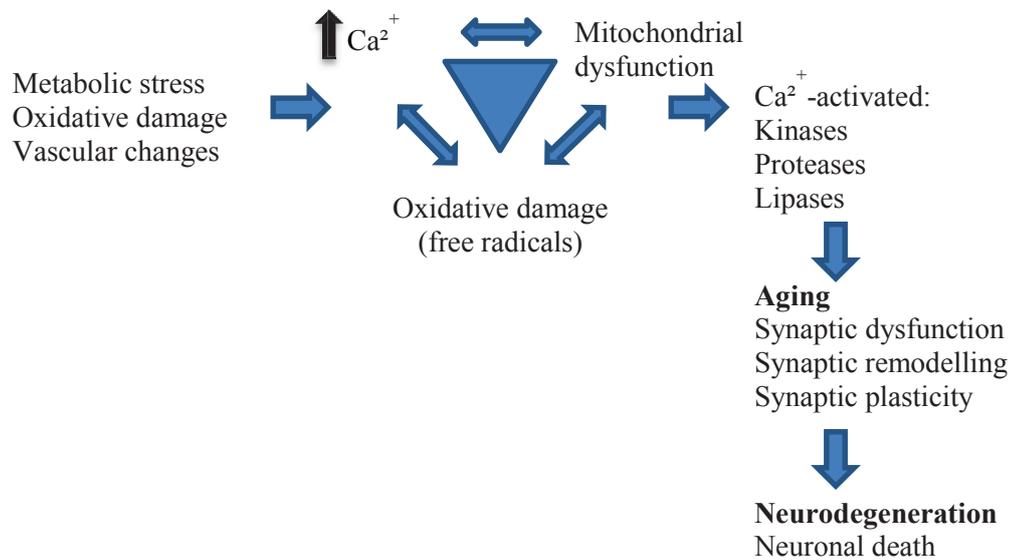


Figure 1.7 depicts the inflammatory pathway that contributes to cerebral changes during aging, according to the oxidative stress hypothesis. The pathway involves an increase in calcium, causing mitochondrial dysfunction of the electron transport chain and oxidative damage from free radicals leading to cell senescence and eventual cell death. Image adapted and modified from Toescu and Vreugdenhil, (2010).

Key: Ca^{2+} = Calcium

The aging brain also naturally undergoes considerable morphological changes resulting in a degree of neuronal loss causing cortical thinning, ventricular enlargement and sulci widening, particularly in the frontal lobes (Ryan et al., 2011). Both white and grey matter change with aging, although more extensively in the case of white matter (Hsu et al., 2008). Research by Bartzokis (2004) hypothesised that axon myelination that developed later in life (frontal lobe) is most vulnerable to age-related degeneration, in contrast to axon myelination that developed earlier in life (posterior lobes), which remain relatively intact. This anterior to posterior atrophy pattern is known as the ‘frontal aging hypothesis’ (Abe et al., 2008, Lehmebeck et al., 2006). The reduction in frontal lobe volume is consistent with aging-related working memory disruption and processing impairments (Ryan et al., 2011).

The ‘cortical disconnection hypothesis’ ascribes the loss of lobe structure communication to white matter tract deterioration (O’Sullivan et al., 2001). Development of white matter lesions results in slower cognitive processing speeds apparent in aging (Turner and Spreng, 2012). Other structural changes in the aging brain (including neurofibrillary

tangles, beta-amyloid plaques, and dendritic spine abnormalities (Figure 1.8), in the absence of AD) also reduce synaptic transmission efficiency, further contributing to cognitive decline seen in healthy aging (Esiri, 2007).

Figure 1.8 Dendritic spine morphology in aging

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Figure 1.8 compares cingulate cortex dendritic spine morphology between two males aged 40 and 85 years. Increasing age significantly reduces dendritic diameter, spine density and volume; providing morphological support for cognitive decline in aging. Adapted from Fjell et al. (2014) and Benavides-Piccione et al. (2013).

Aside from the hypotheses described previously, other research suggests cardiovascular changes that occur with aging also contribute to natural cognitive decline. Vagus nerve activity (as reflected by heart rate variability (HRV)), has been shown to decrease with increasing age (Shiogai et al., 2010, Voss et al., 2015). Individuals with lower cardiac vagal control are less reactive and less adaptable to changes in the external environment and have an increased risk of mortality (Thayer et al., 2010). Reduction in vagal tone has also been linked to increased heart rate (HR) and blood pressure (BP), which are each independent risk factors for cognitive decline (Mori et al., 2014).

A cross-sectional Australian study conducted in 2010 by Carrington's research team assessed the BP of 13825 adults aged 48 ± 16 years (55% female). Their findings showed that with increasing age, systolic blood pressure (SBP) increased considerably while diastolic blood pressure (DBP) peaked midlife and declined thereafter (Carrington et al., 2010). This is consistent with evidence of changes in HRV as age increases, with higher sympathetic dominance in older age contributing to higher BP (Pumprla et al., 2002), which may be an adaptive mechanism to compensate for reduced cerebral perfusion due to weakened arterial elasticity (Paran et al., 2003, Qiu et al., 2005, Kennelly et al., 2009).

The most common geriatric memory complaints involve difficulty accessing semantic memory (naming) (Birren and Schaie, 2001). Research has shown that it is not a loss of internal lexicon, but rather an increased difficulty in accessing existing knowledge, resulting in 'tip-of-the-tongue' experiences (Birren and Schaie, 2001, Kensinger, 2009).

Madhavan et al.'s (2015) neuroimaging research identified that white matter degradation in the superior longitudinal fasciculus provided a neural correlate for language declines seen in aging (n=112, age range 19-76 years, 40% male).

Some aspects of cognition remain stable or even improve with aging. Commonly learned skills (procedural memory) remain intact, possibly linked with a well preserved primary motor cortex (Birren and Schaie, 2001). Other skills such as general knowledge, vocabulary and word defining (crystallised intelligence) also remain intact during aging and may continue to improve over time (Salthouse, 2004). This is often in stark contrast to fluid intelligence skill, where the ability to store and manipulate new information is impaired in older age (Kensinger, 2009).

1.2.2 Sex and hormones

In addition to aging, sex is a significant non-modifiable risk factor for cognitive impairment and dementia (Rosario et al., 2011). Males and females produce different concentrations of sex-steroid hormones: males have a higher amount of circulating androgens (namely, testosterone), whereas pre-menopausal females exhibit higher levels of oestrogens and progestins (Marino et al., 2011). Sex-steroid hormones have been shown to have different effects on cognitive domains between the sexes (Norbury et al., 2003, Cherrier et al., 2001b). Females generally exhibit superior verbal and linguistic skills, while males excel at visuospatial tasks and mathematical reasoning (Table 1.4) (Weiss et al., 2003). However, a recent study by Evans and Hampson (2015) found that females and males do not significantly differ in measures of global cognitive scores (n=92, aged 17-35 years, 49% male).

Research by Hausmann et al. (2000) and Aleman et al. (2004) explored the relationship between sex-steroid hormones and differences in cognitive function by administering testosterone to women. They identified a significant improvement in mental rotation, a trait typically excelled at by males. Interestingly, a fraternal twin study by Heil et al. (2011) also found that females with male twins outperformed a control group in mental rotation (n=400, age range 19-39 years, 100% female). This was attributed to the impact of placental androgens on cerebral development. Other researchers have also shown that oestrogen administration significantly enhances verbal and linguistic performance in women (Berent-Spillson et al., 2015, Ghidoni et al., 2006).

Table 1.4 Sex-specific differences in cognitive performance

Superior cognitive performance	
Males	Females
Visual orientation tasks	Verbal fluency
Spatial orientation tasks	Verbal memory
Target accuracy	Fine motor skills
Mathematical reasoning	Emotional perception

Table 1.4 compares the cognitive strengths in males and females. Despite these differences, there are many more cognitive similarities between the sexes and a particular cognitive strength does not imply dysfunction in the opposite sex. Adapted and modified from p863 Weiss et al., (2003).

Females undergo significant changes in sex-steroid hormones during a midlife period known as menopause, which is signified by the almost complete loss of oestrogen (Rosario et al., 2011). Oestrogen loss has been linked with increased beta-amyloid formation, resulting in synaptic dysfunction and impaired cognition. Without the neuroprotective benefits of oestrogen, women are at higher risk of developing dementia than males (Pike et al., 2009, Aviv, 2007). Manly's research team (2000) showed plasma levels of oestrogen are lower in females with AD (n=50) compared to age-matched controls (n=93). Unexpectedly, the Women's Health Initiative Memory Study (n=4500) assessed women aged 65 to 79 years and found cognition did not improve with hormone replacement therapy (HRT) (Shumaker et al., 2003). However, these results may be attributed to lower hormone responsivity in older age samples (Pike et al., 2009).

In contrast, research by Paganini-Hill and Henderson (1994) found that HRT reduced the risk of developing AD, decreasing relative to the increase in duration and dose of the therapy (n=8877). Several other studies support these findings, showing that women with a history of HRT use were at reduced risk of cognitive impairment and had increased hippocampal grey matter density (Carlson et al., 2001, Zandi et al., 2002, Neufang et al., 2009).

Variations in the study outcomes above may be explained by the age at which HRT is administered, with peri-menopausal treatment linked to the greatest reduction in the risk of developing AD and thus providing a critical window in which HRT effects are most

beneficial (Zandi et al., 2002, Craig et al., 2005). Additionally, women are at higher risk of sporadic AD in the presence of the APOE ϵ 4 allele than men with the allele (Corder et al., 2004). This is potentially due to the pronounced hippocampal atrophy (associated with memory impairments) experienced by women with this allele (Fleisher et al., 2005). In males, the presence of the allele has been linked with lower basal testosterone levels, also increasing susceptibility to AD (Strittmatter and Roses, 1995). A study on rodents by Ramsden et al. (2003) found a correlative triad between the presence of the APOE ϵ 4 allele, lower testosterone levels, and increased risk of AD in male rodents.

While men experience hormonal changes with aging (termed androgen deficiency in aging males), their loss of testosterone occurs gradually, typically beginning after 35 years and declining at an annual rate of 1-3% (Pike et al., 2009). Testosterone also offers neuroprotective benefits including maintaining neuron viability and reducing beta-amyloid levels (Brinton, 2004, Wise, 2006, Rosario and Pike, 2008). Kujawa (1993) found hamsters receiving HRT following damage to facial nerves experienced faster axonal growth and repair than those without. While, Rosario and colleagues (2011) showed lower testosterone levels were linked with MCI, hippocampal atrophy and increased beta-amyloid levels in 36 males aged 60 to 79 years. Testosterone has also been shown to increase visual spatial task performance in men. Cherrier et al. (2001a) demonstrated that testosterone treatment led to significant improvements in spatial and verbal memory in men aged 59-76 years (n=25).

Brain structures used for cognitive processes also differ significantly between males and females. Hill et al. (2014) performed a meta-analysis on working memory with neuroimaging and found that females recruit limbic and prefrontal structures while males access more parietal areas. Sowell's research team (2007) showed females had up to 0.45mm thicker parietal and temporal cortices, as confirmed by an age-matched permutation analyses in a sample aged 7-87 years (n=176). These and other supporting studies (Nopoulos et al., 2000, Allen et al., 2003) suggest there is a morphological basis for the differences in cognitive strengths between the sexes.

Other evolutionary, developmental, psychopathological, and societal factors also contribute to cognitive differences between the sexes, yet are beyond the scope and objectives of the present study. For further information on these factors see extensive

reviews by Miller and Halpern (2014), Hyde (2014), Halpern (2013) and Ceci et al., (2009).

1.2.3 Genetics and ethnicity

Certain genes and ethnic groups have been linked to an increased risk of cognitive impairment. Early onset AD (approximately 2% of cases) has been associated with mutations of the presenilin gene (presenilin-1 and presenilin-2) (Richard and Amouyel, 2001), which affects the proteolytic clearing of amyloid precursor protein resulting in increased beta-amyloid levels, a hallmark characteristic of AD (Haass, 1996).

There is a general consensus in the literature establishing that the APOE ϵ 4 allele as a risk factor for late onset AD (Elias et al., 2008, Kang et al., 2005, Jun et al., 2010, Whitehair et al., 2010). Approximately 40% of late-onset AD cases are carriers of the allele (Alzheimer's Disease Education and Referral Center, 2012), suggesting a significant proportion of AD cases are sporadic (Pastor and Goate, 2004).

The APOE ϵ 4 allele was discovered by Corder's research team (Corder et al., 1993) and has been linked with reducing the catabolism of beta-amyloid, a cerebral plaque characteristic of AD pathology, as well as impairing cholesterol transport, causing increased risk of cardiovascular disease (van Bockxmeer and Mamotte, 1992). Many population-based studies have related presence of the APOE ϵ 4 allele with decreased cognitive function, and in particular, memory dysfunction (Bretsky et al., 2003, Helkala et al., 1996, Small et al., 1998, Yaffe et al., 1997). A longitudinal study by Kang and colleagues (2005) examined a large cohort of women over an eight year period and found APOE ϵ 4 carriers performed worse across all cognitive tests when compared with controls (n=4227, age range 70-80 years). Kang's team also calculated that the presence of one APOE ϵ 4 allele was equivalent to being cognitively 2.5 years older, and carriers with two APOE ϵ 4 alleles aged cognition by 6 years, creating a substantial cognitive shift when regarded at a population level, with approximately 25-30% of the population presenting with the allele (Alzheimer's Disease Education and Referral Center, 2012). An imaging study by Soininen's group (1995) has provided insight into the physical manifestation of APOE ϵ 4 presence; showing that those with the APOE ϵ 4 allele had smaller hippocampal volume (involved in short-term memory). Other imaging research has shown that APOE ϵ 4 carriers exhibit decreased glucose metabolism in temporal and parietal cortices

(Reiman et al., 2004, Small et al., 2000), decreased medial temporal lobe volume (phonological memory) (den Heijer et al., 2002, Lemaitre, 2005, Wishart and Roth, 2006) and thinner cortical thickness in the entorhinal cortex and subiculum (Burggren et al., 2008). These cortical changes are reminiscent of cerebral changes in the early stages of AD (U.S. Department of Health and Human Services, 2012).

Ethnicity has also been correlated to AD risk. Work by Tang's group (1996) compared risks of AD in elderly African American (AD n=106, mean age 78 ± 8 years; control n=154, mean age 74 ± 6), Caucasian (AD n=59, mean age 71 ± 9 years; control n=112 mean age 72 ± 9 years) and Hispanic carriers of the APOE ϵ 4 allele (AD n=140 mean age 77 ± 8 years; n=219 mean age 73 ± 6 years) and found African Americans at lower risk of AD compared to Caucasians and Hispanics. Tang's team hypothesised that this difference may be due to interactions with environmental and genetic factors which may alter the effect of the gene (AD 76% female; control 67% female) (Tang et al., 1996). Overall, risk-adjusted incidence of AD (including non-APOE ϵ 4 carriers) is twice as high in African Americans and Hispanics than in Caucasians (Tang et al., 2001).

1.2.4 Pathologies

Different pathologies increase the risk of cognitive impairment. This may be attributed to various processes involved in those pathologies, such as chronic inflammation, changes in vasculature, changes in the cerebral biochemical environment (diabetes), cerebral blood flow (intra-cranial atherosclerosis), autonomic neuropathy, or infectious diseases (Creutzfeldt-Jakob’s disease). Table 1.5 lists diseases with the highest risk of cognitive impairment.

Table 1.5 Common pathological risk factors for cognitive impairment

Pathology	Factors impairing cognitive function
Normal pressure hydrocephalus	Increased cerebrospinal fluid volume placing abnormally high pressure on the brain (Klassen and Ahlskog, 2011)
Acquired immune deficiency syndrome	Infection of the central nervous system resulting in subacute encephalitis, multinucleate giant cells (fused macrophages with microglia), astrocyte hypertrophy, and dendritic malformations (Saksena et al., 1998)
Down syndrome	Dendritic spine malformations impairing synaptic transmission (Jenkins et al., 2012)
Diabetes mellitus (type 1 and 2)	Insulin resistance, increased production of beta-amyloid and increased risk of autonomic neuropathy, cerebral infarcts, hypertension, and atherosclerosis (Moheet et al., 2015, Roberts et al., 2014, Hamed, 2014, Jacobson et al., 2010)
Depression	Increased circulating glucocorticoids, decreased hippocampal volume, white matter changes and reduced neurotransmitter levels (Lebedeva et al., 2015, Vasudev et al., 2012)
Hyperlipidaemia	Increased risk of atherosclerosis, reducing cerebral blood flow (Etgen et al., 2010, Deckers et al., 2014)
Cardiovascular disease	Impaired cerebral perfusion, altering nutrient and oxygen supply to neurons, increasing risk of vascular dementia (e.g. stroke, hypertension, atrial fibrillation, atherosclerosis, and transient ischemic attacks) (Schneider et al., 2014, Downer et al., 2015, O'Donnell et al., 2012)

Table 1.5 lists common pathological risk factors for cognitive impairment (and dementia). Each disease state involves an altered cerebral biochemical environment or physically distorted neuronal transmission, potentially resulting in cognitive symptoms. Many other diseases may also impair cognitive function for the same reasons, such as brain tumours, syphilis and homocysteinemia.

1.2.4.1 Hypertension

The risk of cognitive impairment increases with the presence of cardiovascular abnormalities, particularly those that alter cerebral perfusion. Neurons require a constant supply of blood to provide nutrients for cell metabolism and to remove metabolic waste products. In instances where this is compromised, such as in ischaemic injury, the neuron cannot function at its optimum level, thereby impairing synaptic transmission, which, over time, may present as cognitive symptoms. Cardiovascular pathologies that compromise cerebral blood flow include abnormal BP (including hypertension), cardiomyopathies, intracranial atherosclerosis and cerebral infarcts (O'Donnell et al., 2012).

In particular, midlife hypertension has been strongly associated with cognitive impairment and the development of dementia later in life (Bendlin et al., 2010, Langbaum et al., 2012, Feinkohl et al., 2015, Yaffe et al., 2014). The longitudinal Atherosclerosis Risk in Communities Neurocognitive Study by Gottesman et al. (2014) assessed 13476 subjects over 20 years and identified those with higher SBP had reduced attention, short term memory, and global cognitive performance scores (mean age 57 ± 6 years). Kilander and others (2000) found that lower BP in midlife predicted better cognitive performance 20 years later ($n=502$, mean age at follow up 72 ± 1 years, 100% male). In older age (over 80 years), higher BP may serve a homeostatic role, to maintain cerebral perfusion in response to age-related decreases in arterial elasticity (Whitmer et al., 2005). Therefore hypotension may also be a risk factor for cognitive decline in older age (Barnes and Yaffe, 2011).

Hypertension has also been linked to an increased risk of dysfunction of the autonomic nervous system (ANS) (Goit, 2015). The ANS is divided into two branches, sympathetic ('fight or flight') and parasympathetic ('rest and digest'), which act in concert to balance the body's metabolism, HR, BP and other physiological processes in response to environmental demands (Figure 1.9) (Furness, 2009). Many studies have demonstrated parasympathetic withdrawal and reduced cognitive performance in those with hypertension, attributed to alterations in the cerebral environment due to inflammation and vascular changes such as capillary shearing (Zulli et al., 2005, Scheatzle, 2009, Shehab and Abdulle, 2011, Thayer et al., 2010).

A meta-analysis by Barnes and colleagues (2011) calculated that approximately 5% of AD cases worldwide (approximately 1.7 million people) may be attributed to treatable midlife hypertension. As a modifiable risk factor, these numbers reinforce how crucial it is to maintain normal BP levels, particularly throughout midlife, to preserve cognitive function later in life.

Figure 1.9 Autonomic nervous system: Parasympathetic and sympathetic effector sites

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Figure 1.9 illustrates the effector sites innervated by the parasympathetic and sympathetic branches of the autonomic nervous system. Parasympathetic withdrawal has been linked to an increased risk of hypertension, cognitive impairment and an adverse cardiac event (Kim et al., 2006, Uchino et al., 2005, Shehab and Abdulle, 2011). Image adapted from Freeman (2005) (online).

1.2.4.2 Diabetes mellitus (DM)

Diabetes mellitus (DM) type 1 and type 2 involves the disordered regulation of insulin and/or insulin receptors, affecting the body's use of glucose. Poor glycaemic control has been associated with a range of immune, cardiovascular, autonomic, and neuronal changes, increasing the risk of cognitive impairment (Koekkoek et al., 2015, Ninomiya, 2014). Both hyperglycaemia (glucose toxicity) and hypoglycaemia (glucose starvation) have been associated with cognitive decline, yet poor glycaemic control (blood glucose fluctuation) has been proposed as the most significant contributor to cognitive decline and diabetic autonomic neuropathy (Kempler et al., 2002, Moțățianu et al., 2013, Tuligenga et al., 2014, Sünram-Lea et al., 2015).

1.2.4.2.1 Type 1 DM

Type 1 DM involves an immune-mediated degeneration of the pancreatic beta cells, reducing the production of endogenous insulin leading to a rise in blood glucose levels (Gispen and Biessels, 2000).

The relationship between cognitive decline and type 1 DM is complex, involving multifactorial metabolic and vascular changes which lead to reduced cognitive performance. Thickening of capillary basement membranes; reduced capillary density; reduced blood flow; production of inflammatory cytokines; reduced diacylglycerol and glutathione production (polyol pathway (hyperglycaemia)); increases in advanced glycation end products (hyperglycaemia); alterations in gene expression; elevated corticosterone levels; and increases in reactive oxygen species causing oxidative damage have all been identified as potential factors in the intricate pathogenesis of cognitive impairment in DM (Gispen and Biessels, 2000, Nasr et al., 2011, Mankovsky, 2003, Kim, 2008, Zheng et al., 2014). Such changes affect oxygen saturation and blood flow to neurons with some studies showing hypoperfusion and hypoxia of the endoneurium (Ibrahim et al., 1999, Tesfaye et al., 1993).

Structural and functional brain changes have also been identified in the hippocampus (involved in memory) as well as the autonomic ganglia (e.g. vagus nerve mediating HRV) in diabetes (Cameron and Cotter, 2001, Manschot et al., 2003, Sasaki et al., 1997). Diabetes-induced rat models have shown reduced vascularisation and circulation to

nerves in the first few days of the disease, followed by decreases in nerve conduction firing (Cameron et al., 1991, Coppey et al., 2000, Wright and Nukada, 1994).

ANS dysfunction is part of the neuropathogenesis of type 1 DM. Javorka et al. (2005) found that patients with type 1 DM had significantly reduced vagal control of HR (n=17, mean age 22 ± 1 years, 59% female). This is supported in a larger study by Jaiswal et al. (2013), which identified lower cardiac vagal activity and early signs of cardiac autonomic neuropathy in diabetic youth, particularly worsened by hyperglycaemia (n=354, mean age 19 ± 3 years). Interestingly, stringent glycaemic control has been shown to reduce ANS deterioration in type 1 DM (n=1441, mean age 27 years, 53% male) (The Diabetes Control and Complications Trial Research Group, 1993).

Vascular scarring from chronic glucose overexposure can lead to arterial stiffness and microvascular damage, resulting in hypertension and autonomic neuropathy. Ryan et al. (2003) found higher SBP, autonomic neuropathy, and macrovascular complications each independently worsened psychomotor speed in subjects with type 1 DM (n=103, mean age 34 ± 7 years, 58% female). These common co-morbidities are individual predictors of cognitive decline and cumulatively potentiate the cognitive decline seen in type 1 DM (Allan et al., 2014, Ferguson et al., 2003, van Ittersum et al., 2004, Machnica et al., 2014, Lurbe et al., 2002).

1.2.4.2.2 Type 2 DM

Type 2 DM is characterized by insulin resistance resulting in hyperglycemia (Hupfeld and Olefsky, 2016). This metabolic dysregulation can have a profound impact on inflammation, vasculature, and neuronal health (see Figure 1.10), increasing the risk of developing dementia by 50% (Biessels et al., 2006). Cognitive symptoms seen in type 2 DM typically involve a reduction in memory, processing speed, executive function, and global cognitive scores (Koekkoek et al., 2015, Feinkohl et al., 2015, Strachan and Price, 2014, Ravona-Springer et al., 2014, Rawlings et al., 2014b).

Figure 1.10 Factors contributing to cognitive dysfunction in type 2 diabetes

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Figure 1.10 displays several interrelated factors that may lead to cognitive impairment in type 2 diabetes. ‘Alzheimer disease pathology’ refers to an increase in beta-amyloid plaques in the brain, impairing neuronal function. Image adapted from Umegaki (2015).

A systematic review by Kloppenburn et al. (2008), examined the leading and often co-occurring vascular risk factors for cognitive impairment: type 2 DM, hyperlipidaemia, hypertension and obesity. They identified that the risk for developing dementia shifted with increasing age; hypertension was the leading risk factor for dementia in midlife, while type 2 DM led later in life. They justified this age differentiation by acknowledging that type 2 DM develops over time, often in the presence of other comorbidities that further deteriorate the vasculature. The additional burden of hyperglycaemia and insulin resistance on tissues could also fasten cognitive decline thereafter (Qiu et al., 2003). The intertwined existence of these risk factors render it difficult to distinguish a causal origin, such as obesity, atherosclerosis, and dyslipidaemia (Sowers et al., 2001).

The metabolic processes involved in chronic hyperglycaemic states also increase the risk of hypertension, such as nitric oxide release causing vasodilation, hyperinsulinaemia causing sympathetic predominance, smooth muscle proliferation, oedema, and renin–angiotensin–aldosterone system activation (Ferrannini and Cushman). Approximately 60% of patients with type 2 DM also have high BP. As discussed in the previous section 1.2.4.1, hypertension is an individual predictor of cognitive impairment and has an acceleratory effect on cognitive decline in type 2 DM (Ferrannini and Cushman). Petrova et al. (2010) found that higher BP in women with type 2 DM experienced significantly greater cognitive decline than normotensives (normotensive: $n=27$, mean age 53 ± 7 years; type 2 DM with hypertension: $n=113$, mean age 56 ± 7 years). Many neuroimaging studies have also identified significant cortical thinning, reductions in grey matter volume, increases in white matter hyperintensities, enlarged ventricle size, and more pronounced hippocampal, anterior cingulate and amygdalar atrophy in patients with type 2 DM, providing a structural correlate for the functional decline in cognition (Tchistiakova et al., 2014, Jongen et al., 2007, Kumar et al., 2008, den Heijer et al., 2003, Reijmer et al., 2011).

Type 2 DM also increases the risk of autonomic neuropathy due to increased inflammation causing oxidative stress, changes in vasculature causing capillary damage, and resultant cerebral pathologies such as anterior cingulate cortex atrophy (involved in

autonomic control). This has been shown by several studies finding reduced cardiac vagal tone in those with type 2 DM (Abubaker et al., 2014, Singh et al., 2000, Li et al., 2014). Subjects with type 2 DM and autonomic neuropathy commonly experience orthostatic hypotension, which can lead to further cognitive impairment due to transient neuronal circulation accompanying postural changes (Kempler, 2003).

1.2.4.3 Depression

Major depression also increases the risk of developing cognitive impairment (Bremner et al., 2000). Depression is a common psychiatric disorder that is characterised by depressed mood and anhedonia, and also involves a reduction in monoamine neurotransmitters: serotonin, dopamine, and norepinephrine (Nutt, 2008, Bremner et al., 2000), neurotransmitter receptor sensitivity and density, and an excess of cortisol in circulation. Increased cortisol levels damage hippocampal neurons which impairs feedback to the hypothalamus (unable to cease the stress response) (Figure 1.11) (Bartsch et al., 2011). Neuroimaging studies have identified reductions in prefrontal cortex and hippocampal volume in subjects with depression (Lebedeva et al., 2015, Ajilore et al., 2010, Bremner et al., 2000). The CA1 neurons of the hippocampus play a role in autobiographical and declarative memory (Brown et al., 2004) and the prefrontal cortex is involved in higher order reasoning and executive function (Lamar et al., 2013). Atrophy of these anatomical structures provides a basis for the cognitive symptoms seen in depression, chronic stress and burnout (e.g. decreased memory performance, verbal fluency, word association skills, selective attention and task switching ability) (Maslach et al., 2001, van der Linden et al., 2005, Sandstrom et al., 2005, Johnco et al., 2015). Wang's group (2012) used data from the Kungsholmen Project and found those with more stressful lives (as a surrogate for cortisol overexposure) had a higher risk for cognitive impairment and AD (n=913, >75 years old, 74% female). Alzheimer's Disease International estimated that depression almost doubles the risk of dementia based on a pooled estimate of recent publications (Prince et al., 2014).

Increased cortisol, inflammatory cytokines, medication use, sleep quality and frequency of depressive episodes all contribute to sympathetic overactivity and the additional risk of developing hypertension (Nabi et al., 2011, Gangwisch et al., 2010, Licht et al., 2009, Kemp et al., 2010). Nabi et al. (2011) found positive correlations between increased

frequency of depressive episodes and increased risk of high BP over 24 years (Whitehall II study) (n=10302, mean age 45 ± 6 years, 67% male). Sympathetic overactivity and high BP have previously been individually associated with cognitive decline (Kim et al., 2006, Nugent et al., 2011a, Thayer et al., 2012, Marin et al., 2011, Reppermund et al., 2011) and may further contribute to the increased risk of cognitive decline associated with depression. Increasing parasympathetic activity has been associated with both better cognitive performance and successful depression recovery and is used as an autonomic biofeedback target (Allen et al., 2015, Hansen et al., 2009, Siepmann et al., 2008).

Figure 1.11 Negative feedback of cortisol in the hypothalamus-pituitary-adrenal axis

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Figure 1.11 shows the negative feedback of cortisol (secreted by the adrenal cortex) on corticotropin-releasing hormone and corticotropin secretion. In the stress response, the amygdala perceives the threat, and activates the hypothalamus to release corticotropin-releasing hormone. The hippocampus detects cortisol levels and inhibits the hypothalamus, ceasing the stress response. Chronic exposure to cortisol withers the hippocampal neurons, disrupting negative feedback to the hypothalamus, resulting in overactivity of the hypothalamus-pituitary-adrenal axis and increased risk of cognitive impairment, anxiety, depression, and other conditions. Image adapted from Antranik.org (2012).

1.2.5 Lifestyle

Various lifestyle influences are modifiable risk factors for cognitive impairment. For example, with increasing age, a lack of mental and social engagement has been shown to increase risks of dementia, and conversely, those maintaining such engagement are less likely to develop cognitive impairment (Wang et al., 2002). This cognitive engagement helps retain neuronal networks, attention control processes and neuronal plasticity over time (Hotting et al., 2013). Other lifestyle risk factors include poor diet and lack of exercise (Reitz and Mayeux, 2014). A brief overview of the most common modifiable risk factors for cognitive impairment is depicted in Table 1.6.

Table 1.6 Modifiable risk factors for cognitive impairment

Modifiable risk factor	Concern for cognitive function
Smoking	Poor cardiovascular health; increased risk of oxidative damage, microvascular damage, stroke, VaD, and AD (Corley et al., 2012, Cataldo et al., 2010)
Chronic alcoholism	Reduced temporal and hippocampal volume, associated thiamine deficiency can lead to Wernicke-Korsakoff dementia (Peters, 2012, Beresford et al., 2006, Zhou et al., 2003)
Poor diet	Nutrient deficiencies, obesity, and cardiovascular diseases such as coronary heart disease and stroke (Hosking et al., 2014, Chugh et al., 2013, Vercambre et al., 2012, Kanoski and Davidson, 2011)
Lack of exercise	Obesity and cardiovascular diseases such as coronary heart disease and stroke (Tarumi et al., 2013, Brown et al., 2010)
Chronic stress	Circulating glucocorticoids wither hippocampal neurons and lead to memory impairments over time (Munoz et al., 2015, Marin et al., 2011)
Low cognitive reserve	Brain reserve hypothesis states fewer years of education increase the risk of AD as reduced synaptic density is less able to cope with the cerebral changes in AD (Alipour and Goldust, 2015)

Table 1.6 summarises common modifiable risk factors for cognitive impairment and dementia. Interestingly light-moderate alcohol intake has been linked with a reduced risk of developing AD (Stampfer et al., 2005). Key: AD = Alzheimer’s disease; VaD = Vascular dementia

1.3 Heart rate variability (HRV)

Spectral analysis of HRV can be employed to investigate the parasympathetic and, to a lesser extent, sympathetic activities of the ANS (Pumprla et al., 2002, Acharya et al., 2008). HRV refers to the variation in time intervals between consecutive heartbeats (Pumprla et al., 2002). As shown in Figure 1.12, the interval between heartbeats is typically measured from one R peak (of the QRS complex from an electrocardiogram (ECG)) to the next R peak (the R-R interval). Increased HRV signifies adaptability and reactivity to one's surroundings (Sztajzel, 2004). While most of the existing literature suggests further research should be undertaken in the area of HRV analysis and cognition (Lopez et al., 2015, Jennings et al., 2015, Luft et al., 2009), some researchers have promoted the use of HRV data as a powerful marker of cognitive decline (Collins et al., 2012).

The sinus node of the heart acts as a pacemaker, regulating the heart rate to accommodate metabolic demand (Figure 1.13). It is densely innervated by both the parasympathetic and sympathetic divisions of the ANS (Pumprla et al., 2002). 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 moderated by the vagus nerve via acetylcholine release, which is quickly metabolised (Pumprla et al., 2002). The distinct turnover rates of the two chemical transmitters result in variations between frequencies and fluctuations of HR producing a complex variability characterised by HRV analysis (Thayer et al., 2009). These variations have been identified and quantified to establish different bandwidth frequency standards at which the two autonomic subsystems function (Thayer et al., 2009). Baseline HR is driven by parasympathetic activity, known as tonic inhibitory control. A pioneering cardiac study illustrated this concept by injecting the heart with atropine and propranolol to block both sympathetic and parasympathetic innervations resulting in a higher intrinsic resting HR than in baseline (Jose and Collison, 1970). Resting parasympathetic cardiac control (vagal modulation) has been hypothesised to favour energy conservation (Thayer and Brosschot, 2005).

Figure 1.12 R-R interval tachogram

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Figure 1.12 represents an electrocardiogram recording. The R-R interval is the duration of time between two consecutive QRS intervals, used to derive HRV data. Depolarisation in the heart triggers mechanical contraction of the myocardium. Adapted and modified from 2nd Hour Anatomy (2011).

Key: P = Atrial depolarisation generated by the sinoatrial node; Q = Depolarisation of the interventricular septum; QRS interval = Duration of time for ventricular depolarisation consisting of the Q, R, and S waves; RR interval = Duration of time between consecutive R waves; S = Ventricular depolarisation; T = Ventricular repolarisation

Figure 1.13 Illustration of the heart's electrical conduction system

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Figure 1.13 illustrates the heart's electrical system, depicting the SA node ((1) upper right atrium) propagating electrical impulses which lead to myocardial contraction. The AV node (2) receives these impulses, which further trigger contraction through the conduction pathways to the ventricles. Image adapted from Belk and Maier (2009) (online).

HRV analysis has been used in a variety of clinical applications, including detection and assessment of severity of autonomic neurodegeneration in diabetic patients (Rizzo et al., 2014), risk assessment for cardiac events and mortality (Ewing et al., 1985, DePace et al., 2014, Thayer et al., 2010), and measuring foetal distress during labour (Van Laar et al., 2013). Studies have established a correlation between low HRV (sustained increased sympathetic activity) and an increased risk of anxiety disorders, affective disorders, and premature death (Pumprla et al., 2002, Thayer and Lane, 2007, Thayer and Brosschot, 2005). High HRV, generally considered a marker of good health, has been linked with pathologies such as bradycardia, apnoea and foetal distress (Porges, 2009).

1.3.1 Frequency domain HRV

Frequency domain measures of HRV are derived based on a number of steps. First, a measurement of the R-R interval is taken from the ECG (Figure 1.14 a)). The time differences between R-R intervals are then plotted on a time series graph (Figure 1.14 b)). Next, the fast Fourier transform (FFT) (a non-parametric algorithm) (Welch, 1967) is applied to produce a spectrogram that models the power densities of the R-R intervals (Figure 1.14 c)). In the spectrogram, power is the unit of measure and is represented by the area underneath the curve (Pichon et al., 2006).

Figure 1.14 Deriving frequency domain HRV data

A)

B)

C)

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Figure 1.14 illustrates the derivation of HRV frequencies; adapted and modified from Pichon et al., (2006). A) The electrocardiogram, showing the R-R intervals. B) The plotting of time intervals between R-R peaks. C) The spectrogram is derived from the time series graph in step B) applied with a FFT algorithm. Power is the unit given for the total area under the curve.

Key: FFT = Fast Fourier transform; HRV = Heart rate variability; Hz = Hertz; ms² = milliseconds squared

Frequency domain data is categorised into two main bandwidth components: high frequency (HF) and low frequency (LF) (Tulppo and Huikuri, 2004). These components have different frequency ranges reflecting autonomic activity (Table 1.9 (see end of section 1.3.2)). The HF band, ranging from 0.15-0.5Hz, is a fairly pure representation of parasympathetic cardiac influence, whereas the LF bandwidth ranges from 0.04-0.15Hz and reflects combined parasympathetic, sympathetic, respiratory, and more recently theorised, baroreceptor activity (Thayer et al., 2010, Reyes del Paso et al., 2013). Billman (2013) suggests that the LF band is driven by 50% parasympathetic, 25% sympathetic, and 25% unknown activity (possibly mechanical change, baroreceptor, and respiratory activity). Cohen and Taylor (2002) suggest the HF band is driven by 90% parasympathetic and 10% sympathetic activity. The apportionments for each band were explored during surgery by selectively chemically antagonising and denervating the parasympathetic and sympathetic cardiac input while monitoring HRV (Akselrod et al., 1981, Randall et al., 1991, Houle and Billman, 1999).

A neurochemical index for cardiac sympathetic activity, known as coronary sinus plasma norepinephrine, has not been shown to be correlated with LF or a majority of the LF band (Moak et al., 2007, Baumert et al., 2009). Experiments selectively denervating cardiac sympathetic input in combination with beta-adrenergic blockade did not abolish LF (Randall et al., 1991). In addition, disease states with known increased sympathetic activity, such as heart failure, have been correlated with low rather than high LF (Moak et al., 2007, Notarius and Floras, 2001, Jardine et al., 2002, Piccirillo et al., 2009, Watson et al., 2007).

These findings highlight contention in the existing research regarding the clinical significance of the LF band and use of the LF/HF ratio to describe ‘sympathovagal balance’ (Billman, 2013). Further, the LF/HF ratio assumes that the branches of the ANS function in a linear reciprocal fashion, that is, where one increases the other decreases. This is not the case for the physiological reality of non-linear ANS activity (Table 1.7) (Berntson et al., 1997, Eckberg, 1997, Parati et al., 2006, Billman, 2011, Billman, 2009).

Each branch of the ANS is dynamic. Berntson et al. developed the autonomic space model as a theory under which LF band activation may be coupled with HF deactivation, or vice versa (Table 1.7) (Berntson et al., 1991). The theory also describes co-activation and co-inhibition where both the LF and HF activity are increased or suppressed (respectively),

known as ‘coupled’ activity. ‘Uncoupled’ activity is where the HRV parameter (LF or HF) either increases or decreases while the other branch remains the same. Berntson et al.’s autonomic space model (1991) allows researchers to better understand the combinations of frequency changes in response to stimuli, and promotes a deeper analysis into links to pathological states such as cognitive impairment.

Table 1.7 Autonomic space model

		HF HRV		
		Decrease	No change	Increase
LF HRV	Increase	Reciprocal LF increase	Uncoupled LF increase	Coupled co-activation
	No change	Uncoupled HF withdrawal	Equilibrium baseline	Uncoupled LF increase
	Decrease	Coupled co-inhibition	Uncoupled LF withdrawal	Reciprocal HF increase

Table 1.7 depicts Berntson et al.’s autonomic space model, explaining the various combinations seen in clinical assessment of HRV parameters. ‘Coupled’ refers to the LF and HF cardiac activity with the same direction whereas ‘uncoupled’ refers to one frequency bandwidth remaining unchanged while the other either increases or decreases power. ‘Reciprocal’ refers to the HRV parameters operating in opposing directions. Adapted and modified from Berntson et al. (1994, 1991).

Key: HF = High frequency; HRV = Heart rate variability; LF = Low frequency

HRV is also influenced by sex. Sloan et al. (2008) compared HRV between the sexes and found that females had lower levels of sympathetic activity and lower sympathovagal balance (n=757, age range 33-47 years, 58% female). Other studies oppose these findings, showing higher parasympathetic dominance (Kuo et al., 1999, Ryan et al., 1994) or no HRV differences at all (Evans et al., 2001, Pikkujamsa et al., 2001), which highlights the need for further analysis.

Table 1.8 provides a summary of studies comparing HRV between sexes. Although it is not fully understood why autonomic activity differs between sexes, experiments

conducted on rat models have discovered that increased levels of oestrogen enhance parasympathetic and suppress sympathetic activation (Li et al., 1997, Baker et al., 1978, Zukowska-Grojec et al., 1991, Sullivan and Davison, 2001). These hormonal effects have also been demonstrated to some extent in female humans, where natural increases in oestrogen over the menstrual cycle (luteal phase) were associated with increased parasympathetic tone (Sato and Miyake, 2004).

Table 1.8 Summary of studies comparing HRV between females and males

	Study	Provided age data (years)	Sample size (% female)
Males have higher HRV	Bonnemeier et al. (2003)	42 ± 15	166 (49)
	Cowan et al. (1994)	54 ± 15	111 (64)
Females have higher HRV	Fagard et al. (2001)	25-89	n=614 (unavailable)
	Snieder et al. (2007)	44 ± 7	406 (48)
Men have higher LF and women have higher HF	Antelmi et al. (2004)	40 ± 12	653 (55)
	Huikuri et al. (1996)	51 ± 6	188 (50)
	Kuo et al. (1999)	40-79	1070 (56)
	Sato and Miyake et al. (2004)	21 ± 2	28 (50)
No significant difference in HRV	Nugent et al. (2011b)	32 ± 9	22 (32)

Table 1.8 shows contention in the literature as researchers have found different results in HRV values between females and males.

Key: HF = High frequency; HRV = Heart rate variability; LF = Low frequency

HRV is also influenced by respiration, which causes a slight cyclical variance at rest seen in both the LF and HF frequencies (and can be controlled for by paced breathing methods) (Brown et al., 1993, Hayano et al., 1996, Tzeng et al., 2009, Ben-Tal et al., 2012, Elstad, 2012). In addition, natural fluctuations in BP that occur at rest also marginally affect LF and HF data (Sleight et al., 1995, Mendonca et al., 2013). Slow cyclical variations occurring below 0.01Hz (very low frequency (VLF) and ultra low frequency (ULF)) have not been entirely quantified yet have been associated with changes in thermoregulation, peripheral chemoreceptors, and the renin-angiotensin system (Duprez et al., 1995, Fleisher et al., 1996, Ponikowski et al., 1997, Jarrin et al., 2012).

1.3.2 Time domain HRV

HRV data can also be examined in time domain indices, providing information on variability over time. The time domain measures used in the present study are HR, mean R-R interval, standard deviation of NN intervals (SDNN), root mean square of successive differences (RMSSD), and the percentage of NN intervals greater than 50 milliseconds (pNN50) (each described in Table 1.9). Other time domain, geometric and non-linear measures require time segments longer than 10 minutes (such as 24 hour readings) (Task Force of The European Society of Cardiology and The North American Society of Pacing and Electrophysiology, 1996) and were therefore inappropriate to include in the present study. Also note that the total amount of time variance in an ECG recording increases with the length of the recording and therefore it is recommended to only compare data from recordings of similar length (Task Force of The European Society of Cardiology and The North American Society of Pacing and Electrophysiology, 1996).

RMSSD and pNN50 provide information on cardiac vagal control and are correlated with HF activity (Luft et al., 2009, Achten and Jeukendrup, 2003, Kim et al., 2006). Research has shown SDNN has more of a mixed autonomic input from both parasympathetic and sympathetic branches as well as circadian and respiratory influence (an equivalent to total power (TP) in the frequency domain) (Billman, 2011, Xhyheri et al., 2012, Friedman et al., 2002).

Many studies agree that decreases in time domain parameters (SDNN, RMSSD, and pNN50) are linked to parasympathetic (vagal) withdrawal (Billman, 2009, Pai et al., 2013, Li et al., 2009). Vagal withdrawal has been associated with various cardiovascular diseases (such as hypertension) and an increased risk of cognitive impairment, as discussed in the following section 1.3.3 (Thayer et al., 2010, Kim et al., 2006, Uchino et al., 2005, Shehab and Abdulle, 2011).

Table 1.9 Frequency and time domain HRV parameters

	Measure	Units	Description
Frequency domain methods	Ultra low frequency (ULF)	ms ²	<0.003 Hz
	Very low frequency (VLF)	ms ²	0.003-0.04 Hz
	Low frequency (LF)	ms²	0.04-0.15 Hz
	High frequency (HF)	ms²	0.15-0.40 Hz
	Total power (TP)	ms²	VLF + LF + HF
	Sympathovagal balance		LF/HF*100
Time domain methods	SDNN	ms	Standard deviation of all NN intervals (square root of the variance)
	SDANN	ms	Standard deviation of averaged NN intervals calculated from a series of epochs of identical durations (commonly 5 minute segments) for the entire recording period
	RMSSD	ms	Square root of the mean squared differences of successive NN intervals
	SDNN index	ms	Mean of the standard deviations of all NN intervals for all 5 minute segments of the entire recording
	SDSD	ms	Standard deviation of differences between adjacent NN intervals
	NN50 count		Total number of interval differences (>50ms) of consecutive NN intervals
	pNN50	%	NN50 count divided by the total number of NN intervals

Table 1.9 describes a range of frequency and time domain HRV measures. The parameters in bold were used in the present study. Adapted and modified from Tarvainen et al. (2008) and The Task Force of the European Society of Cardiology and The North American Society of Pacing and Electrophysiology (1996).

Key: HRV = Heart rate variability; Hz = Hertz; ms = Milliseconds; ms² = Milliseconds squared; NN = Consistent point on the electrocardiogram trace between two cardiac cycles e.g. one R wave to the next R wave

1.3.3 HRV and cognitive function

Spectral analysis of HRV can be used to investigate the parasympathetic and, to a lesser extent, sympathetic activity of the ANS (Pumprla et al., 2002, Acharya et al., 2008). The ANS is controlled by several brain structures known collectively as the central autonomic network, which integrate information to produce sympathetic and/or parasympathetic responses (Thayer and Brosschot, 2005). The central autonomic network includes neural circuits within the prefrontal cortex (PFC), insular cortex and the limbic system (Matsukawa, 2012, Thayer and Brosschot, 2005). The same areas of the brain are also important for cognitive processes, in particular, the PFC, anterior cingulate gyrus, insular cortices, orbitofrontal cortex and the amygdala (Critchley, 2009, Parasuraman and Jiang, 2012, Matthews et al., 2004b). The Braak and Braak theory (1991) states that areas of the central autonomic network undergo the greatest and earliest neuropathological changes in AD (neurofibrillary tangles and beta-amyloid plaques) resulting in autonomic dysfunction. There is therefore a case for the use of HRV analysis to detect early signs of autonomic dysfunction and cognitive impairment (Braak and Braak, 1991).

The PFC, for example, normally maintains inhibition of the amygdala and the stress response via gamma-aminobutyric acid projections (inhibitory neurotransmitter). When the stress response is elicited (sympathetic activation), the PFC becomes hypoactive in order to disinhibit the amygdala, promoting the stress response and consequential innervation of the stellate ganglia to the heart (increased HR, decreased HRV (vagal withdrawal) (Thayer and Sternberg, 2006). As the PFC is hypoactive in this state, its function is compromised, resulting in a hypervigilant and defensive state with impaired cognitive flexibility (e.g. higher order reasoning) (Thayer and Sternberg, 2006, Beaumont et al., 2012, Thayer and Friedman, 2004).

Other research has demonstrated various HRV links to cognitive function, although there remains much contention in the literature. Lacey and Lacey conducted a study in 1958 which first depicted changes in HRV with cognition (Lacey and Lacey, 1958). The team took 15 minute baseline readings of HRV in 42 women aged 23-51 years and noticed that HRV declined during application of mental arithmetic and word fluency tasks. They proposed that cognitive demands influence autonomic fluctuations (later understood as high HRV, parasympathetic dominance) (Lacey and Lacey, 1958). A subsequent study by Richards (1987) expanded on these findings, observing infants with higher HRV were

less distractible (better attention skill). These studies formed the basis for the polyvagal theory developed by Porges (1992), which states that the vagus nerve (mediator for parasympathetic innervation of the heart) plays a large role in attention skill. Porges showed that increased vagal influence was linked to better attention function and increased sympathetic drive is linked to reduced attention skill (Porges, 1992). This polyvagal theory prompted the development of the neurovisceral integration model. This model proposes that cortical control of HR is linked to the level of engagement in the cognitive task (attention), various autonomic feedback processes, and the patient's affective state which interrelate to produce goal-directed behaviour. When these systems are compromised, anxiety disorders may arise (uninhibited stress response) (Thayer and Lane, 2000).

Most studies agree that higher cardiac vagal tone (quantified by increased HF, LF, RMSSD, and pNN50) is associated with better cognitive performance and vice versa. Lopez et al. (2015) examined a large sample of 10623 individuals as part of the Atherosclerosis Risk in Communities study and found that lower HRV was linked to reduced scores in word recall, digit symbol substitution and word fluency tests (mean age 54 years, 57% female). Similarly, a cross-sectional analysis of data from the Irish Longitudinal Study on Aging by Frewen et al. (2013) examined 4763 adults and identified those with lower LF significantly correlated to poorer recall, language, and global Montreal Cognitive Assessment scores (mean age 62 ± 8 years, 45% male). Supporting these findings, others have shown that the opposite relationship is also valid, for example, Gillie et al. (2013) showed higher baseline HF significantly improved cognitive inhibition tasks ($n=85$, mean age 18 years, 64% female). Hansen's team (2003) divided 53 male military personnel aged 18-34 years into high and low HRV groups depending upon their baseline HRV and found those in the high HRV group performed better in calculation, accuracy and memory tasks. Higher LF activity has also been linked to better cognitive performance, attributed to more parasympathetic tone contributing to the LF band (Solernó et al., 2012, Murtazina, 2015).

Interestingly, HRV parameters may affect cognitive domains differently. Luft et al. (2009) showed the LF/HF ratio was lower during working memory and executive functioning tasks yet increased in tasks requiring quick reaction times ($n=30$, age range 16-25 years, 77% male). Mukherjee and colleagues (2011) also found that the LF/HF ratio decreased with increasing difficulty of the task ($n=40$, age range 65-83 years, 65%

female). They hypothesised that HRV is related to the type of cognitive skill, initiated by neuronal engagement and the possible activation of the stress response. Melis and van Boxtel (2001) reported high LF was associated to better performance in spatial tasks yet poorer time-limited verbal reasoning ability, where parasympathetic activity was beneficial (n=52, mean age 22 ± 3 years, 52% female). They hypothesised that the findings were a result of hemispheric lateralisation of autonomic function, with different cognitive domains (associated with different areas of the brain) influenced by ANS activity. In other words, skills needed during ‘fight or flight’ situations (spatial ability, quick reaction times and escape) use the visual and motor cortices, while ‘rest and digest’ skills (working memory and reasoning) recruit the PFC. This is further demonstrated in a recent study by Solernó and co-workers (2012) (n=19, 22 ± 1 years, 53% female), showing that increased time and frequency domain activity (RMSSD, SDNN and HF, reflecting vagal dominance) was correlated to higher verbal reasoning scores over spatial reasoning.

As part of the Women’s Health and Aging Study (Guralnik et al., 1995), Kim’s team (2006) evaluated the links between cognitive function and HRV in disabled women aged over 65 years (n=311). They found that low HF power (with no significant alteration to LF spectra) was linked to 6.7 times the risk of developing cognitive impairment and hypertension. As BP is controlled by the ANS, it may be tentatively deduced that HRV indirectly reflects BP. Therefore HRV depicting vagal withdrawal may be linked to higher BP. In a similar experiment, Collins and colleagues (2012) compared 97 MCI patients (n=97, age range 69-77 years, 59% male) to 36 controls (n=36, age range 68-75 years, 54% female) using a 10 minute ECG to extrapolate HRV data. The MCI group reported significantly reduced cardiac parasympathetic tone compared to the control group. The MCI patients had 5.6 times the risk of autonomic dysfunction than the control group, a similar figure to Kim et al. (2006). Galluzzi et al. (2009) identified low RMSSD and LF, often associated with cognitive impairment, were also significantly linked to white matter lesions in patients with MCI (n=42, mean age 69 ± 7 years, 63% female).

In contrast, Allan and collaborators (2005) found no significant relationships between spectral HRV in AD (n=14, mean age 77 ± 6 years, 71% female) or VaD (n=20, mean age 81 ± 5 years, 75% male) compared to controls (n=80, mean age 76 ± 6 years, 50% male), although HRV durations were shorter (5 minutes), which may reduce the chance of identifying subtle autonomic differences.

Vagal reactivity (degree of change) and recovery (time to return to baseline) have also been linked to cognitive performance. Capuana's research (2014) identified increases in vagal reactivity (measured by respiratory sinus arrhythmia (RSA) reactivity) were associated with improved accuracy during a conscious inhibition task (Stroop task (inhibition task involving naming colours of neutral, congruent and incongruent stimuli) (Stroop, 1935)) (n=17, age range 18-26 years, 35% male). Decreased RSA recovery time from cognitive stressors has also been associated with better executive function skills (inhibition and attention switching), suggesting quicker cardiac recovery enhances executive function (n=817, mean age 57 ± 11 years, 44% male) (Kimhy et al., 2013).

Literature focuses heavily on HR reactivity rather than HRV reactivity. Longitudinal research from the West of Scotland Twenty-07 Study by Ginty and partners (2011) assessed a younger cohort, starting at ages 15, 35 and 55 years (n=1647, 54% female). Cognitive ability and HR reactivity was examined 5 and 12 years later. Significant associations were found between higher HR reactivity (parasympathetic dominance), higher general intelligence and interestingly lower cognitive decline in follow-up years. This may suggest a potential relationship between higher HR reactivity and lower future cognitive decline, however, further research is required to examine the link to HRV reactivity.

In contrast to a majority of the literature, the UK Whitehall II Study by Britton's team assessed a large cohort of 5375 males and females (mean age 56 ± 6 and 61 ± 6 years, respectively) and found no correlations between HRV parameters and cognitive function (2008). In further contrast, Keen's doctoral thesis (2011) identified lower vagal tone (RSA) was linked to increased executive function and acknowledged his findings were inconsistent with existing research (n=106, mean age 20 ± 3 years, 74% female). Similarly, Martinez et al. (2014) identified inverse correlations between executive function and SDNN and RMSSD (n=103, mean age 73 ± 6 years, 100% female). These studies show that low HRV has not been consistently associated with poorer cognitive performance.

Research conducted by de Vilhena Toledo and Junqueira (2008) assessed HRV and cognitive function in 22 AD patients (mean age 80 ± 1 years, 91% female). Those with more severe cognitive impairment, graded according to the Cambridge Cognitive Examination (Roth et al., 1986) and the Mini-Mental State Examination (MMSE)

(Folstein et al., 1975), were significantly linked to lower parasympathetic modulation. This relationship suggests that autonomic dysfunction in dementia may have the potential to be used as an early clinical detection tool. In support, Murakami and colleagues (2002) found dementia patients had significantly lower LF and LF/HF ratio measures than controls (dementia $n=71$, mean age 78 ± 3 years, 61% female; borderline $n=18$, mean age 79 ± 4 years, 67% female; control $n=25$, mean age 83 ± 5 years, 44% female). They suggested that neuro-anatomical dysfunction in those with cognitive impairment paralleled the disease progression; prompting the suggestion that HRV is a useful tool to predict severity of cognitive decline. Zulli et al. (2005) have also illustrated these findings, comparing 24 hour HRV and cognitive function in 33 AD patients (mean age 72 ± 8 years, 61% female), 39 patients with MCI (mean age 70 ± 7 , 59% female) and 29 controls (mean age 70 ± 5 years, 66% female). They concluded that total HRV (both LF and HF spectra) declined proportionally, paralleling the extent of cognitive impairment (AD patients had the lowest HRV compared to MCI, which was lower than the control group).

The disparities in the research highlight the need for further investigation in the area of autonomic activity and cognition. Contention in the literature may be attributed to differences in research methods such as ECG recording duration, sample size, sex (see Table 1.8), age exclusion criteria (health status), circadian rhythm, exercise, years of education, breathing pattern (RSA) and cognitive assessment tools. Most studies agree that HRV has the potential to be used to identify autonomic dysfunction and that there is a link between HRV activity and cognitive function. Refer to Table 1.10 for an outline and comparison of studies assessing HRV parameters and cognitive function.

Table 1.10 Summary of studies examining HRV and cognitive function

Study	Provided age data (years)	Sample size (% female)	HRV parameter
Positive correlation between HRV and cognition			
De Vilhena Toledo and Junqueira (2009)	80 ± 1	22 (91)	pNN50, RMSSD, HF
Frewen et al. (2013)	62 ± 8	4763 (55)	LF
Gillie et al. (2013)	18	85 (64)	HF
Hansen et al.(2003)	18-34	53 (0; (100% male)	RMSSD
Kim et al. (2006)	>65	311 (100)	RMSSD, HF
Lopez et al. (2015)	54	10623 (57)	LF
Melis and van Boxtel (2001)	22 ± 3	52 (52)	HF
Shehab and Abdulle (2011)	38 ± 11	69 (49)	RMSSD
Solernó et al. (2012)	22 ± 1	19 (53)	RMSSD, SDNN, HF
Negative correlation between HRV and cognition			
Galluzzi et al. (2009)	69 ± 7	103 (100)	RMSSD
Keen (2011)	20 ± 3	106 (74)	RSA
No association between HRV and cognition			
Britton et al. (2008)	58 ± 6	5375 (28)	No link

Table 1.10 summarises findings from research conducted on HRV and cognitive function. Most studies identify a positive relationship between vagal activity (as measured by HRV) and cognitive performance.

Key: HF = High frequency; HRV = Heart rate variability; LF = Low frequency; pNN50 = Total number of interval differences (greater than 50 milliseconds) of consecutive NN (beat to beat) intervals divided by the total number of NN intervals; RMSSD = Square root of the mean squared differences of successive NN intervals; RSA = Respiratory sinus arrhythmia; SDNN = SD of all NN intervals (the square root of variance)

1.3.4 Blood pressure (BP) and cognitive function

Over the past two decades many studies have shown relationships between BP and cognitive function. The majority of studies indicate that increased baseline BP is associated with a decline in cognitive ability, particularly those involving executive functions such as reasoning and working memory (Duron and Hanon, 2008, Eftekhari et al., 2007).

A large longitudinal study by Singh-Manoux and Marmot (2005) assessed the BP of 5,838 individuals aged 46-68 years from the Whitehall II Study (29% female). After two follow-ups, a small yet significant inverse relationship was found between high SBP and DBP and cognitive performance. There was also a gender disparity, with women exhibiting more pronounced cognitive deficits to increases in BP than men. High BP has been linked to increased white matter lesions and atherosclerotic plaques which may impair cerebral perfusion, leading to cognitive symptoms (Bos et al., 2012). Another longitudinal study, the Finnish Kuopio and Joensuu Study, examined the BP of 1449 individuals followed-up over 21 years and produced supporting results (mean age at follow-up 71 ± 4 , 62% female). High SBP (> 160 mmHg) during midlife increased the chance of cognitive impairment by 20% in later life (Kivipelto et al., 2001). This may suggest an ideal age range in which BP awareness and intervention is crucial to reduce risks of developing cognitive impairment.

Recent studies further support links between high BP and cognitive decline (Yaffe et al., 2014, Gustat et al., 2011, Exalto et al., 2014). Feinkohl et al. (2015) found that the level of high BP proportionally predicted the extent of cognitive decline four years later ($n=831$, mean age 68 ± 4 years, 52% male). Using data from The Atherosclerosis Risk in Communities Neurocognitive Study, Gottesman et al. (2014) also identified significant and inverse associations between SBP, attention and short term memory measured 20 years later ($n=13476$, mean age 57 ± 6 years). The opposite relationship between BP and cognition is also valid, with lower DBP throughout middle age predicting better cognitive performance at a 20 year follow-up ($n=502$, mean age 72 ± 1 years, 100% male) (Kilander et al., 2000).

Antihypertensive medications such as beta-blockers have been shown to slow cognitive decline progression in many large cohort trials (Forette, 2002, Gelber et al., 2013, The

Progress Collaborative Group, 2003, Starr et al., 1996). DeCarli (2015) promotes the use of antihypertensive treatments earlier in life as their neuroprotective benefits may limit cognitive decline in later years. The Third National Health and Nutrition Examination Survey examined younger age participants (20-59 years) and identified high SBP was a significant predictor for cognitive impairment in verbal learning and attention (n=2727) (Suhr et al., 2004). Such findings show high BP in both younger and older cohorts is a significant modifiable and preventable risk factor for cognitive impairment.

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 (Singh-Manoux and Marmot, 2005, Maillard et al., 2012). These factors often occur unbeknownst to the individual until more severe cognitive symptoms develop (potentially years later), as a cumulative manifestation of neuroanatomical changes.

In contrast, Kähönen-Väre's research team (2004) found individuals aged over 75 years with lower BP achieved poorer scores on the MMSE (n=650). Similarly, clinical studies of BP in AD patients show that BP declines proportionally with progression of the disease (Guo et al., 1996, Morris et al., 2000). This has been attributed to a degree of autonomic dysfunction accompanying dementia. Cross-sectional research as part of the Kungsholmen Project found low BP to be highly prevalent in dementia and AD cases (n=1642, mean age 82 ± 5 years, 76% female) (Guo et al., 1996). It was postulated that low BP was particularly detrimental in older populations due to reductions in basal cerebral blood flow. Reciprocating this concept, other researchers have also reported that increasing BP to borderline hypertensive ranges (150/90mmHg) benefits cognitive performance in those over 80 years old (Beckett et al., 2008). Increasing BP (parasympathetic withdrawal) naturally accompanies aging (Carrington et al., 2010), potentially as a compensatory mechanism to support cerebral perfusion, cognitive processes, and overall longevity in a system with reduced arterial compliance and less cardiac output (Hospers et al., 2014).

The inverted U-shaped hypothesis (Figure 1.15) accounts for the range of findings mentioned above, showing that both low and high BP are detrimental to cognitive

performance. According to this hypothesis, the body has a homeostatic range in which it functions best, with deviations either side of this range impairing optimal function. Morris et al. (2002) deduced that both higher BP ($> 190/95$ mmHg) and lower BP ($< 115/70$ mmHg) impaired cognitive scores ($n=5816$, age range 65-104 years, 61% female). Morris explained high BP increased brain infarcts and white matter lesions, while low BP led to cerebral degeneration and ischemic injury. Both BP extremes thereby alter cerebral blood flow and increase the risk of MCI and AD. This hypothesis suggests monitoring and potential manipulation of both high and low BP may be essential to preserving optimal cognitive function.

Figure 1.15 Inverted U-shaped hypothesis between blood pressure and cognitive performance

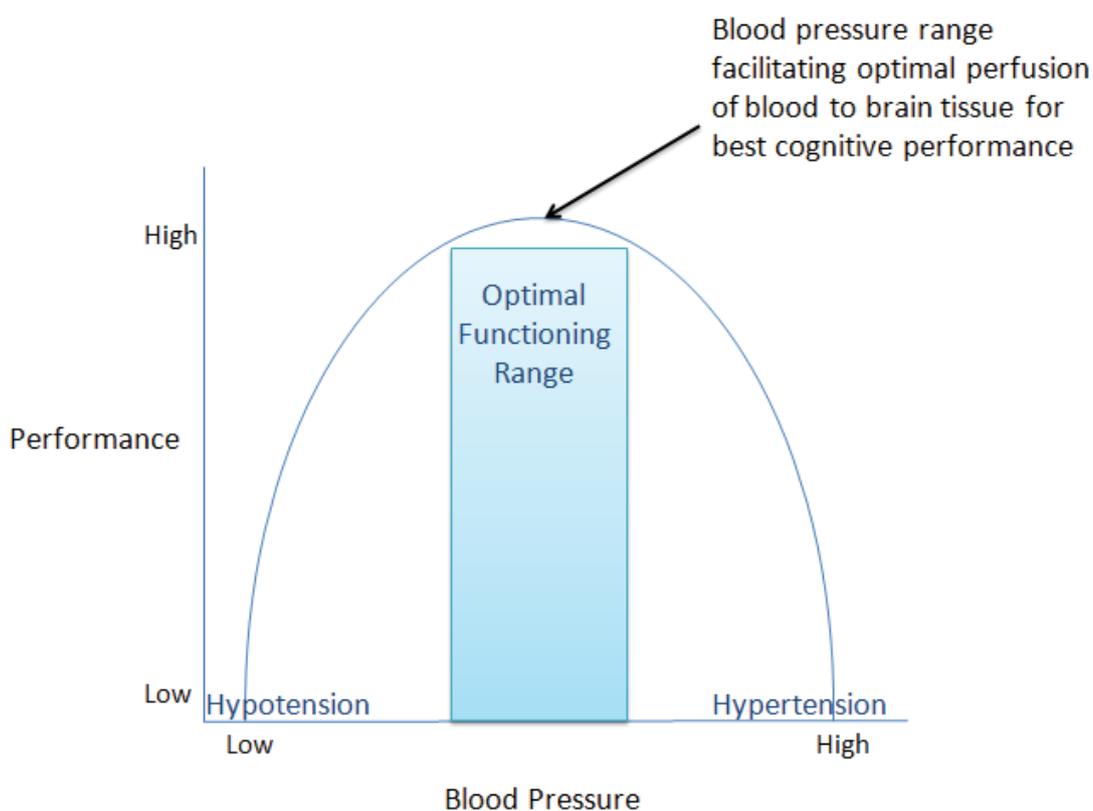


Figure 1.15 illustrates the inverted U-shaped hypothesis, which suggests blood pressure extremes (hypotension and hypertension) are linked to reduced cognitive performance. An adult human's optimal baseline blood pressure is approximately 120/80mmHg. Adapted and modified from Morris et al. (2002) and Waldstein et al. (2005).

Showing no support for these relationships, the Maastricht Aging Study by van Boxtel's group (1997) did not identify any significant associations between cognition and BP (n=936, age range 24-81 years, 49% female). In a subsequent and larger study by Di Carlo et al. (2000) no significant links between BP and scores on the MMSE were found (n=3425, mean age 74 ± 5 years, 52% female). Such disparities in the literature highlight the need for further research in the field of BP and cognitive function.

Research into BP reactivity and cognitive performance present fairly consistent findings. BP reactivity refers to the degree of change from baseline to a stimulus such as cognitive stress (e.g. mental arithmetic) or postural change (Gyekis and Gerin, 2015). Over- and under-exaggerated BP reactivity have each been linked to pathological states. Over-exaggerated BP reactivity has been associated with atherosclerosis, thickened carotid intima (vascular remodelling), hypertension, and an increased risk of a cardiovascular event (Lovallo and Gerin, 2003, Schwartz et al., 2003, Treiber et al., 2003, Carroll et al., 2003). Under-exaggerated BP reactivity has similarly been associated with anxiety, obesity, alcoholism, and overall decreased immune reactivity (Phillips et al., 2009, Panknin et al., 2002, York et al., 2007, Lovallo, 2011). These associations suggest there is an optimal homeostatic range of reactivity (dependent upon the stressor) and that deviation above and below the range increase the likelihood of negative health outcomes.

Waldstein et al. (2005) identified SBP and DBP reactivity was inversely and significantly correlated to verbal memory and executive function (n=94, aged 54-79 years, 38% female). In support, the Coronary Artery Risk Development in Young Adults study found higher BP reactivity earlier in life predicted poor performance in psychomotor speed and verbal memory 25 years later (n=2326, mean age 50 ± 4 years at follow up, 57% female) (Yano et al., 2014). Allen et al. (2011) also identified lower BP and HR reactivity was significantly correlated to better general health and perceived stress scores (n=149, mean age 20 ± 3 years, 56% female). Conversely, Ginty et al. (2012) found a positive relationship between BP reactivity and cognitive performance (n=724, mean age 58 ± 1 years, 47% male). Despite this, a meta-analysis of 39 studies also concluded that increased BP reactivity is worse for cognitive performance (Chida and Steptoe, 2010). Higher BP reactivity has been linked to cardiovascular disease and future hypertension, which are both independent risk factors for cognitive impairment and vascular dementia (Qiu and Fratiglioni, 2015).

Sex has also been shown to influence the relationship between BP and cognitive performance, potentially due to hormonal and cardiovascular differences. Cherbuin et al. (2015) found that BP was positively correlated to cognitive performance in males yet inversely to cognitive performance in females (n=266, age range 68-73 years). Allen et al. (2011) postulated that males may present more ‘vascular’ reactions to stressors (greater BP response), whereas females exhibit more ‘cardiac’ reactions (higher HR response). Ginty et al (2012), however, found no significant differences between BP reactivity in males and females (n=724, mean age 58 ± 1 years, 47% male).

There remains contention in the area of assessing relationships between BP and cognition. Most studies suggest high BP is a major risk factor (especially midlife) (Budge et al., 2002, Suhr et al., 2004), while others suggest low BP is more detrimental (particularly in older age) (Guo et al., 1996, Morris et al., 2000). Others found links between both high and low BP impairing cognitive function (suggesting an inverted U-shaped hypothesis) (Waldstein et al., 2005), high BP reactivity (Waldstein and Katzel, 2005, Yano et al., 2014), or no associations existing at all (Di Carlo et al., 2000). Refer to Table 1.11 for a comparison of studies examining the links between BP and cognitive function.

These varying conclusions or lack thereof may be attributed to disparities in experimental study design such as covariates, psychometric evaluation tools, sample size, age, BP recording method, sex, and exclusion criteria. Disagreement in the literature prompts further research in this area, particularly analysis of the lesser examined younger age groups for inclusion in risk factor analyses.

Table 1.11 Studies assessing BP and increased risk of cognitive impairment

Links to cognitive impairment	Study	Provided age data (years)	Sample size (% female)
High BP	Cerhan et al. (1998)	45-69	13840 (56)
	Crichton et al. (2014)	62 ± 13	972 (59)
	Exalto et al. (2014)	46 ± 4	8469 (55)
	Feinkohl et al. (2015)	68 ± 4	831 (48)
	Gottesman et al. (2014)	57 ± 6	13476 (% unavailable)
	Joas et al. (2012)	45	1462 (100)
	Yaffe et al. (2014)	50 ± 4	3381 (56)
Low BP	Launer et al. (1995)	78	3735 (0) (100% male)
	Pandav et al. (2003)	67 ± 7	4810 (47)
Inverted J-shaped relationship	Bohannon et al. (2002)	73 ± 6	4136 (66)
	Glynn et al. (1999)	74 ± 7	3657 (62)
Inverted U-shaped relationship	Morris et al. (2002)	65-104	5816 (61)
	Waldstein et al. (2005)	71 ± 9	847 (44)
High BP reactivity	Allen et al. (2011)	20 ± 3	149 (56)
	Brown et al. (2009)	70 ± 13	73 (47)
	Waldstein et al. (2005)	54-79	94 (38)
	Yano et al. (2014)	50 ± 4	2326 (57)
No association	Di Carlo et al. (2000)	74 ± 5	3425 (52)

Table 1.11 compares study outcomes in the field of BP and cognitive function. Some studies linked high BP reactivity to cognitive decline, many found high BP increased risk for cognitive decline, and others identified low BP or inverted J and U-shaped hypotheses (where high and low BP states are linked to cognitive dysfunction). Another study did not find a link between BP and cognition (Di Carlo et al., 2000). The majority of BP research focuses on older age participants, which is problematic due to the increased risk of subclinical mild cognitive impairment. There are also variations in sex distribution, sample size, and methodologies which may affect the reliability of results.

Key: BP = Blood pressure

2. Basis for research

Although existing literature in the area of BP and cognitive function is vast there remains some contention in the field. Most studies that have linked BP and cognition are, for the most part, limited to the assessment of older age groups, where cognitive decline is already beginning. Links between BP and cognitive function should be assessed in earlier years in order to determine preceding BP patterns that may otherwise be overlooked until cognitive symptoms present. In addition, some variance in findings persist, with most studies suggesting hypertension as a risk factor for cognitive decline (Stewart et al., 2001, Budge et al., 2002), while others have found that hypotension is linked to cognitive dysfunction (Pandav et al., 2003), or that both high and low BP is correlated to cognitive impairment (Waldstein et al., 2005). There is also a paucity of literature examining the relationships between BP reactivity and cognition.

Fewer studies have been conducted assessing HRV and cognitive function. Those that examine the relationship tend to focus on older age participants (Kim et al., 2006, Murakami et al., 2002), again with existing autonomic dysfunction or cognitive impairments (de Vilhena Toledo and Junqueira, 2008). Assessing both a healthy and clinical sample (aged >18 years) will allow for comparisons to be drawn between clinical groups as well as comparing age and sex effects. Studies on HRV and cognition tend to have small samples sizes (< 100 participants) which may reduce the validity and reliability of research findings. As mentioned earlier, most HRV and cognitive function studies suggest that further research should be undertaken in the area, and a select few have promoted the use of HRV as a powerful marker of cognitive decline (Collins et al., 2012, Kim et al., 2006, Thayer and Sternberg, 2006). In addition, as similar to the lack of research in BP reactivity and cognition, there is a scarcity of research exploring HRV reactivity and cognition.

The disease states explored in the present study have each been previously linked with an increased risk of autonomic neuropathy (reflected in HRV) and cognitive impairment (depression, type 1 DM, type 2 DM, and hypertension) (Vinik et al., 2013, Nahshoni et al., 2004, Kempler, 2003, Lebedeva et al., 2015, Hamed, 2014, DeCarli, 2015). There is a lack of research exploring the relationships between HRV and cognition in clinical samples compared to control groups.

This research endeavours to address these gaps in the literature and to identify possible relationships between cardiac autonomic activity and cognitive status. The findings may be applied to determine risk factor variables that precede MCI.

2.1.1 Hypotheses

1. There will be a significant direct relationship between HRV and cognitive function in clinical and control groups.

Decreases in HRV have been linked to parasympathetic withdrawal, a state that has been associated with various cardiovascular diseases (such as hypertension) and an increased risk of cognitive impairment, providing the basis for hypothesis 1 (Thayer et al., 2010, Kim et al., 2006, Uchino et al., 2005, Shehab and Abdulle, 2011).

2. There will be a significant inverse relationship between BP and cognitive function in clinical and control groups.

Parasympathetic withdrawal may also affect BP (both controlled by the ANS) (Kim et al., 2006). It may be tentatively deduced that HRV indirectly reflects BP. Therefore, as in hypothesis 1, parasympathetic withdrawal resulting in higher BP will also be linked to poorer cognitive function. Other researchers have also supported this hypothesis, finding inverse relationships between BP and cognition (Crichton et al., 2014, Exalto et al., 2014).

3. HRV and BP reactivity will be inversely correlated to cognition in clinical and control groups.

Literature focuses heavily on HR or RSA reactivity rather than HRV reactivity. Comparisons can be drawn as lower HR, high RSA, and high HRV reflect increased cardiac vagal modulation, which has been linked to better cognitive function and provides the basis for this hypothesis (Capuana et al., 2014, Kimhy et al., 2013, Ginty et al., 2011). Previous research has mostly shown BP reactivity is inversely linked to cognitive performance (Allen et al., 2011, Yano et al., 2014)) however others propose that both over- or under-responsive BP changes may be detrimental to cognitive performance (Ginty et al., 2012, Lovallo, 2011, Carroll et al., 2012). Many studies suggest more research is required in the fields of BP and HRV reactivity (Waldstein and Katzel, 2005, Ginty et al., 2011).

2.1.2 Aim

The aim of this research is to examine the links between cardiovascular autonomic activity (as reflected by HRV and BP) with cognitive performance over different age ranges, sexes and clinical samples.

2.1.2.1 Specific aims

1. To identify the relationship between cardiac autonomic activity (HRV and BP) and cognitive function.
2. To examine if age group differences show variable links between cardiac autonomic activity and cognitive function.
3. To examine if sex differences will show variable links between cardiac autonomic activity and cognitive function.
4. To examine if clinical conditions, depression, type 1 DM, type 2 DM, hypertension, will affect the relationship between cardiac autonomic activity and cognition.
5. To identify the relationships between cardiac autonomic reactivity and cognition in clinical and control groups.
6. To identify significant relationships between cardiac autonomic activity and different cognitive domains as a potential predictive marker for identifying those at higher risk of cognitive impairment.

3. Methodology

The following cross-sectional research methodology was developed to address the hypotheses and aims in chapter 2. The study was designed to assess a convenience sample of healthy and clinical participants.

3.1 Participants

Participants aged between 18 and 80 years were recruited from the community under Human Research Ethics Committee (HREC) approval from the University of Technology Sydney (HREC: 2014000110). Recruitment of both the non-clinical and clinical cohorts involved ethics approved poster advertising, online advertising and word of mouth. The majority of participants fell between the ages of 18-65 years and were split into tertiles for age analysis (18-35, 36-50, 51-65 years). Prior to testing, participants were required to abstain from caffeine and nicotine for 4 hours and from alcohol for 12 hours. The purpose of these restrictions was to reduce interference with physiological measurements in order to enhance reliability of the data (Murata et al., 1992, Lorist, 2003, Erbllich et al., 2011).

Testing was conducted between the hours of 8 am to midday to control for circadian changes (Roeser et al., 2012, Vandeput et al., 2012). Participants were excluded if they could not speak fluent English, took illicit drugs or consumed 16 or more alcoholic beverages per day.

3.2 Consent

Before testing commenced, participants were given a general explanation of the study protocol (disclosing that individual results would remain confidential and de-identified) and had an opportunity to ask questions. The participant was then asked if they had any pre-existing chronic illness (e.g. hypertension or depression) to determine which consent form was appropriate for that participant. One consent form was created for healthy participants (appendix 9.1) and another for those with chronic illnesses or who were otherwise taking daily medications (appendix 9.2). The consent form was read and signed

by both the participant and the researcher (who each retained a copy). The study was conducted in a controlled laboratory environment with minimal audio and visual interference.

3.3 BP exclusion criteria

After seating the participant, three brachial arm BP readings were taken using an automated BP monitor (Livingstone OMRON IA1, Japan) (pre-study average referred to as baseline BP) (Figure 3.1). The OMRON BP monitor was chosen as a recommended device (Omboni et al., 2007) and was calibrated against other BP measures such as mercury sphygmomanometers every 6 months. It was also ensured that mmHg count began at zero upon cuff inflation for accuracy of the output reading. Participants presenting BP readings of $\geq 160/100$ mmHg without diagnosed hypertension were excluded from the study and were offered to be escorted to a nearby general practitioner in accordance with the UTS HREC approved emergency protocol (appendix 9.3) and their consent form. Participants with BP readings of $\geq 140/90$ mmHg and $< 160/100$ mmHg were advised to consult their own general practitioner regarding their BP and were able to participate in the study. Those with diagnosed hypertension did not have an upper limit exclusion threshold for BP however were still verbally advised to see a general practitioner (BP readings of $\geq 140/90$ mmHg) and offered to be escorted to a nearby general practitioner if their BP readings $\geq 160/100$ mmHg (appendix 9.3). Table 3.1 depicts the inclusion/exclusion criteria for BP.

Figure 3.1 Method of recording blood pressure using an automated blood pressure monitor

Table/Figure removed due to copyright restrictions for digital thesis submission

Figure 3.1 depicts cuff placement on the upper arm to occlude the brachial artery using an automated BP monitor, adapted from p1 Harvard Medical School (2009). Key: BP = Blood pressure

Table 3.1 BP inclusion and exclusion thresholds

BP	BP classification	Healthy sample	Clinical sample
≤120/80mmHg	Normotensive	Included	Included
>120/80mmHg and <140/90mmHg	Prehypertensive	Included	Included
≥140/90mmHg and <160/100mmHg	Stage 1 hypertensive	Included and advised to see GP	Included and advised to see GP
≥160/100mmHg	Stage 2 hypertensive	Excluded and offered to be escorted to GP	Included and offered to be escorted to GP*

Table 3.1 shows healthy participants with \geq stage 2 (i.e. moderate) hypertension were excluded from participating in the study and offered to be escorted to a nearby GP. Clinical samples with the same readings were also offered to be escorted to a nearby GP but were not excluded from participating in the study if the offer was refused (in accordance with the UTS HREC approved emergency protocol). Those with BP readings of <140/90mmHg were included in the study. Those between 140/90mmHg and 159/99mmHg were also included in the study and were advised to consult their own GP. Table adapted and modified from U.S. Department of Health and Human Services (2003).

Key: BP = Blood pressure; HREC = Human Research Ethics Committee; GP = General practitioner; mmHg = Millimetres of mercury; UTS = University of Technology Sydney; * = If the patient is escorted to a GP the study is ceased and not recommenced.

3.4 Lifestyle exclusion criteria

Participants were instructed to complete the Lifestyle Appraisal Questionnaire (LAQ) to provide relevant demographic and lifestyle data such as body mass index and alcohol intake (Craig et al., 1996). The LAQ is divided into two sections with higher scores in section I indicating an increased risk of a cardiovascular event (maximum score of 70) and higher scores in section II indicating an increased risk of anxiety and decreased stress coping (maximum score of 75) (Craig et al., 1996). Obtaining a maximum score of 145 indicates the highest risk of the participant developing a chronic illness and having a reduced quality of life (Craig et al., 1996). If the participant indicated illicit drug use or excessive alcohol consumption (16 or more alcoholic beverages per day), they were excluded from participating in the study.

The participant was also instructed to complete the Disease State Questionnaire (DSQ) (Giblin, 2013) to obtain information on their chronic disease(s) (if applicable) and formed the basis for which disease group they would join (appendix 9.4). The DSQ collects data regarding medications taken, use of alternative therapies, self-scored disease management (if any) and symptoms experienced by the participant. The participant may skip the DSQ if they do not have a chronic illness.

3.5 Electrocardiogram (ECG) and HRV data

To obtain HRV data, a three-lead electrocardiogram (ECG) was attached to the participant (see Figure 3.2 for electrode placement). The ECG recording was obtained using a FlexComp Infinity ECG (Thought Technology Ltd, Canada) with BioGraph Infiniti computer software programming (Thought Technology Ltd, Canada). A three-lead ECG is sufficient to obtain clear R-R intervals required for HRV analysis (Berntson et al., 1997). Refer to Figure 3.3 for a screenshot of the ECG recording.

Figure 3.2 Electrode placement (three-lead ECG)

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Figure 3.2 shows the electrode placement used in the current study for a three-lead ECG. The black electrode is a reference electrode placed distally under the left clavicle. The yellow and blue recording electrodes are positioned between the fourth and fifth ribs, two centimetres from either side of the sternum. Electrodes may have to be re-positioned slightly due to adipose or breast tissue to obtain a clearer ECG signal (Martin, 2007). Adapted and modified from Health Hype (2006).

Key: ECG = Electrocardiogram

Figure 3.3 Labelled screenshot of the ECG recording

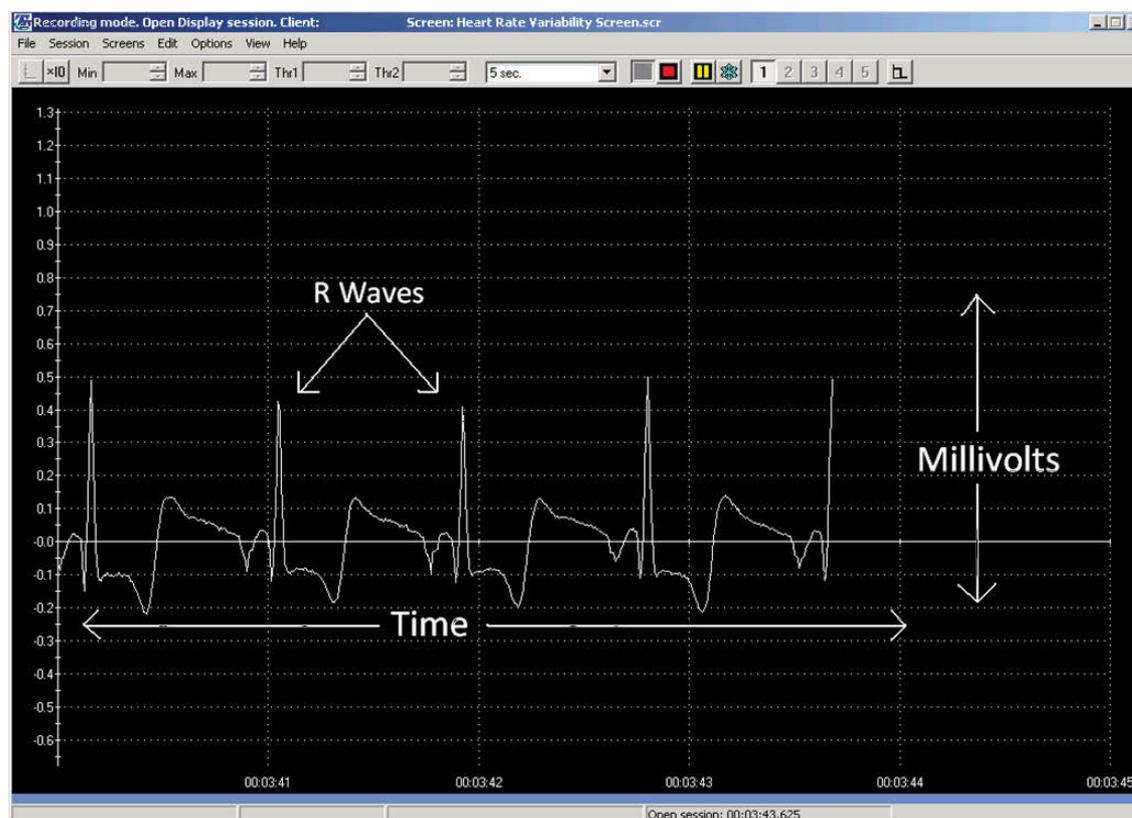


Figure 3.3 shows a screenshot taken during a baseline ECG recording using Biograph Infiniti software (Thought Technology Ltd, Canada), with labels indicating R waves against the time and millivolts axes. The clear R-R intervals are sufficient for accurate HRV analysis.

Key: ECG = Electrocardiogram; HRV = Heart rate variability

The participant underwent a quiet, seated baseline ECG recording for ten minutes (eyes open). The participant was then engaged in a cognitive task of unscripted active neutral conversation for the second ten minute ECG recording. Active neutral conversation is an established experimental technique used to arouse a variety of cognitive domains such as attention, memory and language (Potter, 2006, Turkstra, 2008). Neutral conversation involves a typical verbal interaction whilst avoiding discussion of stressful or emotional topics that would affect the cardiac measurement (e.g. stress leading to increased sympathetic drive resulting in increased heart rate) (Friedman and Thayer, 1998, Lane et al., 2009). HRV data is later extrapolated from the baseline and cognitive task (active) ECG recordings.

HRV was pre-processed using a 5 to 30Hz band pass filter to minimise electrical noise, wandering baseline, muscular interference, and other noise factors. This was coupled with a 3rd order Infinite Impulse Response Butterworth filter with cut-off points at 3.5 and 35Hz. Decision rules were then applied to detect the QRS complex, average heart beat length, and amplitude threshold, attuned adaptively as the detections unfold. The time at which each R wave occurs was logged to produce HRV time series data. The RR intervals were calculated as differences between consecutive R waves (i.e., the nth RR interval is the difference between the R wave occurrence times $RR_n = t_n - t_{n-1}$). R-R interval series are calculated using a power spectrum density estimate (Fast Fourier Transform based Welch's periodogram method using a Hann window). The frequency bands presented are low frequency (LF) (0.04-0.15Hz) and high frequency (HF) (0.15-0.4Hz). Total power (TP) is the addition of power in each frequency band including the very low frequency band (VLF) ($TP = VLF (0.01-0.04Hz) + LF + HF$). Sympathovagal balance is calculated by the ratio of $LF/HF * 100$. Power (ms^2) is calculated for each bandwidth component as the corresponding area under the power spectrum density curve.

HRV data can also be explored in time domain indices, that is, providing information on variability over time. See Table 3.2 for descriptions of the time domain HRV parameters included in the present study (heart rate (HR), mean R-R interval, SDNN, RMSSD, and pNN50).

Table 3.2 Description of time domain HRV parameters

Time domain parameter (unit)	Description
Heart rate (bpm)	Mean number of cardiac cycles per minute
Mean R-R interval (ms)	Mean time between consecutive R waves
SDNN (ms)	Standard deviation of all NN intervals
RMSSD (ms)	Square root of the mean squared differences of successive NN intervals
pNN50 (%)	NN50 count divided by the total number of NN intervals

Table 3.2 describes the time domain HRV parameters used in the current study, which are appropriate for a ten minute electrocardiogram recording. Adapted and modified from the Task Force of the European Society of Cardiology the North American Society of Pacing and Electrophysiology (1996).

Key: bpm = Beats per minute; HRV = Heart rate variability; ms = Milliseconds; NN interval = Consistent consecutive point on the electrocardiogram trace e.g. R-R wave; NN50 = Total number of consecutive NN interval differences >50ms

Other HRV time domain methods, geometric measures and non-linear methods require longer time segments than 10 minutes (such as 24 hour readings) (Task Force of The European Society of Cardiology and The North American Society of Pacing and Electrophysiology, 1996) and thus were inappropriate to include in the analysis. HRV data is inherently skewed (Macfarlane et al., 2011). To satisfy statistical requirements regarding normal distribution, logarithmic transformations were applied to frequency and time domain parameters (LF, HF, LF/HF, TP, SDNN, and RMSSD) (Tarkiainen et al., 2005, Macfarlane et al., 2011).

3.6 Psychometric tests

Two validated and reliable psychometric assessment tools: the MMSE (Folstein et al., 1975) and the Cognistat (Kiernan et al., 1987), were then administered to screen for cognitive impairment in various brain domains.

3.6.1 Mini-Mental State Examination (MMSE)

The MMSE is a reliable and validated psychometric test and has been used extensively in both research and clinical settings to screen for impairment in different cognitive domains. The MMSE is simple to administer, taking approximately 5-10 minutes. It is made up of 11 questions receiving a maximum score of 30. The MMSE screens cognitive domains of orientation to time and place, word registration (memory), attention/calculation, recall (verbal memory), and language (naming, repetition, reading, comprehension, writing and visuo-construction) (Folstein et al., 1975). A score of $\leq 23/30$ is suggestive of cognitive impairment and has been linked to a diagnosis of dementia in at least 79% of cases (Lancu and Olmer, 2006, Folstein et al., 1975). It has been argued, however, that the MMSE is less rigorous than other psychometric tests and that MCI may not be detected by the 23/30 point threshold (Yue et al., 1994, Macaulay et al., 2003). Van Gorp's team (1999) recommends increasing the threshold to $\leq 26/30$ to achieve maximal accuracy, as deduced from their comparative research of VaD (n=19), AD (n=22) and controls (n=12) (average age 69 ± 6 years). The authors of the MMSE more recently stated that a threshold score of >27 reflects normal cognition, with scores of 21-26 suggesting MCI, scores 11-20 showing moderate cognitive impairment, and scores <10 indicating severe cognitive impairment (Folstein et al., 2001).

Age and years of education has been shown to affect MMSE normative data and has been strongly suggested to be taken into account when assessing cognitive health (see normative data Table 3.3 (n=7754, aged over 65 years, 60% female) (Bravo and Herbert, 1997)). Sex has not been shown to have such an impact (Bravo and Herbert, 1997). Additional research by McDowell et al. (1997) suggests that the MMSE is overly simplistic and unspecific in detecting early dementia/MCI or differentiating impairment from varying brain regions in MCI (n=480), dementia (n=368) and control groups (n=752) (aged 65-99 years). Molloy's group (1991) also proposed that the lack of a standard MMSE administration manual increases variability of interpretation, delivery

and scoring. Other researchers suggest that the MMSE is prone to ceiling effects (higher end scores) attributed to the small range of fairly easy questions ($\alpha > 0.8$) (Zadikoff and Fox, 2008, Hoops et al., 2009, Lopez et al., 2005).

Further, the MMSE has been criticised for being a highly verbal based test lacking assessment of subcortical functions, unequal distribution of sensitivity among domains and assuming the serial subtraction of the number 7 from 100 is akin to spelling the word ‘world’ backwards (when evidence suggests they are not equivalent) (Tombaugh and McIntyre, 1992, Byrne et al., 2000). Despite this, sensitivity and specificity psychometric research yields supportive results although there is a lack of recent data (Table 3.4). Sensitivity of the MMSE refers to its ability to correctly identify true positives (cognitive impairment) and specificity refers to its ability to correctly identify true negatives (cognitively intact cases) (Tombaugh and McIntyre, 1992).

Table 3.3 MMSE normative data by age and years of education

Education (years)	Age range									
	65-69 years		70-74 years		75-79 years		80-84 years		85 years and over	
	n	mean (SD)	n	mean (SD)						
0-4	78	25.7 (3.4)	85	25.7 (2.7)	93	25.4 (1.9)	78	24.5 (2.8)	65	24.3 (2.6)
5-8	495	26.9 (2.8)	422	27.0 (2.5)	556	26.4 (2.0)	277	25.8 (2.0)	239	25.2 (1.8)
9-12	942	27.9 (2.2)	752	27.7 (2.1)	921	27.3 (1.5)	455	26.8 (1.7)	332	26.2 (1.4)
> 13	581	28.4 (1.9)	375	28.2 (2.0)	535	27.7 (1.8)	236	27.3 (1.7)	208	26.9 (1.3)
All	2098	27.7 (2.5)	1638	27.5 (2.3)	2112	27.1 (1.8)	1051	26.5 (2.0)	853	25.9 (1.8)

Table 3.3 presents normative data by age and years of education for the MMSE (n=7754; mean age 75 years). Older age and fewer years of education show the greatest cognitive decline and ought to be taken into consideration during analysis. Adapted from Bravo and Herbert (1997).

Key: n = Sample size; SD = Standard deviation

Table 3.4 Comparison of MMSE sensitivity and specificity research

Study	Sensitivity/ Specificity (%)	Sample size (n)	Sample type	Provided age data (years)
Anthony et al. (1982)	87/82	Control n=74; Dementia n=23	Cognitively intact and dementia/delirium	20-89
Davous et al. (1987)	98/100	Control n=56; Dementia n=44	Cognitively intact and dementia	76 ± 11
Fillenbaum et al. (1990)	100/94	Control n=25; Dementia n=56	Cognitively intact and mild/moderate dementia in Caucasians	65+*
Foreman (1987)	82/80	Control n=33; Dementia/delirium n=33	Cognitively intact and dementia/delirium	66-85
Gagnon et al. (1990)	100/78	Control n=2691; Dementia n=101	Cognitively intact and mild/moderate dementia	65+*
Kafonek et al. (1989)	79/86	Control n=22; Dementia/delirium n=47	Cognitively intact and dementia/delirium	*
Kay et al. (1985)	69/89	Control n=235; Dementia n=39	Cognitively intact and mild/moderate dementia	70-80+
Murden et al. (1991)	96/81	Control n=148; Dementia n=110	Cognitively intact and dementia	60-99
O'Connor et al. (1989)	86/92	Control n=285; Dementia/delirium n=196	Cognitively intact and dementia/delirium	75+*

Table 3.4 compares MMSE sensitivity and specificity studies which used the 23-24/30 score threshold for impairment. The majority of research supports the use of the MMSE with sensitivity and specificity scores >80%. Inconsistencies in data may be attributed to sample size and demographics.

Key: * = Incomplete age data available

3.6.2 Cognistat

The Cognistat (formally known as the Neurobehavioural Cognitive Status Examination (Kiernan et al., 1987)) is a more robust screening tool for cognitive impairment that assesses brain domains with increasing sensitivity to produce a graded score (rather than the MMSE's global score) (Macaulay et al., 2003). It takes approximately 15-20 minutes to administer, assessing seven individual brain domains: orientation, attention, language, construction, memory, calculation and reasoning (Macaulay et al., 2003). First, the participant is asked a 'screen' question for a particular domain. The screen question is of average difficulty. Passing the screen question represents a normal level of cognitive function for a certain domain and allows the researcher to move onto the next domain (Deutinger and Alliant International University, 2007). If the participant fails the screen question, the researcher proceeds to ask 'metric' questions for that particular domain. The metric questions progress from simple to more complicated levels, in order to more thoroughly assess the level of impairment potentially present in the cognitive area (Deutinger and Alliant International University, 2007). The Cognistat provides a threshold score for each domain, such that scores lying equal to or below that threshold indicate a degree of cognitive impairment (Table 3.5).

As with the MMSE, age and education level can influence Cognistat scores (see Table 3.6 for normative data) (Drane et al., 2003). Research by Drane et al. (2003), identified age had the largest effect on the domains of memory and attention in the Cognistat, while education level primarily impaired construction skill (n=108, aged 60-96 years, 75% female) (Table 3.6). They also identified that females outperform males at naming tasks yet did not suggest stratifying for this difference. Age cognition research by Macaulay et al. (2003) proposed that memory skill ought to be adjusted for ages 65-74 and construction skill for 75-84 years (n=123, 70% female). Interestingly, they did not recommend using age or sex as a confounder for similarity skill.

Classifying a participant as impaired involves reaching the impairment threshold in one or more domains (sensitivity 100%, specificity 83%) followed by further testing by a medical practitioner to reach a diagnosis. Requiring that two or more domains reach impairment level reduces sensitivity to 94%, increases specificity to 100%, and better differentiates between disease types (Osato et al., 1993). Research supports asking both the screen and metric questions for maximal accuracy and to reduce false negatives (van

Gorp et al., 1999, Drane et al., 2003, Oehlert et al., 1997). A study by Deutinger and researchers (2007) showed that an average cognitively healthy person may fail up to 20% of screen questions. Therefore, to reduce false positives in the present study, both the screen and the metric questions were administered.

Abandoning the ‘screen and metric’ approach to the Cognistat administration has been recommended by Logue et al. (1993) and Pichitino and Green (1999), who criticise the equivalence of tasks in certain domains such as visual construction (where the screen task involves visual memory and the metric task involves a visuospatial tile design task). Interestingly, Drane and Osato (1997) discussed the issue of time being a significant factor for those who passed the screen questions (and thus proceeded more quickly) to those who fail and must answer the metric questions. For instance, in the verbal memory tasks, where participants are required to memorise four words and recall them later in the test, those forced to answer metric questions performed worse than those who passed the screen questions, potentially due to the increased ‘distractions’ (cognitive tasks) between the memorising stage and the recall stage (Drane and Osato, 1997). To improve reliability, Drane and Osato (1997) suggested administering both screen and metric questions from the outset.

Eisenstein’s laboratory (2002) praised the Cognistat’s succinctness, ease of use, cognitive profile design and wide scope of cognitive functions assessed. The Cognistat scores are plotted on a cognitive status profile where points create a grading system of normal, mild, moderate, or severe cognitive impairment per domain (see Table 3.5). This allows researchers to quickly assess the data and see which cognitive skills may be impaired and compare to other normative data sets (see Table 3.6). The Cognistat can also be re-administered to compare cognitive status changes in a participant over time (Eisenstein et al., 2002). Although this tool has been clinically applied extensively on geriatric patients in the past, it is still effective for use on younger participants (minimum age of 18 years) (Mueller et al., 1988). To increase cognitive assessment sensitivity, it has been suggested that the Cognistat and MMSE be administered in conjunction with one another (Schwamm et al., 1987, Macaulay et al., 2003, Dujardin and Dubois, 2010).

Table 3.5 Cognistat cognitive profile grading

Cognitive domain		Maximum score	Level of cognitive impairment		
			Borderline mild	Mild	Moderate
Orientation		12	<10	8	6
Attention		8	<6	5	3
Language	Comprehension	6	<5	4	3
	Repetition	12	<11	9	7
	Naming	8	<7	5	3
Construction		6	<4	3	2
Memory		12	<10	8	6
Calculation		4	<3	2	1
Reasoning	Similarity	8	<5	4	3
	Judgment	6	<4	3	2
Total score		82	<65	51	36

Table 3.5 illustrates the maximum score achievable in the Cognistat domains and respective thresholds for varying degrees of cognitive impairment: borderline, mild, moderate and severe. Adapted from Kiernan et al. (1987).

Table 3.6 Cognistat normative data by age and years of education

Cognitive domain	Age 60-74 years		Age 75-96 years	
	≤12 years education (n=20)	>12 years education (n=35)	≤12 years education (n=15)	>12 years education (n=38)
Orientation	≤11	≤11	≤8	≤11
Attention	≤5	≤6	≤5	≤5
Comprehension	≤5	≤5	≤5	≤5
Repetition	≤11	≤10	≤10	≤10
Naming	≤6	≤7	≤6	≤6
Construction	≤4	≤3	≤1	≤3
Verbal memory	≤6	≤7	≤5	≤6
Free recall	≤3	≤3	≤0	≤0
Semantic cueing	≤3	≤6	≤3	≤4
Recognition recall	≤6	≤7	≤5	≤6
Calculations	≤2	≤3	≤2	≤3
Similarities	≤3	≤6	≤2	≤5
Judgement	≤3	≤4	≤3	≤4
Total score	≤67	≤69	≤62	≤68

Table 3.6 presents normative data for the Cognistat (n=108; aged 60-96 years). Maximum total score for the Cognistat is 82. Older age and fewer years of education showed the greatest cognitive decline and ought to be taken into consideration during analysis. Adapted from Drane et al. (2003).

Key: n = Sample size

3.6.3 Cognitive domains and scoring weight

Table 3.7 defines the different cognitive domains examined by the MMSE and the Cognistat.

Table 3.8 compares the scoring weight of each of those cognitive domains, and the cognitive impairment assessment threshold for each psychometric test.

Table 3.7 Cognitive domains examined by the MMSE and Cognistat

Cognitive domain	Definition	Test
Orientation	Sense of current location, time, and date	MMSE and Cognistat
Registration	Ability to understand and memorise verbal information to be recalled later on	MMSE only
Attention	Sustained selective concentration on a particular aspect, whilst disregarding other stimuli	MMSE and Cognistat
Calculation	Arithmetic accuracy and computation speed	MMSE and Cognistat
Recall/memory	Mental capacity to retain and recall a past event	MMSE and Cognistat
Language	Test of linguistic abilities including naming, repetition, grammar and comprehension	MMSE and Cognistat
Visuo-construction	Ability to memorise, replicate and construct images	Cognistat
Reasoning	Logic and judgement utilised in a situation to produce a rational outcome	Cognistat

Table 3.7 defines different cognitive domains examined by the MMSE (Folstein et al., 1975) and the Cognistat (Kiernan et al., 1987). Adapted and modified from Mueller et al. (1988), Kiernan et al. (1987), and Folstein et al. (1975).

Key: MMSE = Mini Mental-State Examination

Table 3.8 Comparison of scoring weight (maximum) and cognitive impairment thresholds for the MMSE and Cognistat

	MMSE	Cognistat
Cognitive domain (maximum score)	Orientation (10)	Orientation (12)
	Registration (3)	-
	Calculation and attention (5)	Calculation (4)
		Attention (8)
	Recall (3)	Memory (12)
	Language: • Comprehension (3) • Repetition (1) • Naming (2) • Reading and writing (3)	Language: • Comprehension (6) • Repetition (12) • Naming (8)
	-	Visual Memory Task and Visuo-Construction (6)
-	Reasoning: • Similarities (8) • Judgement (6)	
Cognitive impairment threshold	Total score out of 30 (≤ 23 suggests cognitive impairment)	Total score out of 82. Each brain domain is graded (normal, mild, moderate and severe) producing a cognitive status profile

Table 3.8 summarises differences in scoring weight and cognitive impairment thresholds between the MMSE and Cognistat. Note that calculation is the only MMSE domain with a higher point score than in the respective Cognistat domain (and therefore carries more weight in relation to total score). The cognitive status profile for the Cognistat is provided in Table 3.5. Adapted and modified from the MMSE (Folstein et al., 1975) and Cognistat (Kiernan et al., 1987).

Key: MMSE = Mini Mental State Examination

3.7 Final BP measurements

A final three BP measurements (post-study average) were then obtained using the same methods described for the pre-study (baseline) measurements (section 3.3), concluding the experimental protocol.

3.8 Experimental protocol summary

The following table summarises the sequential steps involved in the entire experimental protocol (Table 3.9).

Table 3.9 Step summary of experimental protocol

1.	Preceding test commencement, participant required to abstain from caffeine, nicotine and energy drinks for 4 hours and from alcohol for 12 hours	
2.	Both participant and investigator sign the consent form (one copy is retained by each)	
3.	Participant undergoes a rest period for 2 minutes (seated)	
4.	Three seated pre-study BP readings are taken from the left arm (2 minute intervals)	If BP \geq 140/90 mmHg: The participant may continue to step 5 and is advised to consult their GP regarding their BP
		If BP \geq 160/100 mmHg: If the participant does not have diagnosed hypertension they are excluded from participating further, advised to consult their GP, and offered to be taken to the nearest medical centre If they do have diagnosed hypertension they are advised to consult their GP and offered to be taken to the nearest medical centre and may continue to step 5
5.	Administer LAQ (Craig et al., 1996) (10 minutes) and Disease State Questionnaire (Giblin, 2013) (5 minutes)	
6.	Height and weight obtained for BMI calculation	
7.	Participant undergoes a rest period for 2 minutes (seated)	
8.	Attach three-lead ECG electrodes to the participant's chest and record baseline reading for 10 minutes	
9.	Record a further 10 minute ECG during a cognitive task (neutral conversation)	
10.	Administer the MMSE (Folstein et al., 1975) and Cognistat (Kiernan et al., 1987) in a randomised order (15 minutes)	
11.	Participant undergoes a rest period for 2 minutes	
12.	Three seated post-study BP readings are taken from the left arm (2 minute intervals)	If BP \geq 140/90 mmHg: The participant is advised to consult their GP. The collected data may still be included in the analysis
		If BP \geq 160/100 mmHg: The participant is advised to consult their GP and offered to be taken to the nearest medical centre. The collected data may still be included in the analysis
End of test (approximately 60 minutes total duration)		

Table 3.9 summarises the laboratory experimental protocol employed in this study. Note: the health related exclusion criteria in steps 1 and 4. Time durations vary according to cognitive status and number of chronic illnesses. This study has been approved by the University of Technology Sydney Human Research Ethics Committee.

Key: BMI = Body Mass Index; BP = Blood pressure; ECG = Electrocardiogram; GP = General practitioner; LAQ = Lifestyle appraisal questionnaire; mmHg = Millimetres of mercury; MMSE = Mini-Mental State Examination

3.9 Statistical analysis

Statistical analysis was conducted using the software program SPSS Version 22.0 (IBM Corp., Released 2013) to explore associations within the entire non-clinical sample 18-71 years (n=223) and between females and males in three different age groups: 18-35 years (females n=41; males n=42), 36-50 years (females n=37; males n=37), and 51-65 years (females n=42; males n=23) (n=1 male aged 71 years not included as the sample size was insufficient for a separate age analysis (66-80 years), however was included as part of the total cohort 18-71 years).

Within the clinical sample (n=74), groups were divided by diagnosed condition: depression (n=10), type 1 DM (n=9), type 2 DM (n=38), and hypertension (n=39). The remaining 'other' clinical conditions collected were not included in the analysis. There was some cross-over between groups where participants had more than one condition, which was used as a covariate (number of illnesses).

Matched control groups were created for a comparison between clinical and non-clinical groups. The matched control groups were duplicate copies from the non-clinical cohorts paired to the clinical cohorts by sex and age ± 8 years. If matching was >8 years from the age of the clinical subject, or of the opposite sex, the match was not included. This explains the difference in the sample size of the match groups for hypertension and type 2 DM. Non-clinical matched samples included hypertension (n=31), type 1 DM (n=9), type 2 DM (n=30) and depression (n=10). Parametric analysis was conducted for all groups $n \geq 30$. Non-parametric analysis was conducted for groups $n < 30$, and regressions were not performed in these samples (51-65 year old males (n=23), depression (n=10), and type 1 DM (n=9)).

Normality was inspected visually, with absolute HRV values being log-transformed to normalise. All HRV data underwent outlier removal to reduce the effects of artefact noise (± 3 standard deviations from the sample mean). Statistical significance was reported at a p-value of <0.05 and all values were reported to the nearest two decimal places.

3.10 Statistical methods

3.10.1 Power analysis

Power analysis was applied to determine the minimum sample size required to produce statistically reliable data (Thomas and Krebs, 1997). The minimum sample size required for this research, based on moderate effect ($\rho=0.4$), was $n=44$ with 80% power ($\alpha=0.05$) or $n=26$ based on large effect ($\rho=0.5$) (Faul et al., 2007). Statistical power increases with increasing sample size (Lachin, 1981, Thomas and Krebs, 1997). In groups where $n \leq 30$, descriptive and non-parametric tests were conducted.

3.10.2 Dependent and independent sample t-tests

Dependent sample (paired) t-tests were applied to identify significant differences between baseline and active HRV parameters and between pre- and post-study BP readings in all groups. Independent sample t-tests were applied to identify differences between females and males, and between clinical and non-clinical match groups. The t-tests were used to analyse the magnitude and significance of differences in the means and standard deviations of normally distributed paired and independent samples (Peacock and Peacock, 2011).

3.10.2.1 Wilcoxon signed rank test

The Wilcoxon signed rank test was used as a non-parametric equivalent to a dependent sample t-test when $n \leq 30$ (non-clinical males 51-65 years, depression, and type 1 DM). The test identifies significant differences between medians based on ranked data of paired samples (Lund Research Ltd, 2015). This test was applied between baseline and active HRV parameters and between pre- and post-study BP readings.

3.10.2.2 Mann-Whitney U test

The Mann-Whitney U test was used as a non-parametric equivalent to an independent sample t-test when $n \leq 30$. The test identifies significant differences of distribution based on ranked data between unpaired groups (Lund Research Ltd, 2015). This test was applied

between females and males (non-clinical males 51-65 years $n=23$), and between clinical and non-clinical match groups (depression ($n=10$), and type 1 DM ($n=9$)).

3.10.3 Bivariate Pearson's correlation

Pearson's correlation was used to assess the relationships between cognitive function and HRV and BP, stratified for age and sex in the non-clinical groups and by diagnosed condition in the clinical groups. Pearson's correlation assesses the strength and direction of a linear relationship between two variables in a sample (Lund Research Ltd, 2015). For the test to be valid, at least one variable requires a normal distribution (Peacock and Peacock, 2011).

Pearson's correlation produces a r (*rho*) value, ranging from $r=-1$ to $r=1$ (Peacock and Peacock, 2011). The r value indicates strength of the positive or negative nature of the relationship (Peacock and Peacock, 2011). An $r=-1$ indicates that as one variable increases, the other decreases by the same amount (inverse relationship), whereas an $r=1$ indicates that as one variable increases, so too does the other (direct relationship) (Crooks and Davies, 1998, Peacock and Peacock, 2011). The r value is directly related to sample size; the larger the sample the weaker the r value required to reach statistical significance. Different r values indicate different strengths of association: small correlation = $\pm 0.1-0.3$, moderate correlation = $\pm 0.3-0.5$, strong correlation = $>0.5/<-0.5$ (Cohen, 1988). Although these ranges are widely accepted in the literature, some researchers suggest the strength of the association ought to depend on the type of study (Hemphill, 2003).

3.10.3.1 Spearman's rank-order correlation

A non-parametric alternative to a Pearson's correlation is the Spearman rank-order correlation. The measure similarly produces a r coefficient and p -value calculating the strength and direction of an association between variables (although uses ranks of the data, while the Pearson's correlation uses data values) (Peacock and Peacock, 2011). This test was applied to the small sample size cohorts ($n<30$) (males 51-65 years ($n=23$), depression ($n=10$), and type 1 DM ($n=9$)).

3.10.4 Partial Pearson's correlation

Pearson's correlations were first performed between the covariates and the dependent and independent variables to determine the significant covariates to include in the partial Pearson's correlations. A partial Pearson's correlation was performed when dependent and independent variables were significantly correlated to covariates (years of education, BMI, LAQ part 1 (lifestyle risk factors), LAQ part 2 (stress coping), smoking status, age, number of illnesses (clinical only) and duration of illness (years) (clinical only)). The concept follows that of the Pearson's correlation (previous section 3.10.3) while controlling for covariates that had significantly influenced the variables of interest (Muller and Fetterman, 2002).

3.10.4.1 Partial Spearman's rank-order correlation

Partial Spearman rank-order correlations were conducted when variables were significantly correlated to covariates (years of education, BMI, LAQ part 1 (lifestyle risk factors), LAQ part 2 (stress coping), smoking status, age, number of illnesses (clinical only) and duration of illness (years) (clinical only)). Partial Spearman rank-order correlations are a type of non-parametric alternative to a partial Pearson's correlation and similarly produces a r coefficient and p -value calculating the strength and direction of an association between variables while taking into account the effect of a covariate (Lund Research Ltd, 2015). This test was applied to the small sample size cohorts ($n < 30$) (males 51-65 years ($n=23$), depression ($n=10$), and type 1 DM ($n=9$)).

3.10.5 Comparison of correlations between groups

Comparisons were conducted between females and males and clinical and control groups, where the same correlations had been significant in both groups. Fisher Z transformation converts the correlation r to a z -score and computes the difference between correlations taking into account the sample size of each group (Cohen and Cohen, 1983). This comparison determines whether the correlations are significantly different from one another ($p < 0.05$) (Chalmer, 1986). The first sample entered into the model will affect the sign of the z -score; where r values group 2 $>$ r values group 1 = a positive Z score and where r values group 2 $<$ r values group 1 = a negative z -score.

3.10.6 Bonferroni correction

Bonferroni corrections were applied to all correlations where two or more independent variables were correlated to a dependant variable. The Bonferroni correction technique involves dividing the p-value by the number of variables being examined to make the p-value more conservative and reduces the risk of type 1 errors (false positives) (Bland and Altman, 1995). Three or more independent variables significantly correlated to a dependant variable were required to fall equal to or less than the Bonferroni adjusted p-value to be included in the linear regression model. Correlations that did not fall equal to or below the Bonferroni-adjusted p value were still displayed in data tables yet were not included in the linear regression model (marked with an asterix (*)). It is acknowledged that there is no adjustment for multiple comparisons made using the same patient population.

3.10.7 Regression analysis

Linear regression analysis was used to identify the most significant predictors of HRV and BP with cognitive performance. Following the Pearson's correlations, those with multiple significant predictors (\geq three independent variables to one dependent variable after a Bonferroni correction) were entered into a linear regression model to identify the strongest predictor(s) of cognitive function.

Regression analysis examines the nature of the linear relationship between variables by creating a line of best fit through the sample (straight line equation $y=mx+b$). The line provides the expected value of the dependent variable given the independent variable (Peacock and Peacock, 2011). The coefficient of determination (r^2) provided by a regression describes the proportion of variance in one variable being explained by the other variable (Lund Research Ltd, 2015). Regression outputs were inspected for multicollinearity and independence of residuals. Where correlations were partial, a hierarchical (sequential) regression was performed, allowing the addition and examination of the effect of a covariate (Lund Research Ltd, 2015).

3.10.8 Multiple analysis of variance (MANOVA)

MANOVA was used to identify significant differences between the male and female age groups (18-35, 36-50, and 51-65 years) for HRV, BP, and cognitive variables. An extension of the t-test (section 3.10.2), a two way MANOVA compares the means from three or more independent samples, and produces a p-value (significance <0.05) (Peacock and Peacock, 2011). Being an omnibus test, the MANOVA only indicates where there was a significant difference. Bonferroni post-hoc tests were applied to determine where the differences lay between the samples tested (between which particular age groups).

3.10.8.1 Kruskal Wallis H test

A non-parametric alternative to the one-way analysis of variance (ANOVA) is the Kruskal Wallis H test. It uses rank-based data to determine significant differences between the medians of three or more groups. A post-hoc pairwise Dunn comparison was then applied to determine which groups were significantly different (Dunn, 1964). This test was performed between males aged 18-35, 36-50, and 51-65 years because the eldest age group had a smaller sample size $n < 30$ ($n=23$).

3.10.9 Multiple analysis of covariance (MANCOVA)

MANCOVA was also used to identify significant differences between the male and female age groups (18-35, 36-50, and 51-65 years) for HRV, BP, and cognitive variables. Following the same concept as MANOVA (section 3.10.8), MANCOVA compares the means from two or more independent samples while controlling for a covariate (Lund Research Ltd, 2015). Correlations were first performed with the covariates (years of education, BMI, LAQ part 1 (lifestyle risk factors), LAQ part 2 (stress coping), smoking status, age, number of illnesses (clinical only) and duration of illness (years) (clinical only)). Where covariates were significant, a two way MANCOVA was performed with those particular variables to compare the means between groups (while adjusting for the effect of that covariate). Significant differences were reported at a p-value of <0.05. Bonferroni post-hoc tests were applied to determine where the differences lay between the samples tested (between which particular age groups).

4. HRV and cognition (non-clinical groups)

Earlier research in the field of HRV and cognition have mostly found lower HRV is linked to reduced cognitive performance (Lopez et al., 2015, Frewen et al., 2013), however others have shown relationships between HRV and cognition depend on the cognitive domain being assessed (Solernó et al., 2012, Melis and van Boxtel, 2001, Mukherjee et al., 2011, Luft et al., 2009). Indirect relationships between HRV and cognition (Martinez et al., 2014, Keen, 2011, Stein et al., 2005) or no relationships (Britton et al., 2008) have also been concluded by previous researchers. Fewer studies examine the relationship between HRV and cognition in a wide range of ages (18-35 years) in a non-clinical male and female cohort. Many HRV and cognition studies suggest that additional research should be performed in the area, and several have promoted the use of HRV as a potent marker of cognitive decline (Collins et al., 2012, Kim et al., 2006, Thayer and Sternberg, 2006). In addition, there is a lack of research exploring HRV reactivity and cognition.

Therefore the following results and discussion chapters (4.1 and 4.2, respectively) explore specific aims 1, 2, 3, 5, and 6 (as shown in section 2.1.2.1): to identify the relationship between HRV and cognitive function; to examine if age group differences show variable links between HRV and cognitive function; to examine if sex differences will show variable links between HRV and cognitive function; to identify the relationships between HRV reactivity and cognition; and to identify significant relationships between HRV and different cognitive domains as a potential predictive marker for identifying those at higher risk of cognitive impairment.

4.1 Results: HRV and cognition (non-clinical groups)

A total of 123 volunteers with no chronic illnesses, aged 18-71 years, were recruited for the present study, adding to an existing database of 100 participants obtained using similar experimental protocol and laboratory conditions in the Neuroscience Research Unit at UTS (total females and males n=223) (De Leon, 2009, Smith, 2010).

This chapter reports the descriptive statistics for the total non-clinical sample, followed by results for HRV and cognitive function in females and males for the three age groups (18-35, 36-50, 51-65 years (n=1 male aged 71 years not included)), and provides descriptive statistics and comparisons for the total female and male groups. Figure 4.1 displays the sample distribution per age and sex group.

Figure 4.1 Sample distribution per age and sex group

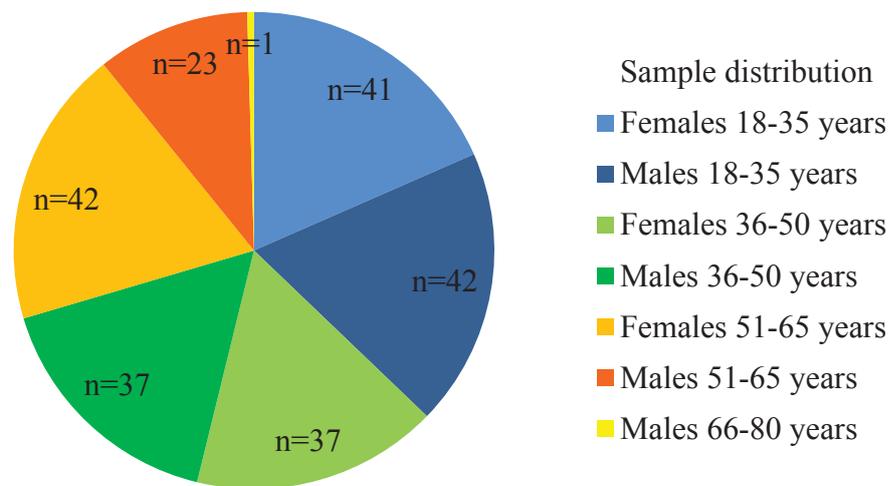


Figure 4.1 shows the sample distribution per age and sex group of the entire non-clinical cohort. Key: n = Sample size

4.1.1 Total non-clinical group demographics (females and males) (n=223)

Mean (\pm SD) demographics for the total non-clinical group (all females and males together) aged 18-71 years (n=223) are provided in Table 4.1.

Table 4.1 Mean demographics for the total non-clinical group (n=223)

Demographics		Value
Total non-clinical n=223	Years of age (mean ± SD)	39.39 ± 14.04
	Male (%)	45.98
	Years of education (mean ± SD)	18.04 ± 3.39
	BMI (mean ± SD)	24.65 ± 4.01
	Smoker (%)	11.61
	LAQ part one (mean ± SD)	13.50 ± 6.51
	LAQ part two (mean ± SD)	19.79 ± 9.76

Table 4.1 shows mean demographic scores for the total non-clinical group (n=223). BMI normal reference range is 19-25 (Garrouste-Orgeas et al., 2004). The maximum score of LAQ part one (lifestyle risk factors) is 70 and LAQ part two (stress coping) is 75. Higher LAQ scores reflect increased risk for developing chronic illnesses (Craig et al., 1996).

Key: BMI = Body mass index; LAQ = Lifestyle Appraisal Questionnaire (Craig et al., 1996); n = Sample size; SD = Standard deviation

Mean (± SD) scores from the MMSE and Cognistat with reference to their respective maximum score and cognitive impairment thresholds are displayed in Table 4.2. All mean scores were above their respective cognitive impairment thresholds, although the lower end of the SD crossed those thresholds for the Cognistat domains of attention (7.61 ± 0.78), comprehension (5.56 ± 0.64), repetition (11.60 ± 1.04), memory (11.15 ± 1.59), and judgment (4.54 ± 1.12).

Mean (± SD) values for HRV frequency and time domains for baseline and active states are displayed in Table 4.3 and Table 4.4, respectively. Cardiac reactivity (CR) refers to the active minus baseline HRV values. Large values are noted in the absolute values of frequency and time domain HRV data. Logarithmic transformation was applied to reduce the effect of skewed HRV data, as recommended by the literature (Tarkiainen et al., 2005, Macfarlane et al., 2011). Logarithmically transformed HRV data were used for all further statistical analyses.

Table 4.2 Mean cognitive scores from the MMSE and Cognistat for the total non-clinical group (n=223)

		Cognitive assessment	Cognitive domain	Maximum possible score	Cognitive impairment threshold	Mean ± SD
Total non-clinical n=223	MMSE		Orientation	10	-	9.86 ± 0.35
			Registration	3	-	3.00 ± 0.07
			Attention	5	-	4.37 ± 1.12
			Recall	3	-	2.79 ± 0.45
			Language	9	-	8.41 ± 0.75
		Total MMSE		30	≤23	28.42 ± 1.67
	Cognistat		Orientation	12	<10	11.84 ± 0.42
			Attention	8	<6	7.61 ± 0.78
			Comprehension	6	<5	5.56 ± 0.64
			Repetition	12	<11	11.60 ± 1.04
			Naming	8	<7	7.79 ± 0.57
			Construction	6	<4	5.24 ± 0.95
			Memory	12	<10	11.15 ± 1.59
			Calculation	4	<3	3.70 ± 0.56
		Similarity	8	<5	7.19 ± 1.21	
		Judgment	6	<4	4.54 ± 1.12	
	Total Cognistat		82	<65	76.20 ± 4.44	

Table 4.2 shows mean cognitive scores from the MMSE (Folstein et al., 1975) and the Cognistat (Kiernan et al., 1987) for the total non-clinical group (n=223). The maximum score possible and the cognitive impairment threshold are provided for each cognitive domain. Scores below the cognitive impairment threshold indicate cognitive impairment. The Cognistat domains where the lower end of the SD crossed the cognitive impairment threshold are shown in **bold**.

Key: MMSE = Mini Mental State Examination; n = Sample size; SD = Standard deviation

Table 4.3 Mean frequency domain HRV values for the total non-clinical group (n=223)

		HRV state	HRV frequency domain	Mean (\pm SD) ms ²
Total non-clinical n=223	Baseline		Low frequency (absolute)	1164.37 \pm 1254.11
			High frequency (absolute)	1276.99 \pm 2814.79
			LF/HF (absolute)	2.07 \pm 2.20
			Total power (absolute)	3763.08 \pm 4108.87
			Log low frequency	2.89 \pm 0.53
			Log high frequency	2.71 \pm 0.60
			Log LF/HF	0.15 \pm 0.41
			Log total power	3.40 \pm 0.41
	Active		Low frequency (absolute)	2524.06 \pm 1941.64
			High frequency (absolute)	1687.91 \pm 2317.37
			LF/HF (absolute)	3.20 \pm 2.96
			Total power (absolute)	6064.22 \pm 4881.84
			Log low frequency	3.29 \pm 0.38
			Log high frequency	2.91 \pm 0.59
			Log LF/HF	0.36 \pm 0.39
			Log total power	3.65 \pm 0.36
	Cardiac reactivity		Low frequency (absolute)	1170.41 \pm 2182.20
			High frequency (absolute)	851.30 \pm 3486.53
			LF/HF (absolute)	1.38 \pm 3.38
			Total power (absolute)	2720.29 \pm 6378.76
			Log low frequency	0.40 \pm 0.41
			Log high frequency	0.22 \pm 0.51
			Log LF/HF	0.21 \pm 0.40
			Log total power	0.27 \pm 0.33

Table 4.3 shows mean frequency domain HRV values for the total non-clinical group (n=223) during baseline and active states. Cardiac reactivity refers to the active minus baseline HRV data. The frequency domain HRV unit is milliseconds squared.

Key: HRV = Heart rate variability; LF/HF = Low frequency divided by high frequency (sympathovagal balance); ms² = Milliseconds squared; n = Sample size; SD = Standard deviation

Table 4.4 Mean time domain HRV values for the total non-clinical group (n=223)

HRV state		HRV time domain (unit)	Mean ± SD
Total non-clinical n=223	Baseline	Mean RR (ms)	875.39 ± 134.58
		SDNN (ms)	59.41 ± 25.69
		Mean heart rate (bpm)	70.45 ± 11.17
		RMSSD (ms)	49.03 ± 33.12
		pNN50 (%)	17.07 ± 16.58
		Log RMSSD (ms)	1.62 ± 0.29
		Log SDNN (ms)	1.75 ± 0.19
	Active	Mean RR (ms)	839.73 ± 122.67
		SDNN (ms)	74.43 ± 26.49
		Mean heart rate (bpm)	73.55 ± 11.08
		RMSSD (ms)	65.11 ± 37.97
		pNN50 (%)	17.55 ± 14.25
		Log RMSSD (ms)	1.75 ± 0.27
		Log SDNN (ms)	1.84 ± 0.17
	Cardiac reactivity	Mean RR (ms)	-36.01 ± 46.62
		SDNN (ms)	16.13 ± 23.81
		Mean heart rate (bpm)	3.11 ± 4.06
		RMSSD (ms)	17.47 ± 33.67
		pNN50 (%)	0.68 ± 8.82
		Log RMSSD (ms)	0.13 ± 0.23
		Log SDNN (ms)	0.11 ± 0.15

Table 4.4 shows mean time domain HRV values for the total non-clinical group (n=223) during baseline and active states. Cardiac reactivity refers to the active minus baseline HRV data.

Key: bpm = Beats per minute; HRV = Heart rate variability; ms = Milliseconds; n = Sample size; pNN50 = Total number of interval differences (greater than 50 milliseconds) of consecutive NN (beat to beat) intervals divided by the total number of NN intervals; RMSSD = Square root of the mean squared differences of successive NN intervals; RR = Duration in milliseconds from one R peak to the next R peak of the electrocardiogram; SD = Standard deviation; SDNN = SD of all NN intervals (the square root of variance)

4.1.2 18-35 years

4.1.2.1 Females (n=41)

Mean (\pm SD) demographics for females aged 18-35 years (n=41) are provided in Table 4.5.

Table 4.5 Mean sample demographics for females 18-35 years (n=41)

Females 18-35 years n=41	Demographics	Value
	Years of age (mean \pm SD)	23.81 \pm 4.12
	Years of education (mean \pm SD)	17.05 \pm 1.60
	BMI (mean \pm SD)	22.56 \pm 3.52
	Smoker (%)	7.32
	LAQ part one (mean \pm SD)	11.71 \pm 6.11
	LAQ part two (mean \pm SD)	23.49 \pm 10.39

Table 4.5 shows mean demographic scores for females 18-35 years (n=41). BMI normal reference range is 19-25 (Garrouste-Orgeas et al., 2004). The maximum score of LAQ part one (lifestyle risk factors) is 70 and LAQ part two (stress coping) is 75. Higher LAQ scores reflect increased risk for developing chronic illnesses (Craig et al., 1996).

Key: BMI = Body mass index; LAQ = Lifestyle Appraisal Questionnaire (Craig et al., 1996); n = Sample size; SD = Standard deviation

Mean (\pm SD) scores from the MMSE and Cognistat with reference to their respective maximum score and cognitive impairment thresholds are displayed in Table 4.6. All mean scores were above their respective cognitive impairment thresholds, although the lower end of the SD crossed those thresholds for the Cognistat domains of comprehension (5.63 \pm 0.66), repetition (11.63 \pm 0.86), calculation (3.51 \pm 0.64), and judgment (4.56 \pm 1.04).

Mean (\pm SD) values for HRV frequency and time domain parameters for baseline and active states are provided in Table 4.7 and Table 4.8, respectively.

Table 4.6 Mean cognitive scores from the MMSE and Cognistat for females 18-35 years (n=41)

		Cognitive assessment	Cognitive domain	Maximum possible score	Cognitive impairment threshold	Mean \pm SD
Females 18-35 years n=41	MMSE		Orientation	10	-	9.81 \pm 0.40
			Registration	3	-	3.00 \pm 0.00
			Attention	5	-	4.43 \pm 0.97
			Recall	3	-	2.85 \pm 0.36
			Language	9	-	8.56 \pm 0.70
		Total MMSE		30	≤ 23	28.42 \pm 1.67
	Cognistat		Orientation	12	<10	11.98 \pm 0.16
			Attention	8	<6	7.73 \pm 0.63
			Comprehension	6	<5	5.63 \pm 0.66
			Repetition	12	<11	11.63 \pm 0.86
			Naming	8	<7	7.81 \pm 0.72
			Construction	6	<4	5.38 \pm 0.90
			Memory	12	<10	11.59 \pm 0.81
			Calculation	4	<3	3.51 \pm 0.64
		Similarity	8	<5	7.20 \pm 1.15	
		Judgment	6	<4	4.56 \pm 1.04	
	Total Cognistat		82	<65	76.20 \pm 4.44	

Table 4.6 shows mean cognitive scores from the MMSE (Folstein et al., 1975) and the Cognistat (Kiernan et al., 1987) for females 18-35 years (n=41). The maximum score possible and the cognitive impairment threshold are provided for each cognitive domain. Scores below the cognitive impairment threshold indicate cognitive impairment. The Cognistat domains where the lower end of the SD crossed the cognitive impairment threshold are shown in **bold**.

Key: MMSE = Mini Mental State Examination; n = Sample size; SD = Standard deviation

Table 4.7 Mean frequency domain HRV values for females 18-35 years (n=41)

HRV state		HRV frequency domain	Mean (\pm SD) ms ²
Female 18-35 years n=41	Baseline	Low frequency (absolute)	1237.03 \pm 1404.81
		High frequency (absolute)	2045.38 \pm 4816.88
		LF/HF (absolute)	1.41 \pm 1.26
		Total power (absolute)	3975.09 \pm 3361.92
		Log low frequency	2.93 \pm 0.45
		Log high frequency	2.92 \pm 0.53
		Log LF/HF	0.01 \pm 0.35
		Log total power	3.51 \pm 0.39
	Active	Low frequency (absolute)	2595.46 \pm 2329.46
		High frequency (absolute)	1427.38 \pm 1636.17
		LF/HF (absolute)	2.76 \pm 2.33
		Total power (absolute)	5864.02 \pm 4319.61
		Log low frequency	3.30 \pm 0.40
		Log high frequency	2.93 \pm 0.47
		Log LF/HF	0.32 \pm 0.32
		Log total power	3.65 \pm 0.33
	Cardiac reactivity	Low frequency (absolute)	1473.91 \pm 1706.76
		High frequency (absolute)	687.52 \pm 4459.10
		LF/HF (absolute)	1.35 \pm 2.12
		Total power (absolute)	2884.25 \pm 7405.86
		Log low frequency	3.30 \pm 0.40
		Log high frequency	2.93 \pm 0.47
		Log LF/HF	0.32 \pm 0.32
		Log total power	3.65 \pm 0.33

Table 4.7 shows mean frequency domain HRV values for females 18-35 years (n=41) during baseline and active states. Cardiac reactivity refers to the active minus baseline HRV data.

Key: HRV = Heart rate variability; LF/HF = Low frequency divided by high frequency (sympathovagal balance); ms² = Milliseconds squared; n = Sample size; SD = Standard deviation

Table 4.8 Mean time domain HRV values for females 18-35 years (n=41)

HRV state		HRV time domain (unit)	Mean ± SD
Female 18-35 years n=41	Baseline	Mean RR (ms)	850.32 ± 141.64
		SDNN (ms)	63.88 ± 23.13
		Mean heart rate (bpm)	72.87 ± 11.59
		RMSSD (ms)	54.83 ± 31.16
		pNN50 (%)	20.51 ± 16.24
		Log RMSSD (ms)	1.70 ± 0.25
		Log SDNN (ms)	1.79 ± 0.18
	Active	Mean RR (ms)	811.44 ± 130.90
		SDNN (ms)	73.80 ± 24.38
		Mean heart rate (bpm)	76.41 ± 11.41
		RMSSD (ms)	62.49 ± 29.37
		pNN50 (%)	20.68 ± 13.68
		Log RMSSD (ms)	1.75 ± 0.22
		Log SDNN (ms)	1.84 ± 0.15
	Cardiac reactivity	Mean RR (ms)	-38.88 ± 46.22
		SDNN (ms)	11.47 ± 21.72
		Mean heart rate (bpm)	3.54 ± 3.84
		RMSSD (ms)	10.17 ± 35.07
		pNN50 (%)	-0.30 ± 7.08
		Log RMSSD (ms)	0.07 ± 0.20
		Log SDNN (ms)	0.07 ± 0.12

Table 4.8 shows mean time domain HRV values for females 18-35 years (n=41) during baseline and active states. Cardiac reactivity refers to the active minus baseline HRV data.

Key: bpm = Beats per minute; HRV = Heart rate variability; ms = Milliseconds; n = Sample size; pNN50 = Total number of interval differences (greater than 50 ms) of consecutive NN (beat to beat) intervals divided by the total number of NN intervals; RMSSD = Square root of the mean squared differences of successive NN intervals; RR = Duration in ms from one R peak to the next R peak of the electrocardiogram; SD = Standard deviation; SDNN = SD of all NN intervals (the square root of variance)

Dependent sample t-tests were performed to determine significant differences between baseline and active (cognitive task) HRV measures (Table 4.9).

Table 4.9 Dependent sample t-test between baseline and active HRV states for females 18-35 years (n=41)

	Variable (unit)	t	df	p	Baseline mean ± SD	Active mean ± SD	Mean difference (active - baseline)
Females 18-35 years n=41	Mean RR (ms)	5.39	40	<0.001	850.32 ± 141.64	811.44 ± 130.90	-38.88
	Mean heart rate (bpm)	-5.90	40	<0.001	72.87 ± 11.59	76.41 ± 11.41	3.54
	Log LF (ms ²)	-7.58	40	<0.001	2.93 ± 0.45	3.30 ± 0.40	0.07
	Log LF/HF	-5.83	40	<0.001	0.01 ± 0.35	0.32 ± 0.32	0.31
	Log total power (ms ²)	-4.27	39	<0.001	3.51 ± 0.39	3.65 ± 0.33	3.14
	Log SDNN (ms)	-3.45	39	0.001	1.79 ± 0.18	1.84 ± 0.15	0.05

Table 4.9 displays significant results from a dependent sample t-test between baseline and active HRV states for females aged 18-35 years (n=41).

Key: bpm = Beats per minute; df = Degrees of freedom; HRV = Heart rate variability; LF = Low frequency; LF/HF = Low frequency divided by high frequency (sympathovagal balance); ms = Milliseconds; ms² = Milliseconds squared; n = Sample size; p = Level of statistical significance (p<0.05); RR = Duration in milliseconds from one R peak to the next R peak of the electrocardiogram; SD = Standard deviation; SDNN = Standard deviation of all NN intervals (the square root of variance); t = T statistic

Pearson’s bivariate and partial correlations were performed separately between HRV and cognitive scores to address aims 1 and 5 (Table 4.10 and Table 4.11, respectively).

Table 4.10 Pearson’s correlation coefficients between cognitive scores and HRV in females 18-35 years (n=41)

Females 18-35 years n=41	Dependent variable	Independent variable	r	p
	Naming Cognistat	Log cardiac reactivity LF	-0.32	0.045
	Calculation Cognistat	Cardiac reactivity mean RR	-0.33	0.03
		Cardiac reactivity mean heart rate	0.39	0.01
	Total Cognistat	Cardiac reactivity mean RR	-0.34	0.03
Cardiac reactivity mean heart rate		0.33	0.03	

Table 4.10 displays significant results from a Pearson’s correlation between cognitive scores (MMSE (Folstein et al., 1975) and Cognistat (Kiernan et al., 1987)) and HRV in females 18-35 years (n=41).

Key: HRV = Heart rate variability; LF = Low frequency; n = Sample size; p = Level of statistical significance (p<0.05); r = Correlation coefficient; RR = Duration in milliseconds from one R peak to the next R peak of the electrocardiogram

A regression was not performed between memory and the four HRV variables as the p-values did not pass a Bonferroni correction (Table 4.11).

Table 4.11 Partial Pearson’s correlation coefficients between cognitive scores and HRV in females 18-35 years (n=41)

	Covariate	Dependent variable	Independent variable	r	p
Females 18-35 years n=41	LAQ part one (lifestyle risk factors)	Construction Cognistat	Log cardiac reactivity LF/HF	0.34	0.03
	BMI	Memory Cognistat	Log baseline SDNN	0.33	0.04*
			Log baseline RMSSD	0.33	0.04*
			Cardiac reactivity mean RR	-0.33	0.04*
			Cardiac reactivity mean heart rate	0.36	0.02*

Table 4.11 displays significant results from a partial Pearson’s correlation between cognitive scores (MMSE (Folstein et al., 1975) and Cognistat (Kiernan et al., 1987)) and HRV in females 18-35 years (n=41).

Key: BMI = Body mass index; HRV = Heart rate variability; LAQ = Lifestyle Appraisal Questionnaire (Craig et al., 1996); LF/HF = Low frequency divided by high frequency (sympathovagal balance); n = Sample size; p = Level of statistical significance; r = Correlation coefficient; RMSSD = Square root of the mean squared differences of successive NN (beat to beat) intervals; RR = Duration in milliseconds from one R peak to the next R peak of the electrocardiogram; SDNN = Standard deviation of all NN intervals (the square root of variance); * = Bonferroni correction excludes this significant correlation

4.1.2.2 Males (n=42)

Mean (\pm SD) demographics for males aged 18-35 years (n=42) are provided in Table 4.12.

Table 4.12 Mean sample demographics for males 18-35 years (n=42)

Demographics		Value
Males 18-35 years n=42	Years of age (mean \pm SD)	23.81 \pm 4.05
	Years of education (mean \pm SD)	16.5 \pm 2.16
	BMI (mean \pm SD)	23.69 \pm 3.18
	Smoker (%)	16.67
	LAQ part one (mean \pm SD)	11.29 \pm 6.07
	LAQ part two (mean \pm SD)	16.81 \pm 10.15

Table 4.12 shows mean demographic scores for males 18-35 years (n=42). BMI normal reference range is 19-25 (Garrouste-Orgeas et al., 2004). The maximum score of LAQ part one (lifestyle risk factors) is 70 and LAQ part two (stress coping) is 75. Higher LAQ scores reflect increased risk for developing chronic illnesses (Craig et al., 1996).

Key: BMI = Body mass index; LAQ = Lifestyle Appraisal Questionnaire (Craig et al., 1996); n = Sample size; SD = Standard deviation

Mean (\pm SD) scores from the MMSE and Cognistat with reference to their respective maximum score and cognitive impairment thresholds are displayed in Table 4.13. All mean scores were above their respective cognitive impairment thresholds, although the lower end of the SD crossed those thresholds for the Cognistat domains of memory (11.14 \pm 1.92) and judgment (4.21 \pm 1.20).

Mean (\pm SD) values for HRV frequency and time domain parameters for baseline and active states are provided in Table 4.14 and Table 4.15, respectively.

Table 4.13 Mean cognitive scores from the MMSE and Cognistat for males 18-35 years (n=42)

		Cognitive assessment	Cognitive domain	Maximum possible score	Cognitive impairment threshold	Mean \pm SD
Males 18-35 years n=42	MMSE		Orientation	10	-	9.86 \pm 0.35
			Registration	3	-	3.00 \pm 0.00
			Attention	5	-	4.52 \pm 0.99
			Recall	3	-	2.83 \pm 0.38
			Language	9	-	8.63 \pm 0.53
		Total MMSE		30	≤ 23	28.85 \pm 1.50
	Cognistat		Orientation	12	<10	11.83 \pm 0.44
			Attention	8	<6	7.69 \pm 0.64
			Comprehension	6	<5	5.64 \pm 0.62
			Repetition	12	<11	11.76 \pm 0.66
			Naming	8	<7	7.88 \pm 0.40
			Construction	6	<4	5.62 \pm 0.62
			Memory	12	<10	11.14 \pm 1.92
			Calculation	4	<3	3.87 \pm 0.37
		Similarity	8	<5	7.45 \pm 1.23	
		Judgment	6	<4	4.21 \pm 1.20	
	Total Cognistat		82	<65	77.11 \pm 4.08	

Table 4.13 shows mean cognitive scores from the MMSE (Folstein et al., 1975) and the Cognistat (Kiernan et al., 1987) for males 18-35 years (n=42). The maximum score possible and the cognitive impairment threshold are provided for each cognitive domain. Scores below the cognitive impairment threshold indicate cognitive impairment. The Cognistat domains where the lower end of the SD crossed the cognitive impairment threshold are shown in **bold**.

Key: MMSE = Mini Mental State Examination; n = Sample size; SD = Standard deviation

Table 4.14 Mean frequency domain HRV values for males 18-35 years (n=42)

HRV state		HRV frequency domain	Mean (\pm SD) ms ²
Males 18-35 years n=42	Baseline	Low frequency (absolute)	1290.77 \pm 1254.89
		High frequency (absolute)	1207.52 \pm 1810.27
		LF/HF (absolute)	2.12 \pm 2.21
		Total power (absolute)	3964.50 \pm 4310.17
		Log low frequency	2.91 \pm 0.53
		Log high frequency	2.73 \pm 0.59
		Log LF/HF	0.18 \pm 0.33
		Log total power	3.39 \pm 0.45
	Active	Low frequency (absolute)	2605.33 \pm 2077.09
		High frequency (absolute)	1467.19 \pm 1957.37
		LF/HF (absolute)	3.50 \pm 2.81
		Total power (absolute)	5668.83 \pm 4524.42
		Log low frequency	3.25 \pm 0.42
		Log high frequency	2.87 \pm 0.63
		Log LF/HF	0.42 \pm 0.34
		Log total power	3.61 \pm 0.39
	Cardiac reactivity	Low frequency (absolute)	1255.74 \pm 2173.22
		High frequency (absolute)	911.88 \pm 4225.82
		LF/HF (absolute)	1.39 \pm 2.59
		Total power (absolute)	2030.47 \pm 5302.91
		Log low frequency	0.41 \pm 0.38
		Log high frequency	0.19 \pm 0.55
		Log LF/HF	0.23 \pm 0.36
		Log total power	0.25 \pm 0.32

Table 4.14 shows mean frequency domain HRV values for males 18-35 years (n=42) during baseline and active states. Cardiac reactivity refers to the active minus baseline HRV data.

Key: HRV = Heart rate variability; LF/HF = Low frequency divided by high frequency (sympathovagal balance); ms² = Milliseconds squared; n = Sample size; SD = Standard deviation

Table 4.15 Mean time domain HRV values for males 18-35 years (n=42)

HRV state		HRV time domain (unit)	Mean ± SD
Males 18-35 years n=42	Baseline	Mean RR (ms)	842.81 ± 104.68
		SDNN (ms)	59.99 ± 28.16
		Mean heart rate (bpm)	72.76 ± 9.82
		RMSSD (ms)	49.39 ± 34.02
		pNN50 (%)	15.42 ± 15.67
		Log RMSSD (ms)	1.61 ± 0.27
		Log SDNN (ms)	1.73 ± 0.20
	Active	Mean RR (ms)	811.24 ± 95.81
		SDNN (ms)	71.36 ± 24.43
		Mean heart rate (bpm)	76.06 ± 9.87
		RMSSD (ms)	59.23 ± 35.13
		pNN50 (%)	15.29 ± 12.63
		Log RMSSD (ms)	1.72 ± 0.29
		Log SDNN (ms)	1.82 ± 0.17
	Cardiac reactivity	Mean RR (ms)	-31.56 ± 47.68
		SDNN (ms)	15.86 ± 21.90
		Mean heart rate (bpm)	3.30 ± 5.73
		RMSSD (ms)	15.87 ± 30.42
		pNN50 (%)	1.16 ± 9.43
		Log RMSSD (ms)	0.13 ± 0.22
		Log SDNN (ms)	0.12 ± 0.15

Table 4.15 shows mean time domain HRV values for males 18-35 years (n=42) during baseline and active states. Cardiac reactivity refers to the active minus baseline HRV data.

Key: bpm = Beats per minute; HRV = Heart rate variability; ms = Milliseconds; n = Sample size; pNN50 = Total number of interval differences (greater than 50 ms) of consecutive NN (beat to beat) intervals divided by the total number of NN intervals; RMSSD = Square root of the mean squared differences of successive NN intervals; RR = Duration in ms from one R peak to the next R peak of the electrocardiogram; SD = Standard deviation; SDNN = SD of all NN intervals (the square root of variance)

Dependent sample t-tests were performed to determine significant differences between baseline and active (cognitive task) HRV states (Table 4.16).

Table 4.16 Dependent sample t-test between baseline and active HRV states for males 18-35 years (n=42)

	Variable (unit)	t	df	p	Baseline mean ± SD	Active mean ± SD	Mean difference (active - baseline)
Males 18-35 years n=42	Mean RR (ms)	4.29	41	<0.001	842.81 ± 104.68	811.24 ± 95.81	-31.57
	Mean heart rate (bpm)	-3.73	41	0.001	72.76 ± 9.82	76.06 ± 9.87	3.30
	Log LF (ms ²)	-5.43	40	<0.001	2.91 ± 0.53	3.25 ± 0.42	0.34
	Log LF/HF	-4.20	41	<0.001	0.18 ± 0.33	0.42 ± 0.34	0.24
	Log total power (ms ²)	-3.60	40	0.001	3.39 ± 0.45	3.61 ± 0.39	0.22
	Log SDNN (ms)	-3.51	40	0.001	1.73 ± 0.20	1.82 ± 0.17	0.09
	Log RMSSD (ms)	-2.50	41	0.02	1.61 ± 0.27	1.72 ± 0.29	0.11

Table 4.16 displays significant results from a dependent sample t-test between baseline and active HRV states for males aged 18-35 years (n=42).

Key: bpm = Beats per minute; df = Degrees of freedom; HRV = Heart rate variability; LF = Low frequency; LF/HF = Low frequency divided by high frequency (sympathovagal balance); ms = Milliseconds; ms² = Milliseconds squared; n = Sample size; p = Level of statistical significance (p<0.05); RMSSD = Square root of the mean squared differences of successive NN intervals; RR = Duration in milliseconds from one R peak to the next R peak of the electrocardiogram; SD = Standard deviation; SDNN = Standard deviation of all NN intervals (the square root of variance); t = T statistic

Pearson’s bivariate and partial correlations (Table 4.17) were performed separately between HRV and cognitive scores and address aims 1 and 5. Bivariate correlations identified negative relationships between orientation and similarity domains (Cognistat) with log baseline LF/HF ($r=-0.33$, $p=0.03$; $r=-0.32$, $p=0.04$, respectively).

Table 4.17 Partial Pearson’s correlation coefficients between cognitive scores and HRV in males 18-35 years (n=42)

	Covariate	Dependent variable	Independent variable	r	p
Males 18-35 years n=42	LAQ part two (stress coping)	Comprehension Cognistat	Log CR total power	0.32	0.045*
			Log CR SDNN	0.42	0.01
	Smoking status	Memory Cognistat	Log baseline LF/HF	-0.34	0.03*
			CR mean RR	0.34	0.03*
			CR mean heart rate	-0.37	0.02
	LAQ part one (lifestyle risk factors) and smoking status	Judgment Cognistat	Log CR SDNN	0.32	0.045
	BMI	Total Cognistat	Log baseline LF/HF	-0.42	0.01
			CR mean RR	0.40	0.01
			CR mean heart rate	-0.42	0.01

Table 4.17 displays significant results from a partial Pearson’s correlation between cognitive scores (MMSE (Folstein et al., 1975) and Cognistat (Kiernan et al., 1987)) and HRV in males 18-35 years (n=42).

Key: BMI = Body mass index; CR = Cardiac reactivity; HRV = Heart rate variability; LAQ = Lifestyle Appraisal Questionnaire (Craig et al., 1996); LF/HF = Low frequency divided by high frequency (sympathovagal balance); n = Sample size; p = Level of statistical significance ($p<0.05$); r = Correlation coefficient; RR = Duration in milliseconds from one R peak to the next R peak of the electrocardiogram; SDNN = Standard deviation of all NN intervals (the square root of variance); * = Bonferroni correction excludes this significant correlation

A multiple regression was performed when three or more independent variables were significantly correlated to one dependent variable (after a Bonferroni correction). Table 4.18 displays the hierarchical multiple regression analysis between total Cognistat score (with BMI as a covariate) and three HRV variables from Table 4.17 to address aim 6. A

regression was not performed between memory (Cognistat) and three HRV variables as two of the p-values did not pass a Bonferroni correction.

Log baseline LF/HF, CR mean RR, and CR mean HR (with BMI as covariate) significantly predicted total Cognistat score in a hierarchical multiple regression model ($F(4,37)=6.94$, $p<0.001$). Together, the independent variables explain 37% of the variability in the total Cognistat score. Log baseline LF/HF and BMI both contributed significantly to the prediction ($p=0.004$). Table 4.18 displays regression coefficients and standard errors.

Table 4.18 Hierarchical multiple regression between total Cognistat score and HRV variables in males 18-35 years (n=42)

Males 18-35 years (n=42)	R	R square	Adjusted R square	Std. error of the estimate	p
Total Cognistat	0.66	0.43	0.37	3.25	<0.001
	B	Std. error	Beta	t	p
(Constant)	90.74	3.89		23.35	<0.001
Log baseline LF/HF	-4.80	1.54	-0.39	-3.12	0.004
Cardiac reactivity mean RR	0.01	0.03	0.11	0.32	0.75
Cardiac reactivity mean heart rate	-0.20	0.25	-0.29	-0.81	0.42
BMI	-0.50	0.16	-0.39	-3.10	0.004

Table 4.18 shows hierarchical multiple regression analysis between total Cognistat score (Kiernan et al., 1987) and HRV variables: log baseline LF/HF, cardiac reactivity mean RR, and mean heart rate (adjusted for BMI) in males 18-35 years (n=42).

Key: B = Unstandardised regression coefficient; Beta = Standardised regression coefficient; BMI = Body mass index; HRV = Heart rate variability; LF/HF = Low frequency divided by high frequency (sympathovagal balance); n = Sample size; p = Level of statistical significance (p<0.05 (in bold)); R = Correlation coefficient; R square = Proportion of variance; RR = Duration in milliseconds from one R peak to the next R peak of the electrocardiogram; Std. = Standard; t = t statistic

4.1.2.3 Comparison between females (n=41) and males (n=42) (18-35 years)

Mean cognitive scores (Cognistat and MMSE) for females and males aged 18-35 years are displayed in Figure 4.2.

Figure 4.2 Mean cognitive scores (Cognistat and MMSE) for females (n=41) and males (n=42) aged 18-35 years

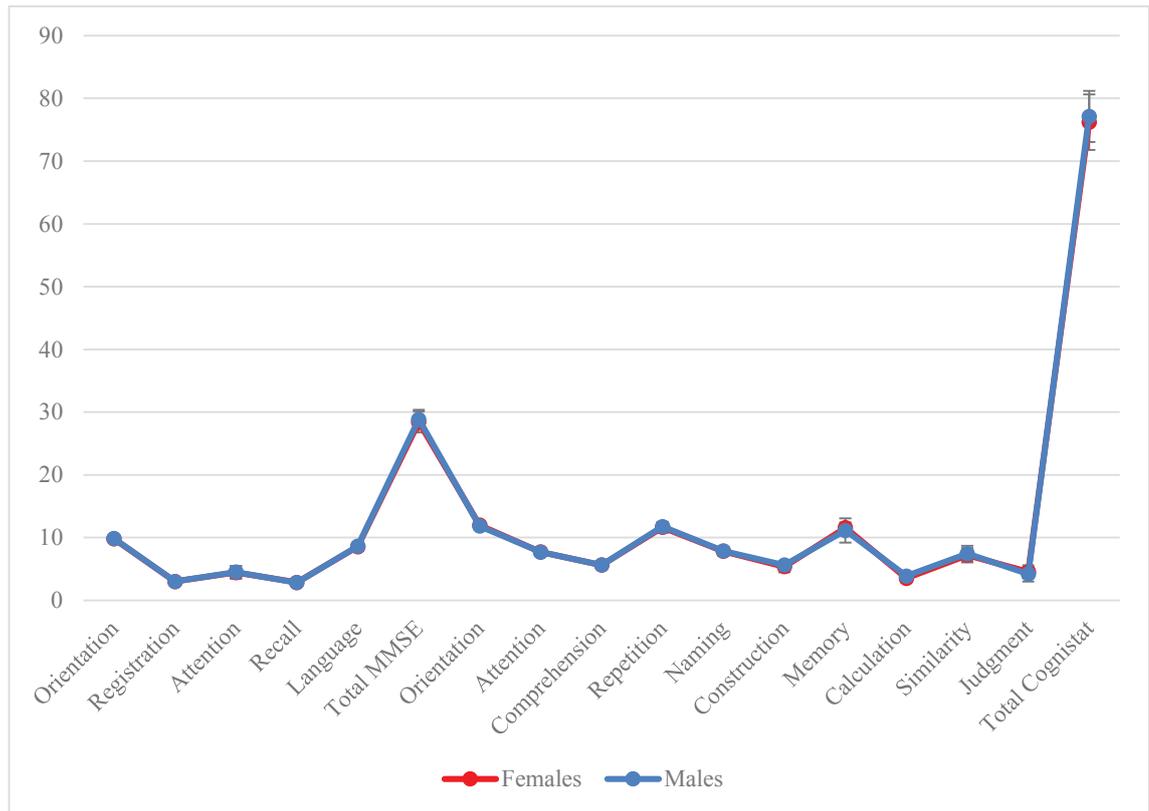


Figure 4.2 displays mean cognitive scores (Cognistat (Kiernan et al., 1987) and MMSE (Folstein et al., 1975)) for females (n=41) and males (n=42) aged 18-35 years.

MMSE = Mini Mental State Examination

An independent sample t-test was used to compare cognitive scores between females and males aged 18-35 years. Calculation (Cognistat) scores were significantly higher in males than females (3.87 ± 0.37 , 3.51 ± 0.64 , respectively) ($t=-3.12$, $df=63.62$, $p=0.002$, Levene’s test $p<0.001$ (equal variances not assumed)).

An independent sample t-test with covariates was used to compare cognitive scores between females and males aged 18-35 years (Table 4.19).

Table 4.19 Independent sample t-test with covariates of cognitive scores between females (n=41) and males (n=42) aged 18-35 years

	Covariate	Variable	F	df	p	Females mean ± SD	Males mean ± SD	Mean difference (males - females)
Females and males 18-35 years	BMI	Memory Cognistat	6.05	2, 78	0.004	11.59 ± 0.81	11.14 ± 1.92	-0.45
		Judgment Cognistat	4.70	2, 78	0.01	4.56 ± 1.04	4.21 ± 1.20	-0.35
		Total Cognistat	4.61	2, 78	0.01	77.01 ± 3.48	77.11 ± 4.08	0.10
	LAQ part two (stress coping)	Recall MMSE	4.17	2, 80	0.02	2.85 ± 0.36	2.83 ± 0.38	-0.02

Table 4.19 displays significant results from an independent sample t-test with covariates (performed by ANCOVA and MANCOVA) of cognitive scores (from the MMSE (Folstein et al., 1975) and Cognistat (Kiernan et al., 1987)) between females (n=41) and males (n=42) aged 18-35 years.

Key: ANCOVA = Analysis of covariance; BMI = Body mass index; df = Degrees of freedom; F = F statistic; LAQ = Lifestyle Appraisal Questionnaire (Craig et al., 1996); MANCOVA = Multiple analysis of covariance; MMSE = Mini Mental State Examination; n = Sample size; p = Level of statistical significance (p<0.05); SD = Standard deviation

An independent sample t-test was used to compare HRV values between females and males aged 18-35 years. Log baseline LF/HF was significantly higher in males than females (0.18 ± 0.33, 0.01 ± 0.35, respectively) (t=0.11, df=81, p=0.02).

An independent sample t-test with covariates was used to compare HRV values between females and males aged 18-35 years (Table 4.20).

Table 4.20 Independent sample t-test with covariance of HRV values between females (n=41) and males (n=42) aged 18-35 years

Covariate		Variable (unit)	F	df	p	Females mean ± SD	Males mean ± SD	Mean difference (males – females)	
Females and males 18-35 years	BMI	Baseline mean RR (ms)	3.20	2, 78	0.046	850.32 ± 141.64	842.81 ± 104.68	-7.51	
		Baseline mean HR (bpm)	3.23	2, 78	0.045	72.87 ± 11.59	72.76 ± 9.82	-0.11	
		Log baseline LF (ms ²)	5.34	2, 78	0.01	2.93 ± 0.45	2.91 ± 0.53	-0.02	
		Log baseline HF (ms ²)	4.45	2, 78	0.02	2.92 ± 0.53	2.73 ± 0.59	-0.19	
		Log baseline TP (ms ²)	5.80	2, 78	0.01	3.51 ± 0.39	3.39 ± 0.45	-3.12	
		Log baseline SDNN (ms)	5.24	2, 78	0.01	1.79 ± 0.18	1.73 ± 0.20	-0.06	
		Log baseline RMSSD (ms)	3.59	2, 78	0.03	1.70 ± 0.25	1.61 ± 0.27	-0.09	
		Active mean RR (ms)	4.57	2, 78	0.01	811.44 ± 130.90	811.24 ± 95.81	-0.20	
		Active mean HR (bpm)	4.79	2, 78	0.01	76.41 ± 11.41	76.06 ± 9.87	-0.35	
		Log active LF (ms ²)	3.33	2, 78	0.04	3.30 ± 0.40	3.25 ± 0.42	-0.05	
		Log active SDNN (ms)	4.83	2, 78	0.01	1.84 ± 0.15	1.82 ± 0.17	-0.02	
		Log active RMSSD (ms)	4.17	2, 78	0.02	1.75 ± 0.22	1.72 ± 0.29	-0.03	
		LAQ part two (stress coping)	Log active LF/HF	4.26	2, 80	0.02	0.32 ± 0.32	0.42 ± 0.34	0.10
		Years of education	Log CR LF (ms ²)	3.42	2, 62	0.04	3.30 ± 0.40	0.41 ± 0.38	-2.89
LAQ part one (lifestyle risk factors) and smoking status	Log CR SDNN (ms)	7.00	2, 79	0.002	0.07 ± 0.12	0.12 ± 0.15	0.05		

Table 4.20 displays significant results from an independent sample t-test with covariance (performed by ANCOVA and MANCOVA) of HRV values between females (n=41) and males (n=42) aged 18-35 years.

Key: ANCOVA = Analysis of covariance; BMI = Body mass index; bpm = Beats per minute; CR = Cardiac reactivity; df = Degrees of freedom; F = F statistic; HF = High frequency; HR = Heart rate; HRV = Heart rate variability; LAQ = Lifestyle Appraisal Questionnaire; LF = Low frequency; LF/HF = Low frequency divided by high frequency (sympathovagal balance); MANCOVA = Multiple analysis of covariance; ms = Milliseconds; ms² = Milliseconds squared; n = Sample size; p = Level of statistical significance (p<0.05); RMSSD = Square root of the mean squared differences of successive NN intervals; RR = Duration in milliseconds from one R peak to the next R peak of the electrocardiogram; SD = Standard deviation; SDNN = Standard deviation of all NN intervals (the square root of variance); TP = Total power

Significant correlations in 18-35 year old females and males were compared using Z scores to address aim 3 (Table 4.21).

Table 4.21 Correlation comparisons using Z scores between females (n=41) and males (n=42) aged 18-35 years

	Dependent variable	Independent variable	Z	p
Females and males 18-35 years	Total Cognistat	Cardiac reactivity mean RR	3.41	<0.001
		Cardiac reactivity mean heart rate	-3.48	<0.001
	Memory Cognistat	Cardiac reactivity mean RR	3.05	0.001
		Cardiac reactivity mean heart rate	-3.34	<0.001

Table 4.21 compares significant correlations ($p < 0.05$) in females (n=41) and males (n=42) aged 18-35 years using z-scores (Cognistat (Kiernan et al., 1987)). Significant p marks the correlations in females and males as significantly different.

Key: n = Sample size; p = Level of statistical significance ($p < 0.05$); RR = Duration in milliseconds from one R peak to the next R peak of the electrocardiogram; Z = Z score

4.1.3 36-50 years

4.1.3.1 Females (n=37)

Mean (\pm SD) demographics for females aged 36-50 years (n=37) are provided in Table 4.22.

Table 4.22 Mean sample demographics for females 36-50 years (n=37)

Demographics		Value
Females 36-50 years n=37	Years of age (mean \pm SD)	42.70 \pm 4.33
	Years of education (mean \pm SD)	18.97 \pm 3.75
	BMI (mean \pm SD)	25.69 \pm 4.80
	Smoker (%)	5.41
	LAQ part one (mean \pm SD)	12.91 \pm 4.81
	LAQ part two (mean \pm SD)	19.16 \pm 7.21

Table 4.22 shows mean demographic scores for females 36-50 years (n=37). BMI normal reference range is 19-25 (Garrouste-Orgeas et al., 2004). The maximum score of LAQ part one (lifestyle risk factors) is 70 and LAQ part two (stress coping) is 75. Higher LAQ scores reflect increased risk for developing chronic illnesses (Craig et al., 1996).

Key: BMI = Body mass index; LAQ = Lifestyle Appraisal Questionnaire (Craig et al., 1996); n = Sample size; SD = Standard deviation

Mean (\pm SD) scores from the MMSE and Cognistat with reference to their respective maximum score and cognitive impairment thresholds are displayed in Table 4.23. All mean scores were above their respective cognitive impairment thresholds, although the lower end of the SD crossed those thresholds for the Cognistat domains of attention (7.60 \pm 0.64), repetition (11.68 \pm 1.08), memory (11.19 \pm 1.43), and judgment (4.70 \pm 1.22).

Table 4.23 Mean cognitive scores from the MMSE and Cognistat for females 36-50 years (n=37)

		Cognitive assessment	Cognitive domain	Maximum possible score	Cognitive impairment threshold	Mean \pm SD
Females 36-50 years n=37	MMSE		Orientation	10	-	9.87 \pm 0.35
			Registration	3	-	3.00 \pm 0.00
			Attention	5	-	4.10 \pm 1.30
			Recall	3	-	2.60 \pm 0.55
			Language	9	-	8.45 \pm 0.65
		Total MMSE		30	≤ 23	28.85 \pm 1.50
	Cognistat		Orientation	12	<10	11.87 \pm 0.35
			Attention	8	<6	7.60 \pm 0.64
			Comprehension	6	<5	5.66 \pm 0.47
			Repetition	12	<11	11.68 \pm 1.08
			Naming	8	<7	7.84 \pm 0.55
			Construction	6	<4	5.04 \pm 0.99
			Memory	12	<10	11.19 \pm 1.43
			Calculation	4	<3	3.60 \pm 0.60
		Similarity	8	<5	6.80 \pm 1.32	
		Judgment	6	<4	4.70 \pm 1.22	
	Total Cognistat		82	<65	77.11 \pm 4.08	

Table 4.23 shows mean cognitive scores from the MMSE (Folstein et al., 1975) and the Cognistat (Kiernan et al., 1987) for females 36-50 years (n=37). The maximum score possible and the cognitive impairment threshold are provided for each cognitive domain. Scores below the cognitive impairment threshold indicate cognitive impairment. The Cognistat domains where the lower end of the SD crossed the cognitive impairment threshold are shown in **bold**.

Key: MMSE = Mini Mental State Examination; n = Sample size; SD = Standard deviation

Mean (\pm SD) values for HRV frequency and time domain parameters for baseline and active states are provided in Table 4.24 and Table 4.25, respectively.

Table 4.24 Mean frequency domain HRV values for females 36-50 years (n=37)

HRV state		HRV frequency domain	Mean (\pm SD) ms ²
Females 36-50 years n=37	Baseline	Low frequency (absolute)	1494.25 \pm 1679.47
		High frequency (absolute)	1293.64 \pm 2382.88
		LF/HF (absolute)	2.22 \pm 2.43
		Total power (absolute)	4737.01 \pm 5122.83
		Log low frequency	3.05 \pm 0.61
		Log high frequency	2.75 \pm 0.51
		Log LF/HF	0.20 \pm 0.50
		Log total power	3.47 \pm 0.43
	Active	Low frequency (absolute)	3031.46 \pm 1843.98
		High frequency (absolute)	2046.02 \pm 2427.25
		LF/HF (absolute)	3.56 \pm 3.18
		Total power (absolute)	7287.51 \pm 5029.19
		Log low frequency	3.39 \pm 0.31
		Log high frequency	3.00 \pm 0.57
		Log LF/HF	0.39 \pm 0.39
		Log total power	3.76 \pm 0.33
	Cardiac reactivity	Low frequency (absolute)	720.32 \pm 2761.50
		High frequency (absolute)	768.01 \pm 2552.24
		LF/HF (absolute)	0.85 \pm 2.72
		Total power (absolute)	2546.26 \pm 5548.79
		Log low frequency	0.34 \pm 0.51
		Log high frequency	0.25 \pm 0.49
		Log LF/HF	0.15 \pm 0.47
		Log total power	0.29 \pm 0.38

Table 4.24 shows mean frequency domain HRV values for females 36-50 years (n=37) during baseline and active states. Cardiac reactivity refers to the active minus baseline HRV data.

Key: HRV = Heart rate variability; LF/HF = Low frequency divided by high frequency (sympathovagal balance); ms² = Milliseconds squared; n = Sample size; SD = Standard deviation

Table 4.25 Mean time domain HRV values for females 36-50 years (n=37)

HRV state		HRV time domain (unit)	Mean ± SD
Females 36-50 years n=37	Baseline	Mean RR (ms)	890.76 ± 105.00
		SDNN (ms)	64.98 ± 30.45
		Mean heart rate (bpm)	68.80 ± 8.52
		RMSSD (ms)	53.56 ± 37.99
		pNN50 (%)	17.38 ± 14.85
		Log RMSSD (ms)	1.67 ± 0.28
		Log SDNN (ms)	1.78 ± 0.21
	Active	Mean RR (ms)	850.86 ± 98.80
		SDNN (ms)	80.22 ± 24.85
		Mean heart rate (bpm)	72.14 ± 8.45
		RMSSD (ms)	71.56 ± 37.50
		pNN50 (%)	20.06 ± 14.99
		Log RMSSD (ms)	1.79 ± 0.25
		Log SDNN (ms)	1.88 ± 0.14
	Cardiac reactivity	Mean RR (ms)	-39.90 ± 46.50
		SDNN (ms)	15.12 ± 23.82
		Mean heart rate (bpm)	3.33 ± 3.52
		RMSSD (ms)	17.96 ± 29.59
		pNN50 (%)	2.25 ± 10.70
		Log RMSSD (ms)	0.12 ± 0.22
		Log SDNN (ms)	0.10 ± 0.16

Table 4.25 shows mean time domain HRV values for females 36-50 years (n=37) during baseline and active states. Cardiac reactivity refers to the active minus baseline HRV data.

Key: bpm = Beats per minute; HRV = Heart rate variability; ms = Milliseconds; n = Sample size; pNN50 = Total number of interval differences (greater than 50 ms) of consecutive NN (beat to beat) intervals divided by the total number of NN intervals; RMSSD = Square root of the mean squared differences of successive NN intervals; RR = Duration in ms from one R peak to the next R peak of the electrocardiogram; SD = Standard deviation; SDNN = SD of all NN intervals (the square root of variance)

Dependent sample t-tests were performed to determine significant differences between baseline and active (cognitive task) HRV states (Table 4.26).

Table 4.26 Dependent sample t-test between baseline and active HRV states for females 36-50 years (n=37)

	Variable (unit)	t	df	p	Baseline mean ± SD	Active mean ± SD	Mean difference (active – baseline)
Females 36-50 years n=37	Mean RR (ms)	5.22	36	<0.001	890.76 ± 105.00	850.86 ± 98.80	-39.90
	Mean HR (bpm)	-5.76	36	<0.001	68.80 ± 8.52	72.14 ± 8.45	3.34
	Log LF (ms ²)	-3.98	36	<0.001	3.05 ± 0.61	3.39 ± 0.31	0.34
	Log HF (ms ²)	-3.04	35	0.004	2.75 ± 0.51	3.00 ± 0.57	0.25
	Log LF/HF	-2.27	35	0.03	0.20 ± 0.50	0.39 ± 0.39	0.19
	Log TP (ms ²)	-4.47	35	<0.001	3.47 ± 0.43	3.76 ± 0.33	0.29
	Log SDNN (ms)	-3.76	36	0.001	1.78 ± 0.21	1.88 ± 0.14	0.10
	Log RMSSD (ms)	-3.39	36	0.002	1.67 ± 0.28	1.79 ± 0.25	0.12

Table 4.26 displays significant results from a dependent sample t-test between baseline and active HRV states for females aged 36-50 years (n=37).

Key: bpm = Beats per minute; df = Degrees of freedom; HF = High frequency; HR = Heart rate; HRV = Heart rate variability; LF = Low frequency; LF/HF = Low frequency divided by high frequency (sympathovagal balance); ms = Milliseconds; ms² = Milliseconds squared; n = Sample size; p = Level of statistical significance (p<0.05); RMSSD = Square root of the mean squared differences of successive NN intervals; RR = Duration in milliseconds from one R peak to the next R peak of the electrocardiogram; SD = Standard deviation; SDNN = Standard deviation of all NN intervals (the square root of variance); t = T statistic; TP = Total power

Correlation coefficients were calculated to identify which covariates were significantly related to dependent and independent variables. Pearson’s bivariate and partial correlations were performed separately between HRV and cognitive scores to address aims 1 and 5 (Table 4.27 and Table 4.28, respectively).

Table 4.27 Pearson’s correlation coefficients between cognitive scores and HRV in females 36-50 years (n=37)

	Dependent variable	Independent variable	r	p
Females 36-50 years n=37	Comprehension Cognistat	Baseline pNN50	-0.54	0.001
		Log baseline RMSSD	-0.38	0.02
	Naming Cognistat	Log baseline LF	0.42	0.01
		Log baseline total power	0.44	0.01
		Log baseline SDNN	0.38	0.02*
		Log cardiac reactivity LF	-0.52	0.001
		Log cardiac reactivity HF	-0.51	0.001
		Log cardiac reactivity total power	-0.64	<0.001
		Log cardiac reactivity SDNN	-0.37	0.02*
	Memory Cognistat	Cardiac reactivity mean RR	-0.33	0.049*
		Cardiac reactivity pNN50	-0.47	0.004
		Log cardiac reactivity total power	-0.39	0.02
	Total Cognistat	Log baseline LF/HF	0.39	0.02
		Log cardiac reactivity HF	-0.39	0.02
		Log cardiac reactivity total power	-0.49	0.002

Table 4.27 displays significant results from a Pearson’s correlation between cognitive scores (MMSE (Folstein et al., 1975) and Cognistat (Kiernan et al., 1987)) and HRV in females 36-50 years (n=37).

Key: HF = High frequency; HRV = Heart rate variability; LF = Low frequency; LF/HF = Low frequency divided by high frequency (sympathovagal balance); n = Sample size; p = Level of statistical significance (p<0.05); pNN50 = Total number of interval differences (greater than 50 milliseconds) of consecutive NN (beat to beat) intervals divided by the total number of NN intervals; r = Correlation coefficient; RMSSD = Square root of the mean squared differences of successive NN (beat to beat) intervals; RR = Duration in milliseconds from one R peak to the next R peak of the electrocardiogram; SDNN = Standard deviation of all NN intervals (the square root of variance); * = Bonferroni correction excludes this significant correlation

Table 4.28 Partial Pearson’s correlation coefficients between cognitive scores and HRV in females 36-50 years (n=37)

	Covariate	Dependent variable	Independent variable	r	p
Females 36-50 years n=37	LAQ part two (stress coping)	Repetition Cognistat	Log cardiac reactivity HF	-0.44	0.01
			Log cardiac reactivity total power	-0.42	0.01
	Age, smoking status and LAQ part one (lifestyle risk factors)	Calculation Cognistat	Cardiac reactivity mean heart rate	0.34	0.048
	Years of education	Similarity Cognistat	Log baseline LF/HF	0.45	0.01

Table 4.28 displays significant results from a partial Pearson’s correlation between cognitive scores (MMSE (Folstein et al., 1975) and Cognistat (Kiernan et al., 1987)) and HRV in females 36-50 years (n=37).

Key: HF = High frequency; HRV = Heart rate variability; LAQ = Lifestyle Appraisal Questionnaire (Craig et al., 1996); LF/HF = Low frequency divided by high frequency (sympathovagal balance); n = Sample size; p = Level of statistical significance (p<0.05); r = Correlation coefficient

After Bonferroni correction on HRV p-values from Table 4.27, two regressions were performed to address aim 6 (naming Cognistat (Table 4.29) and total Cognistat score (Table 4.30)). A regression was not performed between memory (Cognistat) and the three HRV variables as the p-values did not pass a Bonferroni correction.

Log CR LF, log CR HF, and log CR TP significantly predicted naming (Cognistat) ($F(3,32)=8.17, p=0.001$). Together, the independent variables explain 38% of the variability in the naming domain. Log CR TP added significantly to the prediction ($p=0.03$). Table 4.29 displays regression coefficients and standard errors.

Table 4.29 Multiple regression between naming (Cognistat) and HRV variables in females 36-50 years (n=37)

Females 36-50 years (n=37)	R	R square	Adjusted R square	Std. error of the estimate	p
Naming Cognistat	0.66	0.43	0.38	0.44	0.001
	B	Std. error	Beta	t	p
(Constant)	8.11	0.09		88.85	<0.001
Log cardiac reactivity LF	0.39	0.37	0.36	1.07	0.29
Log cardiac reactivity HF	-0.03	0.23	-0.03	-0.13	0.89
Log cardiac reactivity total power	-1.37	0.58	-0.95	-2.36	0.03

Table 4.29 shows a multiple regression analysis between the naming domain from the Cognistat (Kiernan et al., 1987) with HRV variables: log cardiac reactivity of LF, HF and total power in females 36-50 years (n=37).

Key: B = Unstandardised regression coefficient; Beta = Standardised regression coefficient; HF = High frequency; HRV = Heart rate variability; LF = Low frequency; n = Sample size; p = Level of statistical significance ($p<0.05$ (in bold)); R = Multiple correlation coefficient; R square = Proportion of variance; Std. = Standard; t = t statistic

Log baseline LF/HF, log CR HF, and log CR TP significantly predicted total Cognistat score in a multiple regression model ($F(3,31)=4.56, p=0.01$). Together, the independent variables explain 24% of the variability of the total Cognistat score. None of the independent variables added significantly to the prediction model. Table 4.30 displays regression coefficients and standard errors.

Table 4.30 Multiple regression between total Cognistat score and HRV variables in females 36-50 years (n=37)

Females 36-50 years n=37	R	R square	Adjusted R square	Std. error of the estimate	P
Total Cognistat	0.55	0.31	0.24	4.04	0.01
	B	Std. error	Beta	t	p
(Constant)	76.52	1.08		71.11	0.001
Log baseline LF/HF	2.98	1.75	0.32	1.70	0.10
Log cardiac reactivity HF	-2.69	2.42	-0.28	-1.11	0.28
Log cardiac reactivity total power	-1.77	3.38	-0.15	-0.52	0.61

Table 4.30 shows a multiple regression analysis between the total Cognistat (Kiernan et al., 1987) score with HRV variables: log baseline LF/HF, and log cardiac reactivity of HF and total power in females 36-50 years (n=37).

Key: B = Unstandardised regression coefficient; Beta = Standardised regression coefficient; HF = High frequency; HRV = Heart rate variability; LF/HF = Low frequency divided by high frequency (sympathovagal balance); n = Sample size; p = Level of statistical significance ($p < 0.05$ (in bold)); R = Correlation coefficient; R square = Proportion of variance; Std. = Standard; t = t statistic

4.1.3.2 Males (n=37)

Mean (\pm SD) demographics for males aged 36-50 years (n=37) are provided in Table 4.31.

Table 4.31 Mean sample demographics for males 36-50 years (n=37)

	Demographics	Value
Males 36-50 years n=37	Years of age (mean \pm SD)	40.68 \pm 4.52
	Years of education (mean \pm SD)	19.07 \pm 3.10
	BMI (mean \pm SD)	25.47 \pm 3.13
	Smoker (%)	16.22
	LAQ part one (mean \pm SD)	14.97 \pm 6.90
	LAQ part two (mean \pm SD)	18.54 \pm 7.83

Table 4.31 shows mean demographic scores for males 36-50 years (n=37). BMI normal reference range is 19-25 (Garrouste-Orgeas et al., 2004). The maximum score of LAQ part one (lifestyle risk factors) is 70 and LAQ part two (stress coping) is 75. Higher LAQ scores reflect increased risk for developing chronic illnesses (Craig et al., 1996).

Key: BMI = Body mass index; LAQ = Lifestyle Appraisal Questionnaire (Craig et al., 1996); n = Sample size; SD = Standard deviation

Mean (\pm SD) scores from the MMSE and Cognistat with reference to their respective maximum score and cognitive impairment thresholds are displayed in Table 4.32. All mean scores were above their respective cognitive impairment thresholds, although the lower end of the SD crossed those thresholds for the Cognistat domains of comprehension (5.39 \pm 0.70), repetition (11.41 \pm 1.36), and judgment (4.42 \pm 1.08).

Mean (\pm SD) values for HRV frequency and time domain parameters for baseline and active states are provided in Table 4.33 and Table 4.34, respectively.

Table 4.32 Mean cognitive scores from the MMSE and Cognistat for males 36-50 years (n=37)

		Cognitive assessment	Cognitive domain	Maximum possible score	Cognitive impairment threshold	Mean \pm SD
Males 36-50 years n=37	MMSE		Orientation	10	-	9.87 \pm 0.35
			Registration	3	-	2.97 \pm 0.16
			Attention	5	-	4.47 \pm 1.07
			Recall	3	-	2.78 \pm 0.58
			Language	9	-	8.31 \pm 0.74
		Total MMSE		30	≤ 23	28.41 \pm 1.47
	Cognistat		Orientation	12	<10	11.87 \pm 0.42
			Attention	8	<6	7.57 \pm 0.80
			Comprehension	6	<5	5.39 \pm 0.70
			Repetition	12	<11	11.41 \pm 1.36
			Naming	8	<7	7.70 \pm 0.57
			Construction	6	<4	5.26 \pm 1.01
			Memory	12	<10	11.41 \pm 0.99
			Calculation	4	<3	3.72 \pm 0.65
		Similarity	8	<5	7.38 \pm 1.01	
		Judgment	6	<4	4.42 \pm 1.08	
	Total Cognistat		82	<65	76.11 \pm 4.55	

Table 4.32 shows mean cognitive scores from the MMSE (Folstein et al., 1975) and the Cognistat (Kiernan et al., 1987) for males 36-50 years (n=37). The maximum score possible and the cognitive impairment threshold are provided for each cognitive domain. Scores below the cognitive impairment threshold indicate cognitive impairment. The Cognistat domains where the lower end of the SD crossed the cognitive impairment threshold are shown in **bold**.

Key: MMSE = Mini Mental State Examination; n = Sample size; SD = Standard deviation

Table 4.33 Mean frequency domain HRV values for males 36-50 years (n=37)

HRV state		HRV frequency domain	Mean (\pm SD) ms ²
Males 36-50 years n=37	Baseline	Low frequency (absolute)	980.53 \pm 871.38
		High frequency (absolute)	969.92 \pm 2498.05
		LF/HF (absolute)	2.95 \pm 2.92
		Total power (absolute)	3613.23 \pm 5228.12
		Log low frequency	2.93 \pm 0.52
		Log high frequency	2.66 \pm 0.63
		Log LF/HF	0.27 \pm 0.43
		Log total power	3.36 \pm 0.39
	Active	Low frequency (absolute)	2403.07 \pm 1546.17
		High frequency (absolute)	1542.22 \pm 2116.56
		LF/HF (absolute)	3.38 \pm 3.08
		Total power (absolute)	5495.23 \pm 4083.07
		Log low frequency	3.29 \pm 0.30
		Log high frequency	2.89 \pm 0.51
		Log LF/HF	0.40 \pm 0.41
		Log total power	3.64 \pm 0.29
	Cardiac reactivity	Low frequency (absolute)	1003.75 \pm 2691.70
		High frequency (absolute)	596.64 \pm 3312.45
		LF/HF (absolute)	1.09 \pm 4.38
		Total power (absolute)	1953.66 \pm 6852.72
		Log low frequency	0.40 \pm 0.45
		Log high frequency	0.28 \pm 0.57
		Log LF/HF	0.12 \pm 0.40
		Log total power	0.31 \pm 0.31

Table 4.33 shows mean frequency domain HRV values for males 36-50 years (n=37) during baseline and active states. Cardiac reactivity refers to the active minus baseline HRV data.

Key: HRV = Heart rate variability; LF/HF = Low frequency divided by high frequency (sympathovagal balance); ms² = Milliseconds squared; n = Sample size; SD = Standard deviation

Table 4.34 Mean time domain HRV values for males 36-50 years (n=37)

HRV state		HRV time domain (unit)	Mean ± SD
Males 36-50 years n=37	Baseline	Mean RR (ms)	876.85 ± 159.98
		SDNN (ms)	58.08 ± 25.29
		Mean heart rate (bpm)	71.32 ± 14.24
		RMSSD (ms)	44.30 ± 31.92
		pNN50 (%)	17.17 ± 15.43
		Log RMSSD (ms)	1.59 ± 0.25
		Log SDNN (ms)	1.74 ± 0.16
	Active	Mean RR (ms)	830.37 ± 134.72
		SDNN (ms)	73.80 ± 21.87
		Mean heart rate (bpm)	74.95 ± 13.69
		RMSSD (ms)	63.29 ± 37.33
		pNN50 (%)	16.61 ± 12.50
		Log RMSSD (ms)	1.73 ± 0.25
		Log SDNN (ms)	1.85 ± 0.13
	Cardiac reactivity	Mean RR (ms)	-47.53 ± 54.36
		SDNN (ms)	16.58 ± 25.56
		Mean heart rate (bpm)	3.77 ± 4.13
		RMSSD (ms)	19.16 ± 36.77
		pNN50 (%)	-0.09 ± 8.54
		Log RMSSD (ms)	0.12 ± 0.26
		Log SDNN (ms)	0.12 ± 0.15

Table 4.34 shows mean time domain HRV values for males 36-50 years (n=37) during baseline and active states. Cardiac reactivity refers to the active minus baseline HRV data.

Key: bpm = Beats per minute; HRV = Heart rate variability; ms = Milliseconds; n = Sample size; pNN50 = Total number of interval differences (greater than 50 ms) of consecutive NN (beat to beat) intervals divided by the total number of NN intervals; RMSSD = Square root of the mean squared differences of successive NN intervals; RR = Duration in ms from one R peak to the next R peak of the electrocardiogram; SD = Standard deviation; SDNN = SD of all NN intervals (the square root of variance)

Dependent sample t-tests were performed to determine significant differences between baseline and active (cognitive task) HRV states (Table 4.35).

Table 4.35 Dependent sample t-test between baseline and active HRV states for males 36-50 years (n=37)

	Variable (unit)	t	df	p	Baseline mean ± SD	Active mean ± SD	Mean difference (active – baseline)
Males 36-50 years n=37	Mean RR (ms)	5.25	35	<0.001	876.85 ± 159.98	830.37 ± 134.72	-46.48
	Mean heart rate (bpm)	-5.48	35	<0.001	71.32 ± 14.24	74.95 ± 13.69	3.63
	Log LF (ms ²)	-4.07	35	<0.001	2.93 ± 0.52	3.29 ± 0.30	0.36
	Log HF (ms ²)	-2.19	35	0.04	2.66 ± 0.63	2.89 ± 0.51	0.23
	Log total power (ms ²)	-3.98	34	<0.001	3.36 ± 0.39	3.64 ± 0.29	0.28
	Log SDNN (ms)	-4.60	33	<0.001	1.74 ± 0.16	1.85 ± 0.13	0.11
	Log RMSSD (ms)	-3.60	33	0.001	1.59 ± 0.25	1.73 ± 0.25	0.14

Table 4.35 displays significant results from a dependent sample t-test between baseline and active HRV states for males aged 36-50 years (n=37).

Key: bpm = Beats per minute; df = Degrees of freedom; HF = High frequency; HRV = Heart rate variability; LF = Low frequency; ms = Milliseconds; ms² = Milliseconds squared; n = Sample size; p = Level of statistical significance (p<0.05); RMSSD = Square root of the mean squared differences of successive NN intervals; RR = Duration in milliseconds from one R peak to the next R peak of the electrocardiogram; SD = Standard deviation; SDNN = Standard deviation of all NN intervals (the square root of variance); t = Test statistic

Pearson’s bivariate and partial correlations were performed separately between HRV and cognitive scores to address aims 1 and 5 (Table 4.36 and Table 4.37, respectively). After the Bonferroni correction was applied in Table 4.37, a hierarchical regression was performed on judgment (Cognistat) to address aim 6 (Table 4.38).

Table 4.36 Pearson’s correlation coefficients between cognitive scores and HRV in males 36-50 years (n=37)

	Dependent variable	Independent variable	r	p
Males 36-50 years n=37	Comprehension Cognistat	Cardiac reactivity mean RR	-0.33	0.049*
		Cardiac reactivity mean heart rate	0.39	0.02
	Similarity Cognistat	Cardiac reactivity mean RR	-0.34	0.045

Table 4.36 displays significant results from a Pearson’s correlation between cognitive scores (MMSE (Folstein et al., 1975) and Cognistat (Kiernan et al., 1987)) and HRV in males 36-50 years (n=37).

Key: HRV = Heart rate variability; n = Sample size; p = Level of statistical significance (p<0.05); r = Correlation coefficient; RR = Duration in milliseconds from one R peak to the next R peak of the electrocardiogram; * = Bonferroni correction excludes this significant correlation

Table 4.37 Partial Pearson’s correlation coefficients between cognitive scores and HRV in males 36-50 years (n=37)

	Covariate	Dependent variable	Independent variable	r	p
Males 36-50 years n=37	Smoking status	Attention Cognistat	Baseline pNN50	-0.41	0.01
	LAQ part one (lifestyle risk factors)	Memory Cognistat	Log cardiac reactivity LF/HF	0.34	0.045
	Age	Calculation Cognistat	Cardiac reactivity mean RR	0.34	0.049*
			Log cardiac reactivity HF	0.47	0.01
			Log cardiac reactivity RMSSD	0.42	0.01
	Years of education and smoking status	Total Cognistat	Log baseline LF/HF	0.43	0.04
	LAQ part one (lifestyle risk factors) and LAQ part two (stress coping)	Judgment Cognistat	Log baseline LF	-0.44	0.01
			Log baseline HF	-0.48	0.004
			Log baseline total power	-0.48	0.004
			Log baseline SDNN	-0.48	0.01
Log baseline RMSSD			-0.46	0.01	
Cardiac reactivity pNN50			0.44	0.01	
Log cardiac reactivity SDNN			0.45	0.01	
Log cardiac reactivity RMSSD	0.44	0.01			

Table 4.37 displays significant results from a partial Pearson’s correlation between cognitive scores (MMSE (Folstein et al., 1975) and Cognistat (Kiernan et al., 1987)) and HRV in males 18-35 years (n=42).

Key: HF = High frequency; HRV = Heart rate variability; LAQ = Lifestyle Appraisal Questionnaire (Craig et al., 1996); LF = Low frequency; LF/HF = Low frequency divided by high frequency (sympathovagal balance); n = Sample size; p = Level of statistical significance (p<0.05); pNN50 = Total number of interval differences (greater than 50 milliseconds) of consecutive NN (beat to beat) intervals divided by the total number of NN intervals; r = Correlation coefficient; RMSSD = Square root of the mean squared differences of successive NN intervals; RR = Duration in milliseconds from one R peak to the next R peak of the electrocardiogram; SDNN = Standard deviation of all NN intervals (the square root of variance); * = Bonferroni correction excludes this significant correlation

Baseline LF, HF, TP, SDNN, RMSSD, and CR pNN50, CR SDNN, and CR RMSSD significantly predicted judgment (Cognistat) (controlled for LAQ part 1 and 2) ($F(10,23)=2.37$, $p=0.04$). Together, the independent variables explain 29% of the variability in the judgment domain. Table 4.38 displays regression coefficients and standard errors.

Table 4.38 Hierarchical multiple regression between judgment score (Cognistat) and HRV variables in males 36-50 years (n=37)

Males 36-50 years (n=37)	R	R square	Adjusted R square	Std. error of the estimate	p
Judgment Cognistat	0.71	0.51	0.29	0.91	0.04
	B	Std. error	Beta	t	p
(Constant)	5.72	3.87		1.48	0.15
Log baseline LF	-0.28	1.17	-0.11	-0.24	0.82
Log baseline HF	-0.64	1.26	-0.27	-0.50	0.62
Log baseline total power	0.09	2.70	0.03	0.03	0.97
Log baseline SDNN	1.71	4.85	0.25	0.35	0.73
Log baseline RMSSD	-0.71	2.72	-0.16	-0.26	0.80
Cardiac reactivity pNN50	0.02	0.03	0.12	0.62	0.54
Log cardiac reactivity SDNN	3.77	3.85	0.48	0.98	0.34
Log cardiac reactivity RMSSD	-0.88	1.95	-0.19	-0.45	0.65
LAQ part 1	-0.04	0.03	-0.25	-1.50	0.15
LAQ part 2	-0.03	0.02	-0.24	-1.43	0.17

Table 4.38 shows a hierarchical multiple regression analysis between the judgment score (Cognistat) (Kiernan et al., 1987) score with HRV variables: log baseline LF, log baseline HF, log baseline total power, log baseline SDNN, log baseline RMSSD, cardiac reactivity pNN50, log cardiac reactivity SDNN and log cardiac reactivity RMSSD (adjusted for LAQ part 1 and part 2) in males 36-50 years (n=37).

Key: B = Unstandardised regression coefficient; Beta = Standardised regression coefficient; HF = High frequency; HRV = Heart rate variability; LAQ = Lifestyle Appraisal Questionnaire (Craig et al., 1996); LF = Low frequency; n = Sample size; p = Level of statistical significance ($p < 0.05$); pNN50 = Total number of interval differences (greater than 50 milliseconds) of consecutive NN (beat to beat) intervals divided by the total number of NN intervals; R = Correlation coefficient; R square = Proportion of variance; RMSSD = Square root of the mean squared differences of successive NN intervals; SDNN = Standard deviation of all NN intervals (the square root of variance); Std. = Standard; t = t statistic

4.1.3.3 Comparison between females (n=37) and males (n=37) (36-50 years)

Mean cognitive scores (Cognistat and MMSE) for females and males aged 31-50 years are displayed in Figure 4.3.

Figure 4.3 Mean cognitive scores (Cognistat and MMSE) for females (n=37) and males (n=37) aged 36-50 years

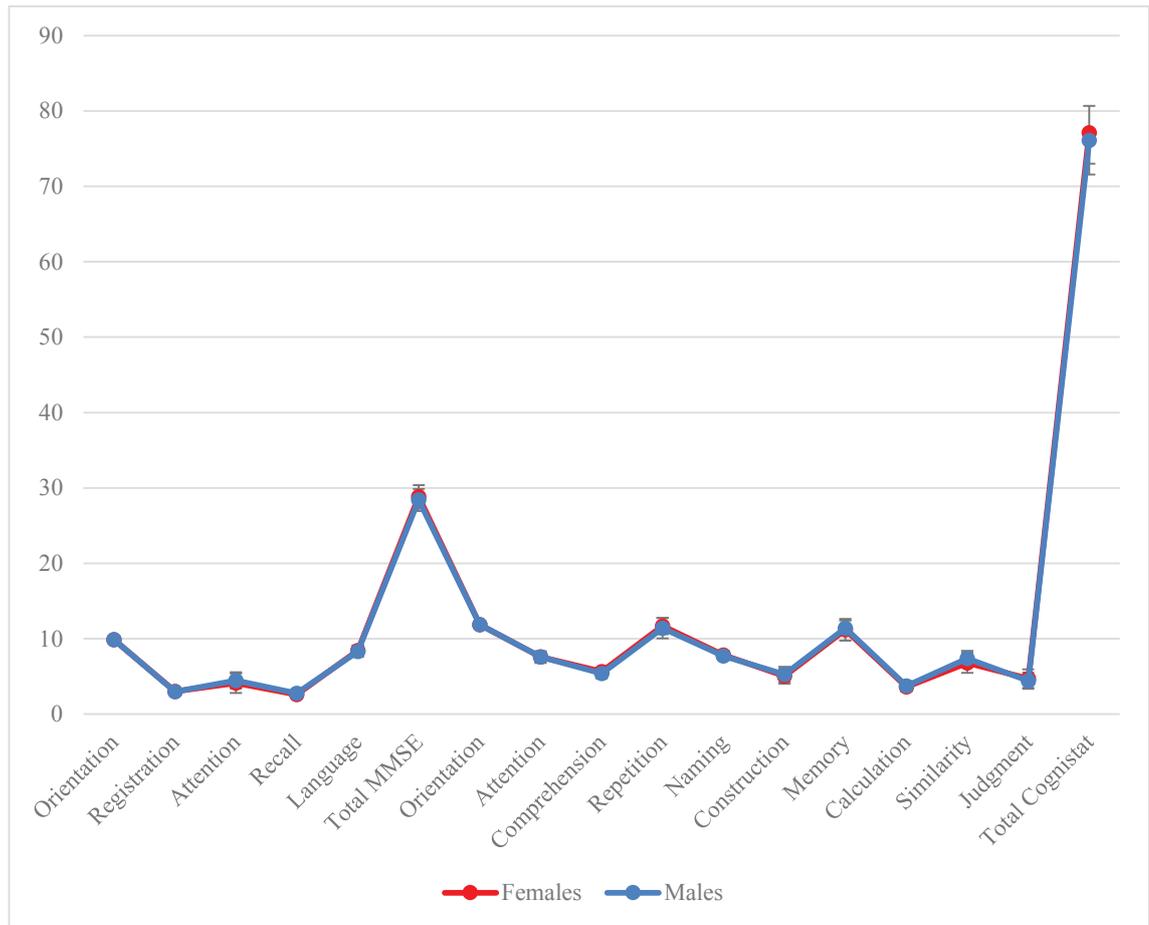


Figure 4.3 displays mean cognitive scores (Cognistat (Kiernan et al., 1987) and MMSE (Folstein et al., 1975)) for females (n=37) and males (n=37) aged 36-50 years.

MMSE = Mini Mental State Examination

An independent sample t-test compared cognitive scores between females and males aged 36-50 years. Similarity (Cognistat) was significantly higher in males (7.38 ± 1.01) than females (6.80 ± 1.32) ($t=-2.13$, $df=72$, $p=0.04$).

An independent sample t-test with covariates was used to compare cognitive scores between females and males aged 36-50 years. Males had significantly lower attention

scores (Cognistat) ($F=3.81$, $df=2$, 71 , $p=0.03$) (7.57 ± 0.80) (controlled for smoking status) yet higher construction scores (Cognistat) (5.26 ± 1.01) (controlled for age) than females (7.60 ± 0.64 , 5.04 ± 0.99 , respectively) ($F=7.05$, $df=2$, 70 , $p=0.002$).

An independent sample t-test was used to compare cognitive scores and HRV values (without covariates) and did not produce statistically significant results.

An independent sample t-test with covariates was used to compare HRV values between females and males aged 36-50 years (Table 4.39).

Table 4.39 Independent sample t-test with covariance of HRV values between females (n=37) and males (n=37) aged 36-50 years

Covariate	Variable (unit)	F	df	p	Females mean ± SD	Males mean ± SD	Mean difference (males - females)
BMI and LAQ part one (lifestyle risk factors)	Log active LF (ms ²)	5.58	2, 71	0.002	3.39 ± 0.31	3.29 ± 0.30	-0.10
	Baseline mean RR (ms)	5.83	2, 68	0.01	890.76 ± 105.00	876.85 ± 159.98	-13.91
LAQ part one (lifestyle risk factors)	Baseline mean HR (bpm)	7.37	2, 68	0.001	68.80 ± 8.52	71.32 ± 14.24	2.52
	Active mean RR (ms)	7.39	2, 68	0.001	850.86 ± 98.80	830.37 ± 134.72	-20.49
	Active mean HR (bpm)	8.43	2, 68	0.001	72.14 ± 8.45	74.95 ± 13.69	2.81
	Log active TP (ms ²)	3.90	2, 68	0.03	3.76 ± 0.33	3.64 ± 0.29	-0.12
	Log active SDNN (ms)	4.14	2, 68	0.02	1.88 ± 0.14	1.85 ± 0.13	-0.03
Age	Log CR RMSSD (ms)	3.44	2, 70	0.04	0.12 ± 0.22	0.12 ± 0.26	0

Table 4.39 displays significant results from an independent sample t-test with covariance (performed by ANCOVA and MANCOVA) of HRV values between females (n=37) and males (n=37) aged 36-50 years.

Key: ANCOVA = Analysis of covariance; bpm = Beats per minute; BMI = Body mass index; CR = Cardiac reactivity; df = Degrees of freedom; F = F statistic; HR = Heart rate; HRV = Heart rate variability; LAQ = Lifestyle Appraisal Questionnaire (Craig et al., 1996); LF = Low frequency; MANCOVA = Multiple analysis of covariance; ms = Milliseconds; ms² = Milliseconds squared; n = Sample size; p = Level of statistical significance (p<0.05); RMSSD = Square root of the mean squared differences of successive NN intervals; RR = Duration in milliseconds from one R peak to the next R peak of the electrocardiogram; SD = Standard deviation; SDNN = Standard deviation of all NN intervals (the square root of variance); TP = Total power

Significant correlations in 36-50 year old females and males were compared using Z scores, which did not produce statistically significant results.

4.1.4 51-65 years

4.1.4.1 Females (n=42)

Mean (\pm SD) demographics for females aged 51-65 years (n=42) are provided in Table 4.40.

Table 4.40 Mean sample demographics for females 51-65 years (n=42)

Demographics		Value
Females 51-65 years n=42	Years of age (mean \pm SD)	55.71 \pm 3.93
	Years of education (mean \pm SD)	18.41 \pm 4.19
	BMI (mean \pm SD)	25.11 \pm 4.59
	Smoker (%)	7.14
	LAQ part one (mean \pm SD)	14.61 \pm 6.34
	LAQ part two (mean \pm SD)	19.02 \pm 11.13

Table 4.40 shows mean demographic scores for females 51-65 years (n=42). BMI normal reference range is 19-25 (Garrouste-Orgeas et al., 2004). The maximum score of LAQ part one (lifestyle risk factors) is 70 and LAQ part two (stress coping) is 75. Higher LAQ scores reflect increased risk for developing chronic illnesses (Craig et al., 1996).

Key: BMI = Body mass index; LAQ = Lifestyle Appraisal Questionnaire (Craig et al., 1996); n = Sample size; SD = Standard deviation

Mean (\pm SD) scores from the MMSE and Cognistat with reference to their respective maximum score and cognitive impairment thresholds are displayed in Table 4.41. All mean scores were above their respective cognitive impairment thresholds, although the lower end of the SD crossed those thresholds for the Cognistat domains of repetition (11.69 \pm 0.87), construction (4.85 \pm 1.02), and memory (10.86 \pm 1.90).

Mean (\pm SD) values for HRV frequency and time domain parameters for baseline and active states are provided in Table 4.42 and Table 4.43, respectively.

Table 4.41 Mean cognitive scores from the MMSE and Cognistat for females 51-65 years (n=42)

		Cognitive assessment	Cognitive domain	Maximum possible score	Cognitive impairment threshold	Mean \pm SD
Females 51-65 years n=42	MMSE		Orientation	10	-	9.86 \pm 0.35
			Registration	3	-	3.00 \pm 0.00
			Attention	5	-	4.51 \pm 0.99
			Recall	3	-	2.88 \pm 0.33
			Language	9	-	8.27 \pm 0.77
		Total MMSE		30	≤ 23	28.52 \pm 1.58
	Cognistat		Orientation	12	<10	11.64 \pm 0.62
			Attention	8	<6	7.79 \pm 0.52
			Comprehension	6	<5	5.58 \pm 0.56
			Repetition	12	<11	11.69 \pm 0.87
			Naming	8	<7	7.88 \pm 0.40
			Construction	6	<4	4.85 \pm 1.02
			Memory	12	<10	10.86 \pm 1.90
			Calculation	4	<3	3.69 \pm 0.52
		Similarity	8	<5	7.17 \pm 1.21	
		Judgment	6	<4	4.95 \pm 0.91	
	Total Cognistat		82	<65	76.10 \pm 4.06	

Table 4.41 shows mean cognitive scores from the MMSE (Folstein et al., 1975) and the Cognistat (Kiernan et al., 1987) for females 51-65 years (n=42). The maximum score possible and the cognitive impairment threshold are provided for each cognitive domain. Scores below the cognitive impairment threshold indicate cognitive impairment. The Cognistat domains where the lower end of the SD crossed the cognitive impairment threshold are shown in **bold**.

Key: MMSE = Mini Mental State Examination; n = Sample size; SD = Standard deviation

Table 4.42 Mean frequency domain HRV values for females 51-65 years (n=42)

HRV state		HRV frequency domain	Mean (\pm SD) ms ²
Females 51-65 years n=42	Baseline	Low frequency (absolute)	841.97 \pm 984.65
		High frequency (absolute)	742.01 \pm 1055.14
		LF/HF (absolute)	1.74 \pm 1.66
		Total power (absolute)	2508.91 \pm 2278.87
		Log low frequency	2.66 \pm 0.50
		Log high frequency	2.50 \pm 0.62
		Log LF/HF	0.12 \pm 0.40
		Log total power	3.24 \pm 0.39
	Active	Low frequency (absolute)	2062.24 \pm 1482.75
		High frequency (absolute)	1652.97 \pm 1748.42
		LF/HF (absolute)	3.00 \pm 3.43
		Total power (absolute)	5453.56 \pm 4332.45
		Log low frequency	3.18 \pm 0.38
		Log high frequency	2.88 \pm 0.65
		Log LF/HF	0.30 \pm 0.43
		Log total power	3.59 \pm 0.38
	Cardiac reactivity	Low frequency (absolute)	1220.27 \pm 1500.71
		High frequency (absolute)	910.95 \pm 1660.89
		LF/HF (absolute)	1.87 \pm 3.82
		Total power (absolute)	2944.66 \pm 3895.81
		Log low frequency	0.52 \pm 0.43
		Log high frequency	0.38 \pm 0.57
		Log LF/HF	0.22 \pm 0.41
		Log total power	0.35 \pm 0.34

Table 4.42 shows mean frequency domain HRV values for females 51-65 years (n=42) during baseline and active states. Cardiac reactivity refers to the active minus baseline HRV data.

Key: HRV = Heart rate variability; LF/HF = Low frequency divided by high frequency (sympathovagal balance); ms² = Milliseconds squared; n = Sample size; SD = Standard deviation

Table 4.43 Mean time domain HRV values for females 51-65 years (n=42)

HRV state		HRV time domain (unit)	Mean ± SD
Females 51-65 years n=42	Baseline	Mean RR (ms)	907.12 ± 140.78
		SDNN (ms)	51.83 ± 23.20
		Mean heart rate (bpm)	67.20 ± 10.73
		RMSSD (ms)	43.95 ± 32.88
		pNN50 (%)	14.77 ± 18.89
		Log RMSSD (ms)	1.53 ± 0.32
		Log SDNN (ms)	1.67 ± 0.19
	Active	Mean RR (ms)	880.56 ± 125.90
		SDNN (ms)	70.52 ± 28.48
		Mean heart rate (bpm)	69.20 ± 10.10
		RMSSD (ms)	67.20 ± 40.53
		pNN50 (%)	15.02 ± 15.13
		Log RMSSD (ms)	1.74 ± 0.29
		Log SDNN (ms)	1.81 ± 0.18
	Cardiac reactivity	Mean RR (ms)	-27.93 ± 46.23
		SDNN (ms)	18.69 ± 24.71
		Mean heart rate (bpm)	2.00 ± 3.15
		RMSSD (ms)	23.24 ± 34.93
		pNN50 (%)	1.54 ± 9.08
		Log RMSSD (ms)	0.21 ± 0.25
		Log SDNN (ms)	0.14 ± 0.16

Table 4.43 shows mean time domain HRV values for females 51-65 years (n=42) during baseline and active states. Cardiac reactivity refers to the active minus baseline HRV data.

Key: bpm = Beats per minute; HRV = Heart rate variability; ms = Milliseconds; n = Sample size; pNN50 = Total number of interval differences (greater than 50 ms) of consecutive NN (beat to beat) intervals divided by the total number of NN intervals; RMSSD = Square root of the mean squared differences of successive NN intervals; RR = Duration in ms from one R peak to the next R peak of the electrocardiogram; SD = Standard deviation; SDNN = SD of all NN intervals (the square root of variance)

Dependent sample t-tests were performed to determine significant differences between baseline and active (cognitive task) HRV states (Table 4.44).

Table 4.44 Dependent sample t-test between baseline and active HRV states for females 51-65 years (n=42)

	Variable (unit)	t	df	p	Baseline mean ± SD	Active mean ± SD	Mean difference (active – baseline)
Females 51-65 years n=42	Mean RR (ms)	3.70	40	0.001	907.12 ± 140.78	880.56 ± 125.90	-26.56
	Mean heart rate (bpm)	-4.11	41	<0.001	67.20 ± 10.73	69.20 ± 10.10	2.00
	Log LF (ms ²)	-7.73	41	<0.001	2.66 ± 0.50	3.18 ± 0.38	0.52
	Log HF (ms ²)	-4.34	41	<0.001	2.50 ± 0.62	2.88 ± 0.65	0.38
	Log LF/HF	-2.60	40	0.01	0.12 ± 0.40	0.30 ± 0.43	0.18
	Log total power (ms ²)	-6.79	41	<0.001	3.24 ± 0.39	3.59 ± 0.38	0.35
	Log SDNN (ms)	-5.51	41	<0.001	1.67 ± 0.19	1.81 ± 0.18	0.14
	Log RMSSD (ms)	-5.36	41	<0.001	1.53 ± 0.32	1.74 ± 0.29	0.21

Table 4.44 displays significant results from a dependent sample t-test between baseline and active HRV states for females aged 51-65 years (n=42).

Key: bpm = Beats per minute; df = Degrees of freedom; HF = High frequency; HRV = Heart rate variability; LF = Low frequency; LF/HF = Low frequency divided by high frequency (sympathovagal balance); ms = Milliseconds; ms² = Milliseconds squared; n = Sample size; p = Level of statistical significance (p<0.05); RMSSD = Square root of the mean squared differences of successive NN intervals; RR = Duration in milliseconds from one R peak to the next R peak of the electrocardiogram; SD = Standard deviation; SDNN = Standard deviation of all NN intervals (the square root of variance); t = T statistic

Pearson’s bivariate and partial correlations were performed separately between HRV and cognitive scores to address aims 1 and 5 (Table 4.45 and Table 4.46, respectively).

Table 4.45 Pearson’s correlation coefficients between cognitive scores and HRV in females 51-65 years (n=42)

	Dependent variable	Independent variable	r	p
Females 51-65 years n=42	Orientation MMSE	Baseline mean heart rate	0.35	0.02
		Log baseline HF	-0.34	0.03
	Recall MMSE	Cardiac reactivity mean RR	-0.43	0.01
		Cardiac reactivity mean heart rate	0.41	0.01
	Total MMSE	Baseline mean heart rate	0.33	0.03
		Cardiac reactivity pNN50	-0.35	0.02
	Naming Cognistat	Log cardiac reactivity LF	0.36	0.02
		Log cardiac reactivity HF	0.36	0.02
		Log cardiac reactivity total power	0.37	0.02
	Similarity Cognistat	Log baseline LF/HF	0.42	0.01

Table 4.45 displays significant results from a Pearson’s correlation between cognitive scores (MMSE (Folstein et al., 1975) and Cognistat (Kiernan et al., 1987)) and HRV in females 51-65 years (n=42).

Key: HF = High frequency; HRV = Heart rate variability; LF = Low frequency; LF/HF = Low frequency divided by high frequency (sympathovagal balance); MMSE = Mini Mental State Examination; n = Sample size; p = Level of statistical significance (p<0.05); pNN50 = Total number of interval differences (greater than 50 milliseconds) of consecutive NN (beat to beat) intervals divided by the total number of NN intervals; r = Correlation coefficient; RR = Duration in milliseconds from one R peak to the next R peak of the electrocardiogram

Table 4.46 Partial Pearson’s correlation coefficients between cognitive scores and HRV in females 51-65 years (n=42)

	Covariate	Dependent variable	Independent variable	r	p
Females 51-65 years n=42	LAQ part two (stress coping)	Recall MMSE	Log cardiac reactivity SDNN	-0.32	0.04
	Smoking status	Orientation MMSE	Baseline pNN50	-0.39	0.01
		Total Cognistat	Baseline pNN50	-0.32	0.04

Table 4.46 displays significant results from a partial Pearson’s correlation between cognitive scores (MMSE (Folstein et al., 1975) and Cognistat (Kiernan et al., 1987)) and HRV in females 51-65 years (n=42).

Key: HRV = Heart rate variability; LAQ = Lifestyle Appraisal Questionnaire (Craig et al., 1996); MMSE = Mini Mental State Examination; n = Sample size; p = Level of statistical significance (p<0.05); pNN50 = Total number of interval differences (greater than 50 milliseconds) of consecutive NN (beat to beat) intervals divided by the total number of NN intervals; r = Correlation coefficient; SDNN = Standard deviation of all NN intervals (the square root of variance)

After Bonferroni correction on HRV p-values from Table 4.45, a multiple regression was performed on naming (Cognistat) and three HRV variables to address aim 6 (Table 4.47). Log CR LF, log CR HF, and log CR TP statistically significantly predicted naming (Cognistat) in a multiple regression model ($F(3,38)=2.87$, $p=0.049$). Together the three independent variables explain 12% of the variability in the naming domain. None of the three variables alone were statistically significant in the model. Table 4.47 displays regression coefficients and standard errors.

Table 4.47 Multiple regression between naming (Cognistat) and HRV variables in females 51-65 years (n=42)

Females 51-65 years (n=42)	R	R square	Adjusted R square	Std. error of the estimate	p
Naming Cognistat	0.43	0.19	0.12	0.37	0.049
	B	Std. error	Beta	t	p
(Constant)	7.69	0.09		85.29	<0.001
Log cardiac reactivity LF	0.27	0.25	0.301	1.094	0.28
Log cardiac reactivity HF	0.20	0.14	0.279	1.360	0.18
Log cardiac reactivity total power	-0.08	0.39	-0.07	-0.21	0.84

Table 4.47 shows a multiple regression analysis between naming (Cognistat (Kiernan et al., 1987)) and HRV variables: log cardiac reactivity of LF, HF and total power in females 51-65 years (n=42).

Key: B = Unstandardised regression coefficient; Beta = Standardised regression coefficient; HF = High frequency; HRV = Heart rate variability; LF = Low frequency; n = Sample size; p = Level of statistical significance ($p < 0.05$ (in bold)); R = Correlation coefficient; R square = Proportion of variance; Std. = Standard; t = t statistic

4.1.4.2 Males (n=23)

Mean (\pm SD) demographics for males aged 51-65 years (n=23) are provided in Table 4.48.

Table 4.48 Mean sample demographics for males 51-65 years (n=23)

Demographics		Value
Males 51-65 years n=23	Years of age (mean \pm SD)	57.00 \pm 4.37
	Years of education (mean \pm SD)	18.81 \pm 4.59
	BMI (mean \pm SD)	26.21 \pm 3.43
	Smoker (%)	17.39
	LAQ part one (mean \pm SD)	16.74 \pm 7.78
	LAQ part two (mean \pm SD)	22.74 \pm 9.94

Table 4.48 shows mean demographic scores for males 51-65 years (n=23). BMI normal reference range is 19-25 (Garrouste-Orgeas et al., 2004). The maximum score of LAQ part one (lifestyle risk factors) is 70 and LAQ part two (stress coping) is 75. Higher LAQ scores reflect increased risk for developing chronic illnesses (Craig et al., 1996).

Key: BMI = Body mass index; LAQ = Lifestyle Appraisal Questionnaire (Craig et al., 1996); n = Sample size; SD = Standard deviation

Mean (\pm SD) scores from the MMSE and Cognistat with reference to their respective maximum score and cognitive impairment thresholds are displayed in Table 4.49. All mean scores were above their respective cognitive impairment thresholds, although the lower end of the SD crossed those thresholds for the Cognistat domains of attention (7.13 \pm 1.32), comprehension (5.26 \pm 0.81), repetition (11.26 \pm 1.42), naming (7.52 \pm 0.67), memory (10.39 \pm 2.13), and judgment (4.24 \pm 1.18).

Mean (\pm SD) values for HRV frequency and time domain parameters for baseline and active states are provided in Table 4.50 and Table 4.51, respectively.

Table 4.49 Mean cognitive scores from the MMSE and Cognistat for males 51-65 years (n=23)

		Cognitive assessment	Cognitive domain	Maximum possible score	Cognitive impairment threshold	Mean \pm SD
Males 51-65 years n=23	MMSE		Orientation	10	-	9.96 \pm 0.21
			Registration	3	-	3.00 \pm 0.00
			Attention	5	-	4.04 \pm 1.49
			Recall	3	-	2.74 \pm 0.45
			Language	9	-	8.09 \pm 1.13
		Total MMSE		30	≤ 23	27.83 \pm 2.23
	Cognistat		Orientation	12	<10	11.91 \pm 0.29
			Attention	8	<6	7.13 \pm 1.32
			Comprehension	6	<5	5.26 \pm 0.81
			Repetition	12	<11	11.26 \pm 1.42
			Naming	8	<7	7.52 \pm 0.67
			Construction	6	<4	5.35 \pm 1.03
			Memory	12	<10	10.39 \pm 2.13
			Calculation	4	<3	3.83 \pm 0.49
		Similarity	8	<5	7.13 \pm 1.29	
		Judgment	6	<4	4.24 \pm 1.18	
	Total Cognistat		82	<65	74.02 \pm 6.11	

Table 4.49 shows mean cognitive scores from the MMSE (Folstein et al., 1975) and the Cognistat (Kiernan et al., 1987) for males 51-65 years (n=23). The maximum score possible and the cognitive impairment threshold are provided for each cognitive domain. Scores below the cognitive impairment threshold indicate cognitive impairment. The Cognistat domains where the lower end of the SD crossed the cognitive impairment threshold are shown in **bold**.

Key: MMSE = Mini Mental State Examination; n = Sample size; SD = Standard deviation

Table 4.50 Mean frequency domain HRV values for males 51-65 years (n=23)

HRV State		HRV frequency domain	Mean (\pm SD) ms ²
Males 51-65 years n=23	Baseline	Low frequency (absolute)	1240.22 \pm 1125.27
		High frequency (absolute)	1506.63 \pm 2809.32
		LF/HF (absolute)	2.10 \pm 2.39
		Total power (absolute)	4152.22 \pm 3692.93
		Log low frequency	2.90 \pm 0.46
		Log high frequency	2.79 \pm 0.63
		Log LF/HF	0.11 \pm 0.44
		Log total power	3.47 \pm 0.40
	Active	Low frequency (absolute)	2586.60 \pm 2384.14
		High frequency (absolute)	2358.12 \pm 4346.64
		LF/HF (absolute)	2.82 \pm 2.92
		Total power (absolute)	7542.58 \pm 7754.65
		Log low frequency	3.35 \pm 0.49
		Log high frequency	2.95 \pm 0.71
		Log LF/HF	0.33 \pm 0.45
		Log total power	3.73 \pm 0.46
	Cardiac reactivity	Low frequency (absolute)	1399.76 \pm 2273.46
		High frequency (absolute)	1486.18 \pm 4274.91
		LF/HF (absolute)	1.78 \pm 4.75
		Total power (absolute)	4929.45 \pm 9851.28
		Log low frequency	0.38 \pm 0.31
		Log high frequency	0.16 \pm 0.45
		Log LF/HF	0.21 \pm 0.44
		Log total power	0.25 \pm 0.34

Table 4.50 shows mean frequency domain HRV values for males 51-65 years (n=23) during baseline and active states. Cardiac reactivity refers to the active minus baseline HRV data.

Key: HRV = Heart rate variability; LF/HF = Low frequency divided by high frequency (sympathovagal balance); ms² = Milliseconds squared; n = Sample size; SD = Standard deviation

Table 4.51 Mean time domain HRV values for males 51-65 years (n=23)

HRV state		HRV time domain (unit)	Mean ± SD
Males 51-65 years n=23	Baseline	Mean RR (ms)	894.40 ± 153.38
		SDNN (ms)	58.98 ± 19.88
		Mean heart rate (bpm)	69.36 ± 11.16
		RMSSD (ms)	49.47 ± 29.00
		pNN50 (%)	18.53 ± 19.07
		Log RMSSD (ms)	1.66 ± 0.33
		Log SDNN (ms)	1.77 ± 0.21
	Active	Mean RR (ms)	863.44 ± 145.23
		SDNN (ms)	82.36 ± 37.29
		Mean heart rate (bpm)	72.15 ± 11.49
		RMSSD (ms)	71.80 ± 52.77
		pNN50 (%)	18.83 ± 17.17
		Log RMSSD (ms)	1.82 ± 0.35
		Log SDNN (ms)	1.89 ± 0.21
	Cardiac reactivity	Mean RR (ms)	-30.96 ± 31.39
		SDNN (ms)	22.01 ± 27.12
		Mean heart rate (bpm)	2.78 ± 2.70
		RMSSD (ms)	20.16 ± 36.85
		pNN50 (%)	-1.43 ± 7.13
		Log RMSSD (ms)	0.13 ± 0.19
		Log SDNN (ms)	0.12 ± 0.13

Table 4.51 shows mean time domain HRV values for males 51-65 years (n=23) during baseline and active states. Cardiac reactivity refers to the active minus baseline HRV data.

Key: bpm = Beats per minute; HRV = Heart rate variability; ms = Milliseconds; n = Sample size; pNN50 = Total number of interval differences (greater than 50 ms) of consecutive NN (beat to beat) intervals divided by the total number of NN intervals; RMSSD = Square root of the mean squared differences of successive NN intervals; RR = Duration in ms from one R peak to the next R peak of the electrocardiogram; SD = Standard deviation; SDNN = SD of all NN intervals (the square root of variance)

Wilcoxon signed rank tests were performed to determine significant differences between baseline and active (cognitive task) HRV states (Table 4.52).

Table 4.52 Wilcoxon signed rank test between baseline and active HRV states for males 51-65 years (n=23)

	Variable (unit)	Z	p	Baseline median (IQR)	Active median (IQR)	Median difference (active – baseline)
Males 51-65 years n=23	Mean RR (ms)	-3.50	<0.001	849.32 (172.13)	818.83 (156.97)	-30.49
	Mean heart rate (bpm)	-3.68	<0.001	71.03 (14.30)	73.84 (12.76)	2.81
	Log LF (ms ²)	-3.74	<0.001	3.06 (0.51)	3.32 (0.70)	3.26
	Log LF/HF	-2.09	0.04	0.04 (0.53)	0.30 (0.59)	0.26
	Log total power (ms ²)	-2.87	0.004	3.49 (0.49)	3.71 (0.64)	0.22
	Log SDNN (ms)	-3.46	0.001	1.80 (0.24)	1.87 (0.32)	0.07
	Log RMSSD (ms)	-2.62	0.01	1.67 (0.40)	1.76 (0.47)	0.10

Table 4.52 displays significant results from a Wilcoxon signed rank test between baseline and active HRV states for males aged 51-65 years (n=23).

Key: bpm = Beats per minute; HRV = Heart rate variability; IQR = Interquartile range; LF = Low frequency; LF/HF = Low frequency divided by high frequency (sympathovagal balance); ms = Milliseconds; ms² = Milliseconds squared; n = Sample size; p = Level of statistical significance (p<0.05); RMSSD = Square root of the mean squared differences of successive NN intervals; RR = Duration in milliseconds from one R peak to the next R peak of the electrocardiogram; SDNN = Standard deviation of all NN intervals (the square root of variance); Z = Z score

Spearman’s bivariate and partial correlations were performed separately between HRV and cognitive scores to address aims 1 and 5 (Table 4.53 and Table 4.54, respectively).

Table 4.53 Spearman’s correlation coefficients between cognitive scores and HRV in males 51-65 years (n=23)

	Dependent variable	Independent variable	r	p
Males 51-65 years n=23	Attention MMSE	Baseline mean RR	0.46	0.03
		Baseline mean heart rate	-0.54	0.01
	Total MMSE	Baseline mean heart rate	-0.42	0.045
	Attention Cognistat	Baseline mean heart rate	-0.43	0.043*
		Log baseline LF	0.44	0.04*
		Log baseline total power	0.54	0.01
		Log baseline SDNN	0.43	0.04*

Table 4.53 displays significant results from a Spearman’s correlation between cognitive scores (MMSE (Folstein et al., 1975) and Cognistat (Kiernan et al., 1987)) and HRV in males 51-65 years (n=23).

Key: HRV = Heart rate variability; LF = Low frequency; MMSE = Mini Mental State Examination; n = Sample size; p = Level of statistical significance (p<0.05); r = Correlation coefficient; RR = Duration in milliseconds from one R peak to the next R peak of the electrocardiogram; SDNN = Standard deviation of all NN intervals (the square root of variance); * = Bonferroni correction excludes this significant correlation

Table 4.54 Spearman’s partial correlation coefficients between cognitive scores and HRV in males 51-65 years (n=23)

	Covariate	Dependent variable	Independent variable	r	p
Males 51-65 years n=23	LAQ part two (stress coping)	Comprehension Cognistat	Log baseline LF/HF	0.44	0.02
		Judgment Cognistat	Log baseline LF/HF	0.41	0.03
	LAQ part one (lifestyle risk factors) and part two (stress coping)	Orientation MMSE	Log cardiac reactivity HF	-0.42	0.03
		Recall MMSE	Log cardiac reactivity LF/HF	-0.50	0.01
		Naming Cognistat	Log cardiac reactivity HF	0.41	0.04

Table 4.54 displays significant results from a partial Spearman’s correlation between cognitive scores (MMSE (Folstein et al., 1975) and Cognistat (Kiernan et al., 1987)) and HRV in males 51-65 years (n=23).

Key: HF = High frequency; HRV = Heart rate variability; LAQ = Lifestyle Appraisal Questionnaire (Craig et al., 1996); LF/HF = Low frequency divided by high frequency (sympathovagal balance); MMSE = Mini Mental State Examination; n = Sample size; p = Level of statistical significance (p<0.05); r = Correlation coefficient

4.1.4.3 Comparison between females (n=42) and males (n=23) (51-65 years)

Mean cognitive scores (Cognistat and MMSE) for females and males aged 51-65 years are displayed in Figure 4.4.

Figure 4.4 Mean cognitive scores (Cognistat and MMSE) for females (n=42) and males (n=23) aged 51-65 years

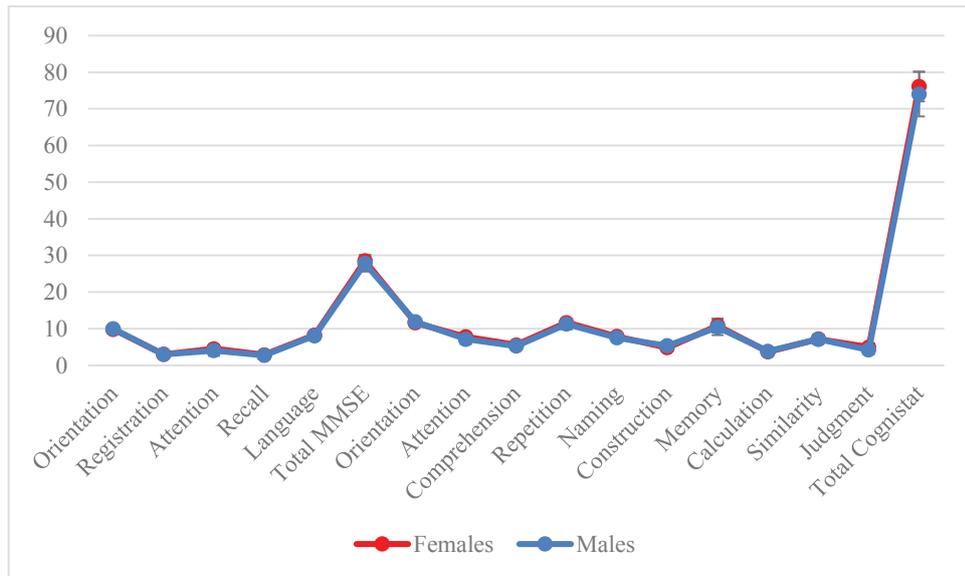


Figure 4.4 displays mean cognitive scores (Cognistat (Kiernan et al., 1987) and MMSE (Folstein et al., 1975)) for females (n=42) and males (n=23) aged 51-65 years.

MMSE = Mini Mental State Examination

Mann-Whitney U test was used to compare cognitive scores between females and males aged 51-65 years.

Table 4.55 Mann-Whitney U Test comparing cognitive scores between females (n=42) and males (n=23) 51-65 years

	Variable	U	Z	p	Mean rank females	Mean rank males	Median females (IQR)	Median males (IQR)
Females and males 51-65 years	Naming Cognistat	340.50	-2.81	0.01	36.39	26.80	8 (0)	8 (1)
	Attention Cognistat	357	-2.29	0.02	36	27.52	8 (0)	8 (2)
	Construction Cognistat	634.50	2.19	0.03	29.39	39.59	5 (2)	6 (1)
	Judgment Cognistat	301.50	-2.59	0.01	37.32	25.11	5 (0.75)	4.5 (1)

Table 4.55 displays significant results from a Mann-Whitney U-test of cognitive scores (from the MMSE (Folstein et al., 1975) and Cognistat (Kiernan et al., 1987)) between females (n=42) and males (n=23) aged 51-65 years.

Key: IQR = Interquartile range; MMSE = Mini Mental State Examination; n = Sample size; p = Level of statistical significance (p<0.05); U = U test statistic; Z = Z score

Mann-Whitney U test compared HRV values between females and males aged 51-65 years (Table 4.56).

Table 4.56 Mann-Whitney U Test comparing HRV values between females (n=42) and males (n=23) 51-65 years

	Variable (unit)	U	Z	p	Mean rank females	Mean rank males	Median females (IQR)	Median males (IQR)
Females and males 51-65 years	Log baseline LF (ms ²)	628	1.99	0.047	29.55	39.30	2.65 (0.73)	3.06 (0.51)
	Log baseline total power (ms ²)	640	2.15	0.03	29.26	39.83	3.23 (0.60)	3.49 (0.49)

Table 4.56 displays significant results from a Mann-Whitney U-test of HRV values between females (n=42) and males (n=23) aged 51-65 years.

Key: HRV = Heart rate variability; IQR = Interquartile range; LF = Low frequency; ms² = Milliseconds; n = Sample size; p = Level of statistical significance (p<0.05); U = U test statistic; Z = Z score

Statistically significant correlations in 51-65 year old females and males were compared using Z scores. In females and males, the correlation between baseline mean HR and the total MMSE score was significantly different (Z=2.87, p=0.002) (r=-0.42, p=0.045; r=0.33, p=0.03, respectively).

4.1.5 Females and males total sample (18-65 years)

4.1.5.1 Females 18-65 years (n=120)

Mean (\pm SD) demographics for the total female cohort (18-65 years, n=120) are provided in Table 4.57.

Table 4.57 Mean sample demographics for total females 18-65 years (n=120)

Demographics		Value
Females 18-65 years n=120	Years of age (mean \pm SD)	40.80 \pm 13.99
	Years of education (mean \pm SD)	18.15 \pm 3.46
	BMI (mean \pm SD)	24.42 \pm 4.50
	Smoker (%)	6.67
	LAQ part one (mean \pm SD)	13.09 \pm 5.91
	LAQ part two (mean \pm SD)	20.59 \pm 9.95

Table 4.57 shows mean demographic scores for females 18-65 years (n=120). BMI normal reference range is 19-25 (Garrouste-Orgeas et al., 2004). The maximum score of LAQ part one (lifestyle risk factors) is 70 and LAQ part two (stress coping) is 75. Higher LAQ scores reflect increased risk for developing chronic illnesses (Craig et al., 1996).

Key: BMI = Body mass index; LAQ = Lifestyle Appraisal Questionnaire (Craig et al., 1996); n = Sample size; SD = Standard deviation

Mean (\pm SD) scores from the MMSE and Cognistat with reference to their respective maximum score and cognitive impairment thresholds are displayed in Table 4.58. All mean scores were above their respective cognitive impairment thresholds, although the lower end of the SD crossed those thresholds for the Cognistat domains of repetition (11.67 \pm 0.93), memory (11.21 \pm 1.47), and judgment (4.74 \pm 1.06).

Mean (\pm SD) values for HRV frequency and time domain parameters for baseline and active states are provided in Table 4.59 and Table 4.60, respectively.

Table 4.58 Mean cognitive scores from the MMSE and Cognistat for total females 18-65 years (n=120)

		Cognitive assessment	Cognitive domain	Maximum possible score	Cognitive impairment threshold	Mean \pm SD
Females 18-65 years n=120	MMSE		Orientation	10	-	9.84 \pm 0.37
			Registration	3	-	3.00 \pm 0.00
			Attention	5	-	4.35 \pm 1.10
			Recall	3	-	2.78 \pm 0.43
			Language	9	-	8.43 \pm 0.71
		Total MMSE		30	≤ 23	28.40 \pm 1.65
	Cognistat		Orientation	12	<10	11.83 \pm 0.44
			Attention	8	<6	7.71 \pm 0.60
			Comprehension	6	<5	5.63 \pm 0.57
			Repetition	12	<11	11.67 \pm 0.93
			Naming	8	<7	7.84 \pm 0.57
			Construction	6	<4	5.09 \pm 0.99
			Memory	12	<10	11.21 \pm 1.47
			Calculation	4	<3	3.60 \pm 0.59
		Similarity	8	<5	7.06 \pm 1.23	
		Judgment	6	<4	4.74 \pm 1.06	
	Total Cognistat		82	<65	76.37 \pm 4.06	

Table 4.58 shows mean cognitive scores from the MMSE (Folstein et al., 1975) and the Cognistat (Kiernan et al., 1987) for females 18-65 years (n=120). The maximum score possible and the cognitive impairment threshold are provided for each cognitive domain. Scores below the cognitive impairment threshold indicate cognitive impairment. The Cognistat domains where the lower end of the SD crossed the cognitive impairment threshold are shown in **bold**.

Key: MMSE = Mini Mental State Examination; n = Sample size; SD = Standard deviation

Table 4.59 Mean frequency domain HRV values for total females 18-65 years (n=120)

Females 18-65 years n=120	HRV State	HRV frequency domain	Mean (\pm SD) ms ²
	Baseline	Low frequency (absolute)	1166.56 \pm 1373.76
		High frequency (absolute)	1357.95 \pm 3199.48
		LF/HF (absolute)	1.76 \pm 1.82
		Total power (absolute)	3685.68 \pm 3782.03
		Log low frequency	2.88 \pm 0.54
		Log high frequency	2.72 \pm 0.58
		Log LF/HF	0.11 \pm 0.42
		Log total power	3.40 \pm 0.41
	Active	Low frequency (absolute)	2542.83 \pm 1937.20
High frequency (absolute)		1699.35 \pm 1951.38	
LF/HF (absolute)		3.09 \pm 3.00	
Total power (absolute)		6161.75 \pm 4583.79	
Log low frequency		3.29 \pm 0.37	
Log high frequency		2.94 \pm 0.57	
Log LF/HF		0.34 \pm 0.38	
Log total power		3.66 \pm 0.35	
Cardiac reactivity	Low frequency (absolute)	1160.11 \pm 2023.57	
	High frequency (absolute)	790.92 \pm 3109.09	
	LF/HF (absolute)	1.38 \pm 2.98	
	Total power (absolute)	2805.50 \pm 5748.57	
	Log low frequency	0.41 \pm 0.43	
	Log high frequency	0.23 \pm 0.50	
	Log LF/HF	0.23 \pm 0.41	
	Log total power	0.27 \pm 0.33	

Table 4.59 shows mean frequency domain HRV values for females 18-65 years (n=120) during baseline and active states. Cardiac reactivity refers to the active minus baseline HRV data.

Key: HRV = Heart rate variability; LF/HF = Low frequency divided by high frequency (sympathovagal balance); ms² = Milliseconds squared; n = Sample size; SD = Standard deviation

Table 4.60 Mean time domain HRV values for total females 18-65 years (n=120)

HRV state		HRV time domain (unit)	Mean ± SD
Females 18-65 years n=120	Baseline	Mean RR (ms)	882.46 ± 132.19
		SDNN (ms)	59.93 ± 26.10
		Mean heart rate (bpm)	69.63 ± 10.62
		RMSSD (ms)	50.57 ± 34.04
		pNN50 (%)	17.49 ± 16.88
		Log RMSSD (ms)	1.63 ± 0.29
		Log SDNN (ms)	1.75 ± 0.20
	Active	Mean RR (ms)	847.51 ± 122.45
		SDNN (ms)	74.64 ± 26.13
		Mean heart rate (bpm)	72.57 ± 10.47
		RMSSD (ms)	66.97 ± 36.03
		pNN50 (%)	18.52 ± 14.70
		Log RMSSD (ms)	1.76 ± 0.25
		Log SDNN (ms)	1.85 ± 0.16
	Cardiac reactivity	Mean RR (ms)	-35.36 ± 46.25
		SDNN (ms)	15.12 ± 23.44
		Mean heart rate (bpm)	2.94 ± 3.55
		RMSSD (ms)	17.14 ± 33.63
		pNN50 (%)	1.16 ± 9.03
		Log RMSSD (ms)	0.13 ± 0.23
		Log SDNN (ms)	0.10 ± 0.15

Table 4.60 shows mean time domain HRV values for females 18-65 years (n=120) during baseline and active states. Cardiac reactivity refers to the active minus baseline HRV data.

Key: bpm = Beats per minute; HRV = Heart rate variability; ms = Milliseconds; n = Sample size; pNN50 = Total number of interval differences (greater than 50 ms) of consecutive NN (beat to beat) intervals divided by the total number of NN intervals; RMSSD = Square root of the mean squared differences of successive NN intervals; RR = Duration in ms from one R peak to the next R peak of the electrocardiogram; SD = Standard deviation; SDNN = SD of all NN intervals (the square root of variance)

4.1.5.1.1 Female age group comparison (18-35, 36-50, 51-35 years)

Mean cognitive scores (Cognistat and MMSE) for females aged 18-35, 36-50 and 51-65 years are displayed in Figure 4.5

Figure 4.5 Mean cognitive scores (Cognistat and MMSE) for females aged 18-35 (n=41), 36-50 (n=37) and 51-65 years (n=23)

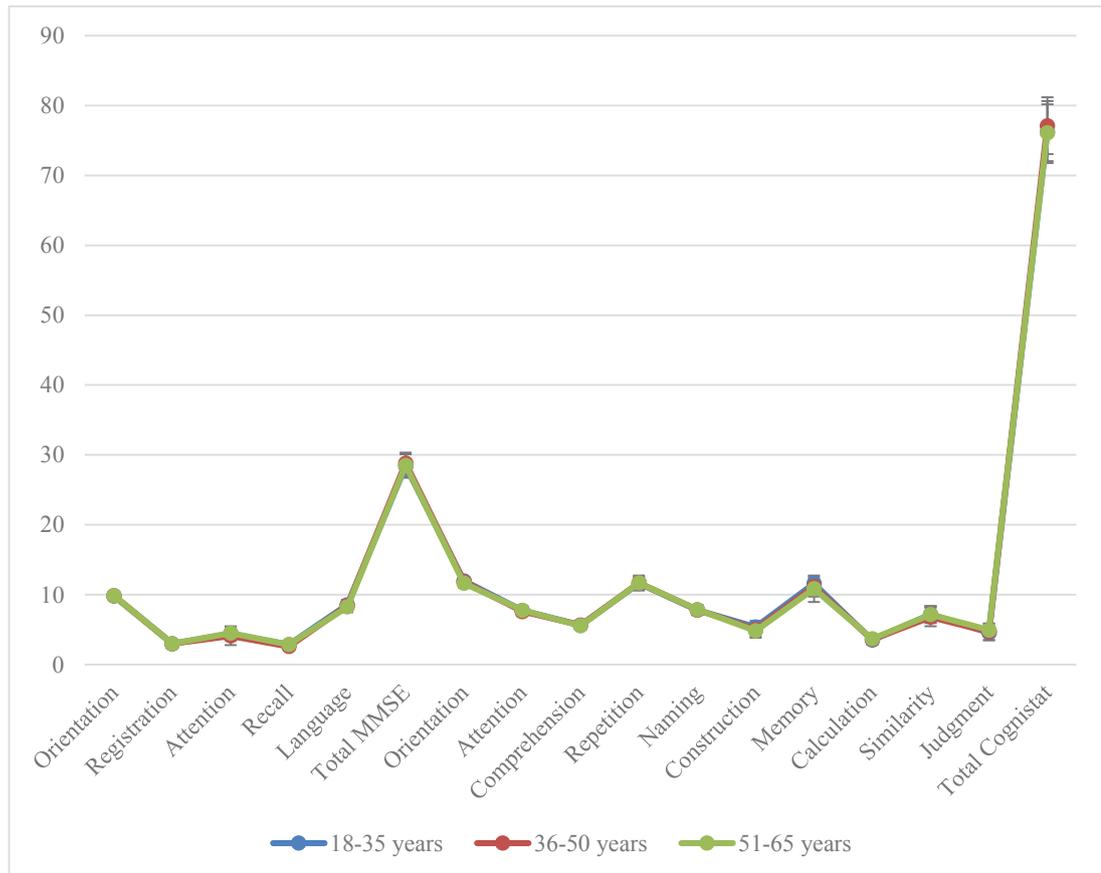


Figure 4.5 displays mean cognitive scores (Cognistat (Kiernan et al., 1987) and MMSE (Folstein et al., 1975)) for females aged 18-35 (n=41), 36-50 (n=37) and 51-65 years (n=23).

MMSE = Mini Mental State Examination

Observations were made to compare the previously conducted dependent sample t-tests between baseline and active states across the three female age groups to address aim 2 (Table 4.9, Table 4.26, and Table 4.44). It was observed that mean RR significantly fell across all groups whereas mean HR, log LF, log LF/HF, log TP, and log SDNN all significantly rose. Log HF and log RMSSD also significantly rose in the middle and older

age sample yet were not significantly different between baseline and active states in the youngest age group.

Correlations with covariates were initially performed to determine whether to apply ANOVA or ANCOVA in order to compare cognitive scores and HRV values in the female age groups. If statistical significance ($p < 0.05$) was achieved with ANOVA, Bonferroni post hoc tests were performed to determine which groups were significantly different. The ANOVA and ANCOVA tests for differences in cognitive scores between female age groups are displayed in Table 4.61 and Table 4.62, respectively.

Table 4.61 ANOVA comparing cognitive scores between female age groups 18-35 (n=41), 36-50 (n=37), and 51-65 (n=42) years

	Variable	F	df	ANOVA p	18-35 years mean \pm SD	51-65 years mean \pm SD	Bonferroni p
Females 18-35, 36-50 and 51-65	Orientation Cognistat	6.65	2, 117	0.002	11.98 \pm 0.16	11.64 \pm 0.62	0.001
	Construction Cognistat	3.20	2, 117	0.04	5.38 \pm 0.90	4.85 \pm 1.02	0.04

Table 4.61 displays significant results from an ANOVA comparing cognitive scores (MMSE (Folstein et al., 1975) and Cognistat (Kiernan et al., 1987)) between females aged 18-35 (n=41), 36-50 (n=37) and 51-65 (n=42) years. The 36-50 year old female group was not significantly different.

Key: ANOVA = Analysis of variance; df = Degrees of freedom; F = F statistic; n = Sample size; p = Level of statistical significance ($p < 0.05$); SD = Standard deviation

Table 4.62 ANCOVA comparing cognitive scores between female age groups 18-35 (n=41), 36-50 (n=37) and 51-65 (n=42) years

Females 18-35, 36-50 and 51-65 years	Covariate	Variable	F	df	ANOVA p	18-35 years mean ± SD	36-50 years mean ± SD	51-65 years mean ± SD	Bonferroni p
		Covariate	Total MMSE score	3.05	3, 11	0.03	-	28.00 ± 1.81	28.52 ± 1.58
	Age and LAQ part one	Recall MMSE	10.15	3, 11	<0.001	2.85 ± 0.36	2.60 ± 0.55	2.88 ± 0.33	0.03 (18-35 and 51-65 years); <0.001 (36-50 and 51-65 years)

Table 4.62 displays significant results from a ANCOVA comparing cognitive scores (MMSE (Folstein et al., 1975) and Cognistat (Kiernan et al., 1987)) between females aged 18-35 (n=41), 36-50 (n=37), and 51-65 (n=42) years.

Key: ANCOVA = Analysis of covariance; df = Degrees of freedom; F = F statistic; LAQ = Lifestyle Appraisal Questionnaire (Craig et al., 1996); MMSE = Mini Mental State Examination; n = Sample size; p = Level of statistical significance (p<0.05); SD = Standard deviation

The ANOVA tests for differences in HRV values between female age groups are displayed in Table 4.63. The ANCOVA tests performed for differences in HRV values between female age groups did not yield statistically significant results.

Table 4.63 ANOVA comparing HRV values between female age groups 18-35 (n=41), 36-50 (n=37), and 51-65 (n=42) years

	Variable	F	df	ANOVA p	18-35 years mean \pm SD	36-50 years mean \pm SD	51-65 years mean \pm SD	Bonferroni p
Females 18-35, 36-50 and 51-65 years	Log baseline TP (ms ²)	3.45	2, 101	0.04	3.51 \pm 0.39	-	3.24 \pm 0.39	0.03
	Log baseline SDNN (ms)	3.38	2, 101	0.04	1.79 \pm 0.18	-	1.67 \pm 0.19	0.03
	Active mean HR (bpm)	4.14	2, 101	0.02	76.41 \pm 11.41	-	69.20 \pm 10.10	0.02
	CR pNN50 (%)	4.47	2, 101	0.01	-0.30 \pm 7.08	2.25 \pm 10.70	-	0.02
	Log CR TP (ms ²)	3.94	2, 101	0.02	3.65 \pm 0.33	0.29 \pm 0.38	-	0.04
	Log CR SDNN (ms)	4.48	2, 101	0.01	0.07 \pm 0.12	0.10 \pm 0.16	0.14 \pm 0.16	0.03 (18-35 and 36-50 years); 0.04 (18-35 and 51-65 years)
	Log CR RMSSD (ms)	4.04	2, 101	0.02	0.07 \pm 0.20	-	0.21 \pm 0.25	0.02

Table 4.63 displays significant results from an ANOVA comparing HRV values between females aged 18-35 (n=41), 36-50 (n=37), and 51-65 (n=42) years.

Key: ANOVA = Analysis of variance; bpm = Beats per minute; CR = Cardiac reactivity; df = Degrees of freedom; F = F statistic; HR = Heart rate; HRV = Heart rate variability; n = Sample size; LF = Low frequency; ms = Milliseconds; ms² = Milliseconds squared; p = Level of statistical significance (p<0.05); pNN50 = Total number of interval differences (greater than 50 milliseconds) of consecutive NN (beat to beat) intervals divided by the total number of NN intervals; r = Correlation coefficient; RMSSD = Square root of the mean squared differences of successive NN intervals; SD = Standard deviation; SDNN = Standard deviation of all NN intervals (the square root of variance); TP = Total power

4.1.5.2 Males 18-65 years (n=102)

Mean (\pm SD) demographics for the total male cohort (18-65 years, n=102) are provided in Table 4.64.

Table 4.64 Mean sample demographics for total males 18-65 years (n=102)

Demographics		Value
Males 18-65 years n=102	Years of age (mean \pm SD)	37.74 \pm 13.98
	Years of education (mean \pm SD)	17.91 \pm 3.31
	BMI (mean \pm SD)	24.92 \pm 3.35
	Smoker (%)	17.48
	LAQ part one (mean \pm SD)	13.97 \pm 7.15
	LAQ part two (mean \pm SD)	18.85 \pm 9.50

Table 4.64 shows mean demographic scores for males 18-65 years (n=102). BMI normal reference range is 19-25 (Garrouste-Orgeas et al., 2004). The maximum score of LAQ part one (lifestyle risk factors) is 70 and LAQ part two (stress coping) is 75. Higher LAQ scores reflect increased risk for developing chronic illnesses (Craig et al., 1996).

Key: BMI = Body mass index; LAQ = Lifestyle Appraisal Questionnaire (Craig et al., 1996); n = Sample size; SD = Standard deviation

Mean (\pm SD) scores from the MMSE and Cognistat with reference to their respective maximum score and cognitive impairment thresholds are displayed in Table 4.65. All mean scores were above their respective cognitive impairment thresholds, although the lower end of the SD crossed those thresholds for the Cognistat domains of comprehension (5.47 \pm 0.70), repetition (11.51 \pm 1.15), memory (11.08 \pm 1.72), and judgment (4.30 \pm 1.14).

Mean (\pm SD) values for HRV frequency and time domain parameters for baseline and active states are provided in Table 4.66 and Table 4.67, respectively.

Table 4.65 Mean cognitive scores from the MMSE and Cognistat for total males 18-65 years (n=102)

		Cognitive assessment	Cognitive domain	Maximum possible score	Cognitive impairment threshold	Mean \pm SD
Males 18-65 years n=102	MMSE		Orientation	10	-	9.88 \pm 0.32
			Registration	3	-	2.99 \pm 0.10
			Attention	5	-	4.38 \pm 1.16
			Recall	3	-	2.80 \pm 0.47
			Language	9	-	8.39 \pm 0.79
		Total MMSE		30	≤ 23	28.45 \pm 1.70
	Cognistat		Orientation	12	<10	11.86 \pm 0.40
			Attention	8	<6	7.50 \pm 0.94
			Comprehension	6	<5	5.47 \pm 0.70
			Repetition	12	<11	11.51 \pm 1.15
			Naming	8	<7	7.72 \pm 0.57
			Construction	6	<4	5.42 \pm 0.88
			Memory	12	<10	11.08 \pm 1.72
			Calculation	4	<3	3.81 \pm 0.51
		Similarity	8	<5	7.34 \pm 1.17	
		Judgment	6	<4	4.30 \pm 1.14	
	Total Cognistat		82	<65	76.00 \pm 4.86	

Table 4.65 shows mean cognitive scores from the MMSE (Folstein et al., 1975) and the Cognistat (Kiernan et al., 1987) for males 18-65 years (n=102). The maximum score possible and the cognitive impairment threshold are provided for each cognitive domain. Scores below the cognitive impairment threshold indicate cognitive impairment. The Cognistat domains where the lower end of the SD crossed the cognitive impairment threshold are shown in **bold**.

Key: MMSE = Mini Mental State Examination; n = Sample size; SD = Standard deviation

Table 4.66 Mean frequency domain HRV values for total males 18-65 years (n=102)

HRV State		HRV frequency domain	Mean (\pm SD) ms ²
Males 18-65 years n=102	Baseline	Low frequency (absolute)	1161.79 \pm 1104.28
		High frequency (absolute)	1181.59 \pm 2292.43
		LF/HF (absolute)	2.41 \pm 2.52
		Total power (absolute)	3853.50 \pm 4478.15
		Log low frequency	2.90 \pm 0.52
		Log high frequency	2.70 \pm 0.62
		Log LF/HF	0.20 \pm 0.39
		Log total power	3.39 \pm 0.42
	Active	Low frequency (absolute)	2501.73 \pm 1956.42
		High frequency (absolute)	1674.44 \pm 2695.75
		LF/HF (absolute)	3.34 \pm 2.91
		Total power (absolute)	5948.15 \pm 5235.52
		Log low frequency	3.29 \pm 0.39
		Log high frequency	2.88 \pm 0.62
		Log LF/HF	0.40 \pm 0.39
		Log total power	3.64 \pm 0.38
	Cardiac reactivity	Low frequency (absolute)	1182.68 \pm 2367.88
		High frequency (absolute)	921.15 \pm 3892.40
		LF/HF (absolute)	1.38 \pm 3.79
		Total power (absolute)	2619.74 \pm 7079.03
		Log low frequency	0.40 \pm 0.39
		Log high frequency	0.21 \pm 0.53
		Log LF/HF	0.19 \pm 0.39
		Log total power	0.27 \pm 0.32

Table 4.66 shows mean frequency domain HRV values for males 18-65 years (n=102) during baseline and active states. Cardiac reactivity refers to the active minus baseline HRV data.

Key: HRV = Heart rate variability; LF/HF = Low frequency divided by high frequency (sympathovagal balance); ms² = Milliseconds squared; n = Sample size; SD = Standard deviation

Table 4.67 Mean time domain HRV values for total males 18-65 years (n=102)

HRV state		HRV time domain (unit)	Mean ± SD
Males 18-65 years n=102	Baseline	Mean RR (ms)	867.14 ± 137.52
		SDNN (ms)	58.81 ± 25.31
		Mean heart rate (bpm)	71.42 ± 11.77
		RMSSD (ms)	47.22 ± 32.06
		pNN50 (%)	16.58 ± 16.30
		Log RMSSD (ms)	1.61 ± 0.28
		Log SDNN (ms)	1.74 ± 0.19
	Active	Mean RR (ms)	830.73 ± 122.90
		SDNN (ms)	74.17 ± 27.05
		Mean heart rate (bpm)	74.69 ± 11.70
		RMSSD (ms)	62.89 ± 40.22
		pNN50 (%)	16.42 ± 13.70
		Log RMSSD (ms)	1.74 ± 0.30
		Log SDNN (ms)	1.84 ± 0.17
	Cardiac reactivity	Mean RR (ms)	-36.77 ± 47.26
		SDNN (ms)	17.34 ± 24.30
		Mean heart rate (bpm)	3.32 ± 4.59
		RMSSD (ms)	17.87 ± 33.89
		pNN50 (%)	0.14 ± 8.58
		Log RMSSD (ms)	0.13 ± 0.22
		Log SDNN (ms)	0.12 ± 0.14

Table 4.67 shows mean time domain HRV values for males 18-65 years (n=102) during baseline and active states. Cardiac reactivity refers to the active minus baseline HRV data.

Key: bpm = Beats per minute; HRV = Heart rate variability; ms = Milliseconds; n = Sample size; pNN50 = Total number of interval differences (greater than 50 ms) of consecutive NN (beat to beat) intervals divided by the total number of NN intervals; RMSSD = Square root of the mean squared differences of successive NN intervals; RR = Duration in ms from one R peak to the next R peak of the electrocardiogram; SD = Standard deviation; SDNN = SD of all NN intervals (the square root of variance)

4.1.5.2.1 Male age group comparison (18-35, 36-50, 51-35 years)

Mean cognitive scores (Cognistat and MMSE) for males aged 18-35, 36-50 and 51-65 years are displayed in Figure 4.6

Figure 4.6 Mean cognitive scores (Cognistat and MMSE) for males aged 18-35 (n=42), 36-50 (n=37) and 51-65 years (n=42)

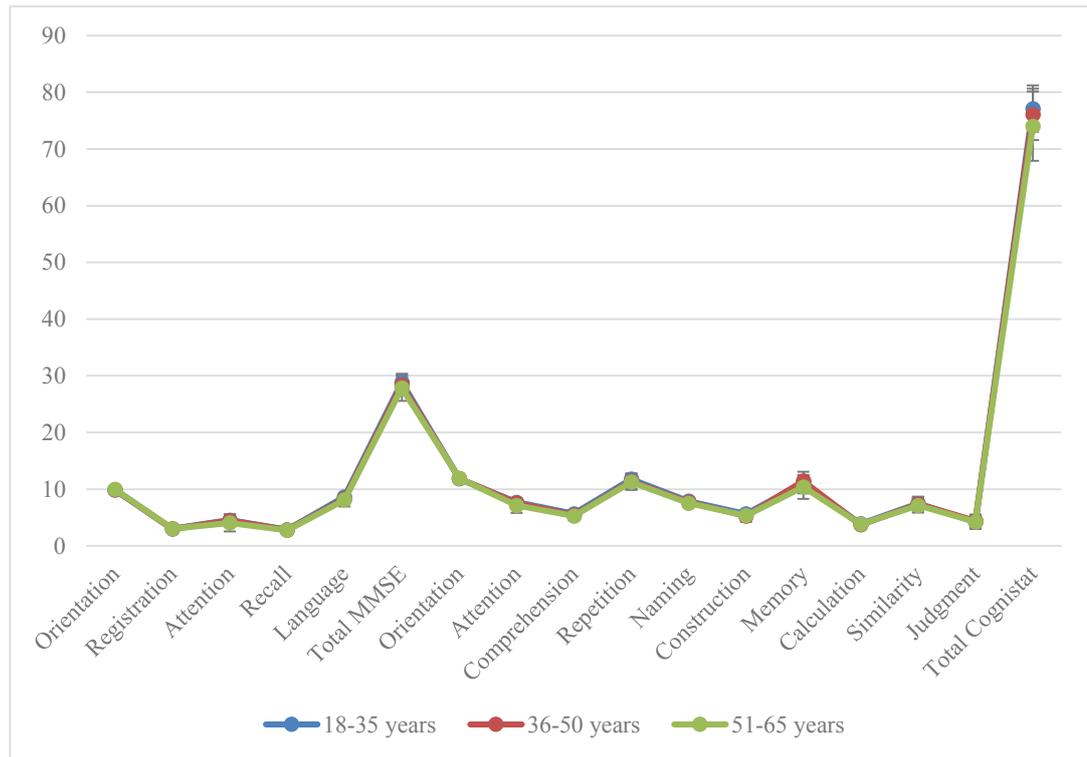


Figure 4.6 displays mean cognitive scores (Cognistat (Kiernan et al., 1987) and MMSE (Folstein et al., 1975)) for males aged 18-35 (n=42), 36-50 (n=37) and 51-65 years (n=42).

MMSE = Mini Mental State Examination

Observations were made to compare the previously conducted dependent sample t-tests (18-35 years and 36-50 years) and Wilcoxon signed rank test (51-65 years) between baseline and active states across the three male age groups to address aim 2 (Table 4.16, Table 4.35, and Table 4.52). It was observed that mean RR significantly fell across all groups, whereas mean HR, log LF, log TP, log SDNN, and log RMSSD all significantly rose. Log HF was significantly higher in the middle age group, yet was not significantly different between baseline and active states in the youngest or oldest groups where there was a significant increase in log LF/HF from baseline to active states.

A comparison between males in the three age groups was conducted using a Kruskal Wallis test (non-parametric ANOVA equivalent). This was performed instead of ANOVA as the males in the 51-65 year group had a lower sample size than the other two groups (18-35 years n=42; 36-50 years n=37; 51-65 years n=23). The medians of naming (Cognistat) were significantly different ($p=0.02$). Dunn's (1964) pairwise comparison was performed as a post hoc analysis, identifying the difference lay between the 18-35 year old (median (IQR): 8 (0)) and 51-65 year old males (median (IQR): 8 (1)) ($p=0.02$) ($\chi^2 = 7.75$ (df = 2)). It is not clear which age group had higher or lower values as the median appeared the same (however the mean score was higher in the 18-35 year group (7.88 ± 0.40) than in the 51-65 year group (7.52 ± 0.67)).

There were no significant differences identified for HRV values between these three male age groups.

4.1.5.3 Comparison between total females (n=120) and males (n=102)

Mean cognitive scores (Cognistat and MMSE) for the total females and males aged 18-65 years are displayed in Figure 4.7.

Figure 4.7 Mean cognitive scores (Cognistat and MMSE) for the total females (n=120) and males (n=102) aged 18-65 years

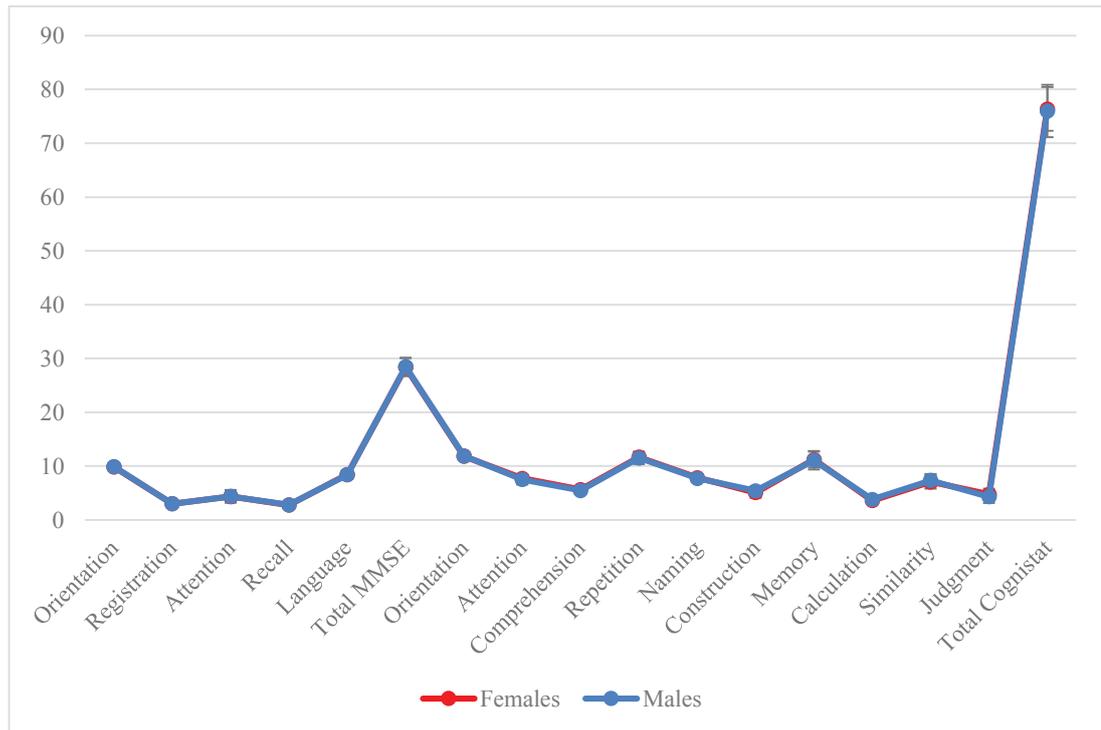


Figure 4.7 displays mean cognitive scores (Cognistat (Kiernan et al., 1987) and MMSE (Folstein et al., 1975)) for the total females (n=120) and males (n=102) aged 18-65 years.

MMSE = Mini Mental State Examination

An independent sample t-test was used to compare cognitive scores (without covariates) between total females and total males (18-65 years) and did not produce separate statistically significant results to those identified in the covariate model.

An independent sample t-test with covariates is shown in Table 4.68.

Table 4.68 Independent sample t-test with covariance of cognitive scores between females (n=120) and males (n=102) aged 18-65 years

	Covariate	Variable	F	df	p	Females mean \pm SD	Males mean \pm SD	Mean difference (males - females)
Females and males 18-65 years	Smoking status	Attention Cognistat	3.81	2	0.02	7.71 \pm 0.60	7.50 \pm 0.94	-0.21
	Age	Language MMSE	4.84	2	0.01	8.44 \pm 0.71	8.42 \pm 0.76	-0.02
		Orientation Cognistat	5.29	2	0.01	11.83 \pm 0.44	11.86 \pm 0.41	0.03
		Construction Cognistat	4.54	2	0.01	5.11 \pm 0.98	5.47 \pm 0.82	0.36
		Total Cognistat score	76.57	2	0.02	76.40 \pm 4.06	76.10 \pm 4.93	-0.30
	LAQ part two (stress coping)	Calculation Cognistat	3.56	2	0.03	3.60 \pm 0.59	3.80 \pm 0.51	0.20

Table 4.68 displays significant results from an independent sample t-test with covariates (performed by ANCOVA and MANCOVA) of cognitive scores (from the MMSE (Folstein et al., 1975) and Cognistat (Kiernan et al., 1987)) between females (n=120) and males (n=102) aged 18-65 years.

Key: ANCOVA = Analysis of covariance; df = Degrees of freedom; F = F statistic; LAQ = Lifestyle Appraisal Questionnaire (Craig et al., 1996); MANCOVA = Multiple analysis of covariance; MMSE = Mini Mental State Examination; n = Sample size; p = Level of statistical significance (p<0.05); SD = Standard deviation

An independent sample t-test of HRV scores without covariates between females and males (18-65 years) did not produce significant results.

An independent sample t-test of HRV scores between males and females with covariates is displayed in Table 4.69.

Table 4.69 Independent sample t-test with covariance of HRV values between females (n=120) and males (n=102) aged 18-65 years

Covariate		Variable	F	df	p	Females mean \pm SD	Males mean \pm SD	Mean difference (males - females)
Females and males 18-65 years	Age	Log baseline LF (ms ²)	3.06	2	0.049	2.86 \pm 0.53	2.89 \pm 0.47	0.03
		Log baseline SDNN (ms)	4.38	2	0.01	1.74 \pm 0.19	1.73 \pm 0.18	-0.01
		Active mean RR (ms)	3.84	2	0.02	848.48 \pm 122.51	833.03 \pm 119.83	-15.45
		Log CR HF (ms ²)	4.85	2	0.01	0.22 \pm 0.51	0.22 \pm 0.49	0
		Log CR RMSSD (ms)	4.41	2	0.01	0.14 \pm 0.23	0.14 \pm 0.21	0
	LAQ part one (lifestyle risk factors)	Log CR LF/HF	3.76	2	0.03	0.23 \pm 0.41	0.19 \pm 0.39	-0.04
	BMI and age	Log baseline HF (ms ²)	5.63	2	0.004	2.72 \pm 0.58	2.68 \pm 0.59	-0.04
		Log baseline TP (ms ²)	5.31	2	0.01	3.40 \pm 0.42	3.39 \pm 0.42	-0.01

Table 4.69 displays significant results from an independent sample t-test with covariance (performed by ANCOVA and MANCOVA) of HRV values between females (n=120) and males (n=102) aged 18-65 years.

Key: ANCOVA = Analysis of covariance; BMI = Body mass index; CR = Cardiac reactivity; df = Degrees of freedom; F = F statistic; HF = High frequency; HRV = Heart rate variability; LAQ = Lifestyle Appraisal Questionnaire (Craig et al., 1996); LF = Low frequency; LF/HF = Low frequency divided by high frequency (sympathovagal balance); MANCOVA = Multiple analysis of covariance; ms = Milliseconds; ms² = Milliseconds squared; n = Sample size; p = Level of statistical significance (p<0.05); RMSSD = Square root of the mean squared differences of successive NN intervals; RR = Duration in milliseconds from one R peak to the next R peak of the electrocardiogram; SD = Standard deviation; SDNN = Standard deviation of all NN intervals (the square root of variance); TP = Total power

4.2 Discussion: HRV and cognition (non-clinical groups)

This chapter discusses findings with respect to HRV and cognition. It examines these, in turn, in three age groups (18-35 years, 36-50 years, and 51-65 years), comparing results found in females and males.

4.2.1 18-35 years

4.2.1.1 Females (n=41)

In younger females, mean HR, LF, LF/HF, TP, and SDNN all significantly increased upon cognitive interaction (baseline compared to active state). Mean RR fell, confirming the established inverse relationship between HR and RR (that is, as HR increases, the distance between RR intervals decreases) (Sacha, 2013, Fleiss et al., 1992). It is well understood that HR increases upon cognitive stimulation, circulating oxygen and glucose to firing neurons (Ginty et al., 2011). However, HRV parameters have been shown to decline with cognitive challenge (linked to vagal withdrawal in response to a stressor (e.g. the Stroop task)) (Li et al., 2009, Byrd et al., 2014). The neutral conversation technique, used in the present analysis, aims to engage various cognitive domains without evoking a stress response (e.g. recall, social inhibition, verbal reasoning) (Potter, 2006). Neutral conversation has been shown to increase (Sloan et al., 1991) and decrease HRV parameters (Bernardi et al., 2000). In the current study, HRV activity consistently increased during the conversation active phase, potentially attributed to increased RSA during speaking.

Cardiac reactivity (a measure of LF derived from active minus baseline states, to account for baseline differences) was inversely correlated to naming (Cognistat). Naming is a subgroup of language skill, integrating one's ability to recognise and correctly identify subject matter (Melby-Lervåg et al., 2012). Clinical interpretation of LF HRV information is contested, some studies suggest LF reflects sympathetic drive, others suggest a mixture of sympathetic, parasympathetic, baroreflex and RSA influences are involved (Martelli et al., 2014, Rajajeyakumar et al., 2014, Goldstein et al., 2011b, Koskinen et al., 2009, Goedhart et al., 2008, Introna et al., 1995). Decreased vagal tone (LF) was also found to benefit executive functioning in a doctoral thesis by Keen (2011), yet the author acknowledges his incongruent results compared to others research (n=106,

mean age 20 ± 3 years, 73% female). Other experiments have not found significant relationships between HRV and cognition in young females (Sato and Miyake, 2004), and many others suggesting higher vagal tone is better for executive function (Mathewson et al., 2011, Hansen et al., 2004, Kim et al., 2006).

Cardiac reactivity of mean RR fell and mean HR rose as Cognistat domains of calculation, total score and memory rose. HR is known to increase during cognitive stimulation in domains involving strong emotions (except disgust), cognitive challenge, reward, and the stress response, and to decrease in attentive waiting (anticipation) (Jennings, 2007, Vuksanović and Gal, 2007). Increases in HR have also been shown to improve cognitive performance in verbal learning tasks and problem solving (Andreassi and Whalen, 1967, Goldstein et al., 1975).

Baseline SDNN and RMSSD were also positively linked to memory (Cognistat). The time domain measure of SDNN is a marker of overall HRV and RMSSD is a reflection of cardiac vagal tone, where lower SDNN and RMSSD reveals lower cardiac vagal tone (Xhyheri et al., 2012). Literature strongly supports the view that increased vagal tone is beneficial to cognitive performance (Hansen et al., 2003, Gillie et al., 2013, Kim et al., 2006). Research by Gillie's team (2013), for instance, identified increased baseline HF was linked to improved cognitive inhibition tasks in 85 students (mean age 18 years, 64% female).

Cardiac reactivity LF/HF showed a positive correlation to construction performance (Cognistat). Literature suggests a rise in the LF/HF ratio is consistent with increases in vagal modulation (Xhyheri et al., 2012), which has also been shown to be beneficial for cognitive processing (Luft et al., 2009, Kimhy et al.). As mentioned earlier, however, debates regarding clinical interpretation of LF HRV information also impacts upon the discussion of the utility of the LF/HF ratio. Some studies refer to the LF/HF ratio as sympathovagal balance (Pagani et al., 1997, Choi et al., 2006), although this suggests the LF band singularly reflects sympathetic cardiac control (not supported by recent studies (Quintana and Heathers, 2014, Billman, 2013, Heathers, 2012)). Others suggest not to use the LF/HF ratio because the relevance of the ratio depends on whether the nominator and denominator are increasing and/or decreasing (Billman, 2013) (in other words, the ratio appears the same if both LF and HF increase or decrease by the same amount, rather than demonstrating the change in cardiac activity). In the present research it was found

that both LF and HF increased from baseline to active states, with LF increasing by a greater magnitude, raising the numerical value of the LF/HF ratio.

4.2.1.2 Males (n=42)

In males in the younger age group, mean HR, LF, LF/HF, TP, SDNN, and RMSSD all significantly increased upon cognitive interaction (baseline compared to active state). As previously discussed, increases in HR accompany cognitive engagement. Increases in HRV are attributed to the type of cognitive intervention, neutral conversation, which can increase cardiac vagal tone. Reactivity to cognitive stimulation is a marker of health and adaptability to the external environment (Thayer et al., 2012).

The LF/HF ratio showed an inverse relationship to domains of similarity and orientation (Cognistat). Both LF and HF decreased, however LF decreased with greater magnitude than HF, increasing the proportion of cardiac vagal tone. Luft and researchers (2009) assessed 30 young athletes (aged 16-25, 77% male) and found LF/HF ratio was lower in cognitive domains requiring working memory skills (executive function) (tested via the one back test and the one card learning task), whereas LF/HF was higher when performing tasks requiring quick reaction times. They postulated that higher HF activity (hence lower LF/HF ratio) is beneficial to executive function tasks, and higher sympathetic tone is beneficial to tasks requiring speedy responses. However, this would assume the LF band is an accurate reflection of cardiac tonic control, which has been convincingly disputed by other researchers (Goldstein et al., 2011b, Houle and Billman, 1999, Martelli et al., 2014, Moak et al., 2007).

Increased vagal tone was shown to aid cognitive performance in several other domains, with positive correlations identified between CR SDNN and comprehension (Cognistat) as well as judgment (Cognistat) and CR TP with comprehension (Cognistat). It is difficult, however, to compare CR findings to other research as CR depends on the type of cognitive intervention, such as executive function tasks or assessing emotional perception skills. Additionally, literature focuses heavily on HR reactivity rather than HRV reactivity, hence these data provide new knowledge to the field of CR and cognition. Gao's team (2015a), for example, assessed 340 young children (aged 8-9 years) and, despite the young age, findings suggested similar results, with HR reactivity being positively correlated to increased performance in fluid intelligence and perceptual

reasoning (executive functioning). Ginty and colleagues (2011) found similar results in older samples in the longitudinal West of Scotland Twenty-07 Study where cognitive ability and HR reactivity was examined in 1647 participants, starting at ages of 15, 35, and 55 years and followed up 5 and 12 years later (46% male). Those with higher HR reactivity had higher intelligence quotient (IQ) scores and the least decline in cognitive ability between follow-up years, which implies that higher CR can serve to protect from future cognitive decline.

Baseline LF/HF and CR mean HR were both negatively correlated to memory (Cognistat) and total score (Cognistat). A hierarchical regression identified baseline LF/HF, CR mean RR, and CR mean HR significantly accounted for 37% of the variability in total score (Cognistat). Individually, baseline LF/HF alone significantly influenced the regression model. This further supports the finding that vagal tone supports cognitive performance, as discussed previously (Hansen et al., 2003). It was surprising to note that CR HR was inversely correlated to total score (Cognistat), when literature suggests that high HR reactivity supports cognition. In Backs and Seljos' experiments (1994), 24 participants performed significantly better on memory load tasks with decreased heart periods (higher HR) (age range 18-42 years, 50% male). Contrastingly, Matthews' group did not identify significant changes in HR between cognitively demanding tertiary exam periods versus non-exam periods, although correlations between cognitive scores and HR change were not assessed (n=14, mean age 21 ± 2 years, 57 % male) (Matthews et al., 2012).

4.2.1.3 Comparison between females (n=41) and males (n=42) (18-35 years)

Females received better scores in memory (Cognistat), recall (MMSE), and judgment (Cognistat) domains, while males scored higher in the calculation (Cognistat) domain. These findings are in agreement with the majority of the literature, which shows that females generally exhibit superior verbal and linguistic skills, while males excel at visuospatial tasks and mathematical reasoning (Weiss et al., 2003). Interestingly, some have argued that male success in spatial orientation tasks may be a basis for enhanced mathematics ability, particularly geometry and physical modelling where spatial skills are essential (Casey, 1995). Guenzel and researchers (2014) also found spatial memory to be worse in females when undergoing a stressful task (n=70, mean age 24 ± 1 years, 50% male). Hill's group conducted a meta-analysis to assess neuro-functional differences

in working memory between sexes and found that during tasks such as the n-back test and the delayed match to sample test, females accessed limbic and PFC structures while males activated a range of parietal areas (Hill et al., 2014). Kaufman's study (2007) showed males performed significantly better in tasks of mental rotation and spatial visualisation in a sample aged 16-18 years (n=100, 50% male).

In contrast to literature (Weiss et al., 2003), total score (Cognistat) was found to be significantly higher in males than females aged 18-35 years. Evans and Hampson, comparing a similar sample of 92 healthy young adults (aged 17-35 years, 49% male), showed that females and males do not significantly differ in measures of global cognitive scores (Evans and Hampson, 2015). There have been fewer analyses of the differences in HRV between females and males. HRV reactivity, for example, has not been previously tested to compare females and males although it has been noted that HR reactivity was significantly higher in males in response to upright posture changes than in females (n=374, mean age 50 ± 6 years, 50% male) (Huikuri et al., 1996).

Males had significantly higher baseline LF/HF ratio and CR SDNN than females. The heightened LF/HF ratio was due to decreased HF, yet males had higher overall HRV (SDNN). In support, several studies show males have higher overall HRV values than females (particularly low frequency components) whereas females exhibit increased vagally mediated values (HF, RMSSD), attributed to sex hormone effects on the ANS (Bonnemeier et al., 2003, Yamasaki et al., 1996, Huikuri et al., 1996, Cowan et al., 1994, Vandeput et al., 2012). It also ought to be noted that previous research has not examined sex and CR HRV hence the present research contributes new knowledge to the literature. These findings suggest normative HRV ranges ought to take sex into consideration.

Females had higher baseline HF, TP, and baseline and active mean RR, mean HR, LF, SDNN, and RMSSD than males. It was surprising to find mean RR and mean HR were both significantly higher in females as mean RR and mean HR are usually reciprocal in nature, in other words, the closer the RR intervals (smaller mean RR) the higher the HR. It was also found that females had significantly higher CR LF than males. It is important to note that despite finding such significantly different measures between females and males, the clinical relevance of these differences is debatable, particularly differences of <1bpm, <1ms, or <1ms².

Memory (Cognistat) and total score (Cognistat) negatively correlated to CR mean HR in males yet positively in females (correspondingly inversely related to mean RR for both sexes). This difference in CR mean HR suggests that responsiveness to a cognitive stimulus may affect cognition differently between the sexes. As previously mentioned, studies have shown females and males use different neural pathways in working memory skills (Evans and Hampson, 2015, Hill et al., 2014), which may be involved in downstream cardiac effects, specifically involving the insular cortex, proposed as the neuroanatomical link between cardiac vagal control and executive function (Kimhy et al., Nagai et al., 2010, Hanamori, 2005, Lane et al., 2009, Critchley et al., 2005).

4.2.2 36-50 years

4.2.2.1 Females (n=37)

As expected in middle aged females, mean HR rose upon cognitive stimulation, accompanied by a decline in mean RR intervals (Fleiss et al., 1992). Total HRV power (TP and SDNN) also increased as well as the sub-components LF and HF (for TP), and RMSSD (associated with cardiac vagal control). This overall increase in HRV activity is consistent with cognitive stimulation in the absence of a stressor (Kimhy et al., 2013).

Correlations in this cohort presented interesting findings. Comprehension (Cognistat) was negatively linked to baseline pNN50 and RMSSD, although literature shows strong support for positive relationships between cognition and increased vagal tone (Hansen et al., 2003, Kim et al., 2013, Zulli et al., 2005, de Vilhena Toledo and Junqueira, 2008). However, certain cognitive domains may relate differently to changes in cardiac control, as it is proposed that they utilise similar yet distinct neural pathways, particularly executive function skills (Miyake et al., 2000).

Naming (Cognistat) was positively linked to baseline LF, TP, and SDNN. Total power and SDNN both reflect total HRV, where increases suggest higher vagal tone (Rajajeyakumar et al., 2014). Previous studies have also found high resting LF is correlated to better cognitive performance, in support of the theory of parasympathetic tone within the LF band (Solernó et al., 2012, Murtazina, 2015). Solernó's team (2012) found positive correlations between LF and spatial tasks as well as positive correlations

between verbal tasks and all vagally mediated time and frequency domain HRV variables in a small sample of 19 young students (mean age 22 ± 1 years, 43% female).

Shi's laboratory (2013) proposed that different cognitive tasks can have distinct effects on HRV. They noted LF significantly decreased during reading aloud and free talking tasks ($n=10$, mean age 20 ± 2 years, 100% male) (despite disparities in sample demographics). HRV decreases upon cognitive stimulation were shown to benefit certain cognitive variables in the current study (inverse correlations): naming (Cognistat) and CR SDNN; memory (Cognistat) and CR mean RR and CR pNN50; total score (Cognistat) and CR HF; repetition (Cognistat) and CR HF and CR TP; naming, memory, and total score (Cognistat) and CR TP. This was also found by Byrd et al., (2014), where HF activity was suppressed during inhibition and working memory tasks in a similar sample size ($n=34$), yet younger age group (age range 18-25 years, 56% male). Further, calculation skill (Cognistat) was found to improve with increases in HR. HR generally increases upon cognitive stimulation to support neuronal demand for circulating oxygen and glucose (Vincent et al., 1996).

4.2.2.2 Males (n=37)

As expected, in middle aged males, HR significantly rose upon cognitive stimulation (neutral conversation), accompanied by a corresponding drop in mean RR intervals. LF, HF, TP, SDNN, and RMSSD all significantly rose from baseline to active state. As previously discussed, changes in HRV are dependent on the cognitive stimulation, where neutral conversation triggered increases in both frequency and time domain HRV parameters (vagal activation).

The larger the change from baseline mean RR to active mean RR (CR mean RR), the more similarity score decreased (Cognistat). Increases in the mean RR interval reflects longer time periods between heart beats and hence a slower HR (Fleiss et al., 1992). Capuana and colleagues (2014) assessed working memory performance in 17 students and also found slower baseline HR is correlated to better memory performance in a modified Stroop task (Stroop, 1935) (age range 18-26 years, noting only 35% male).

CR pNN50, SDNN, and RMSSD were all positively correlated with judgment (Cognistat). Judgment is a subdomain of executive functioning, involving reasoning,

decision making, and prefrontal neuronal recruitment (Deouell and Knight, 2009). As the areas involved with executive function and attention are also involved with autonomic control (e.g., anterior cingulate, insula, and orbitofrontal cortices), activation of these cognitive domains may surge assembly of autonomic resources (Critchley, 2005, Benarroch, 1993, Capuana et al., 2014). It has been theorised that increases in CR recruit additional resources to support neurofunctional demand. Capuana's research (2014) also postulates that the type of cognitive domain being executed affects the cardiac autonomic response, as opposed to the level of difficulty of the task itself. This forms a basis for justifying the differences between distinct cognitive domains and autonomic activity and contributes new knowledge in the field on CR HRV and cognition.

These differences were particularly noted where increases in baseline HRV variables were significantly correlated to decreases in the Cognistat's judgment (LF, HF, TP, SDNN, and RMSSD) and attention domains (pNN50), which is in contrast to other research (Hansen et al., 2003, Thayer et al., 2009). This inverse correlation was also seen in Keen's doctoral thesis (2011) between vagal tone measured by respiratory sinus arrhythmia (RSA) and executive function, however, Keen also acknowledges that these results are inconsistent with other literature findings (n=106, mean age 20 ± 3 years, noting only 27% male).

Comprehension (Cognistat) was positively correlated to CR mean HR (inversely correlated to CR mean RR). Memory scores were higher as CR LF/HF increased and calculation (Cognistat) also increased with higher CR mean RR, CR HF, and CR RMSSD. Additionally, increases in baseline LF/HF were linked to increases in total score (Cognistat). Overall, these correlations support prior research, that greater vagal tone supports cognitive performance (Hansen et al., 2003, Gillie et al., 2013, Hansen et al., 2004, Jennings et al., 2015, Thayer et al., 2009).

Increased vagal tone and CR have been regarded as markers for good cardiac health and have been used as markers for mortality, where less vagally mediated hearts are more likely to undergo arrhythmias or cardiac arrest (Thayer and Lane, 2007, Thayer et al., 2010). There has been less attention, however, on exploring CR relationships with cognitive performance. Most studies assess HR or RSA reactivity rather than HRV reactivity. Comparisons can be drawn as lower HR, high RSA, and high HRV reflect increased cardiac vagal modulation (Overbeek et al., 2014, Capuana et al., 2014, Kimhy

et al., 2013). Capuana's research (2014), as mentioned in the previous section 4.1.3.1, found increases in vagal reactivity (measured by RSA reactivity) were linked to better accuracy during conscious inhibition tasks involving the PFC (modified Stroop task (Hester et al., 2005, Stroop, 1935)) (n=17, age range 18-26 years, noting only 35% male). Similarly, Kimhy's team (2013) found a positive relationship between increased RSA recovery (active to baseline) and better executive function skills (inhibition and attention switching), suggesting better cardiac vagal control enhances executive function (n=817, mean age 57 ± 11 years, noting only 44% male). In contrast, Overbeek's group (2014) found declines in RSA supported continuous working memory yet increased vagal tone was beneficial to prolonged attention tasks in a young and middle-aged group (young age group: n=42, mean age 20 ± 2 , 50% male; middle age group: n=41, mean age 46 ± 7 , 51% male). This highlights the dynamic relationship between HRV and cognition, where different HRV indices may support distinct cognitive processes.

4.2.2.3 Comparison between females (n=37) and males (n=37) (36-50 years)

Males had significantly higher scores in similarity (Cognistat) and construction (Cognistat) and females had higher scores in the attention (Cognistat) domain. Research supports these findings, for instance, that males score better in visual construction, mental orientation, and mapping skills than females (on average) (Rubia et al., 2010, Kaufman, 2007, Aleman et al., 2004, Lewin et al., 2001, Hill et al., 2014). It is understood that the type of memory task affects the sex differences observed, as memory skills are vast and may involve a number of cognitive modalities (Halpern, 2013). In a study by Lewin et al., (2001), 94 females outperformed 91 males in verbal episodic memory tasks whereas males excelled at visuospatial episodic memory tasks (noting mean age 30 ± 6 years). In support, it is worth noting that the attention section of the Cognistat involves verbal/phonological memory (digit spans and word registration), justifying female advantage in that domain (Lejbak et al., 2011, Kiernan et al., 1987).

Hormonal factors account for the majority of cognitive differences seen between sexes, having direct effects on cerebral development (de Vries and Södersten, 2009). For example, a meta-analysis by Puts et al. (2008) explored in utero female babies with congenital adrenal hyperplasia and found that infants with the condition (which are exposed to excess androgens) scored higher in spatial performance when examined in

later life, an ability typically better performed by males. Further research also demonstrated similar findings in female infants with fraternal male twins (where uterine circulating androgens are also increased), which outperformed a control group (fraternal female twins) in mental rotation skills (n=400) (Heil et al., 2011).

Baseline and active mean RR, active LF, TP, and SDNN were all significantly higher in females than in males. Literature supports that females have higher vagal tone than males (Spina et al., 2015, Dart et al., 2002). Snieder's laboratory (2007) identified similar results, as females showed higher HRV scores than males despite stringent covariate adjustment (n=406, mean age 44 ± 7 years, 48% male). In contrast, Bonnemeier and team (2003) assessed 166 healthy individuals and found males had significantly higher SDNN than females, although they noted that sex differences declined with increasing age (mean age 42 ± 15 years, 51% male).

Males had higher mean HR than females in both baseline and active states, yet other studies support that HR is higher in females than males (Umetani et al., 1998, Antelmi et al., 2004) or are not significantly different (Gianaros et al., 2004). Additionally, both females and males showed positive correlations between the total score (Cognistat) and baseline LF/HF, further endorsing existing literature that increased parasympathetic activity (by increased HF activity in the ratio) is beneficial to cognitive performance (Capuana et al., 2014, Allen et al., 2015, Montano et al., 2009). Again, the clinical relevance of the sympathovagal ratio is debatable, with authors theorising that an undefined nominator (LF) cannot produce a reliable clinical tool (Billman, 2013, Heathers, 2012).

Many other factors also affect the cognitive differences between sexes (culture, stereotype, and biopsychosocial theories) yet are beyond the scope of the current analysis, for further information see extensive reviews by Miller and Halpern (2014), Hyde (2014), Halpern (2013) and Ceci et al., (2009).

4.2.3 51-65 years

4.2.3.1 Females (n=42)

As expected, in older aged females, HR increased during conversational cognitive stimulation (coupled by a decrease in mean RR), as did overall frequency domain HRV measures and their sub-divisions: TP, LF/HF, LF, and HF, and time domain measures SDNN and RMSSD. Specifically, increased baseline mean HR was correlated to higher orientation skill (MMSE) and total score (MMSE), while higher baseline LF/HF was linked to an increased similarity skill (Cognistat). Despite the contentious LF band, as discussed previously, Shibasaki's team (2013) identified a comparable positive relationship, where a decreased LF/HF ratio was linked to an increased risk of overall mortality in an elderly and mostly female sample (n=105, mean age 87 ± 6 years, 71% female). However, considering the contention in the LF band and the effect on the LF/HF ratio, it may be more informative to assess LF and HF indices separately. Kim et al. (2006) found low HF power (with no significant alteration to LF spectra) was linked to an increased risk of developing cognitive impairment and hypertension by 6.7 times in females >65 years old (also using the MMSE) (n=311). As autonomic activity is reflected by HRV parameters, and BP is controlled by the ANS it may be tentatively deduced that HRV indirectly reflects BP. Therefore HRV depicting parasympathetic withdrawal may be linked to higher BP.

CR showed interesting yet conflicting relationships in females aged 51-65 years. On one hand, positive correlations were seen between CR mean HR and recall (MMSE) and also between CR LF, CR HF, CR TP, and naming (Cognistat). These findings are supported by the longitudinal West of Scotland Twenty-07 Study (2011) where higher HR reactivity was linked to higher general IQ scores and lower decline in cognition between follow-up years (5 and 12 years later) (as previously mentioned in section 4.1.2.2) (n=1647, mean age at study commencement 15, 35, and 55 years, 54% female). This may imply that higher HRV can serve to protect from future cognitive decline. It has also been found that quicker HR recovery (from on-task to post-task baseline state) is linked to better perceptual reasoning and episodic memory tasks using subtests from the Wechsler memory scale III (Wechsler, 1997) (n=139, mean age 71 ± 4 years, 43% male) (Wright et al., 2005). These results suggest degrees of HR responsivity can influence the

relationship to cognitive function and contribute new knowledge to the field of CR HRV and cognition which has not previously been examined.

On the other hand, negative relationships were seen between the orientation domain (MMSE) with baseline HF, and total MMSE score with CR pNN50. It was unanticipated to find a negative relationship between orientation and baseline LF, as literature strongly supports the cognitive benefits of increased cardiac vagal tone (Thayer et al., 2009). Negative correlations were also found between recall skill (MMSE) and CR SDNN, and both orientation (MMSE) and total Cognistat score with baseline pNN50, despite studies suggesting more ‘reactive’ hearts show adaptability to surroundings (Ginty et al., 2011). It was also surprising to discover this sample showed total Cognistat score decreased as baseline pNN50 increased, another reflection of cardiac vagal control. Several other research groups have found similar results (Britton et al., 2008, Martinez et al., 2014, Stein et al., 2005), in contrast to the general consensus. Martinez and colleagues (2014), in a cross-sectional assessment of HRV and executive function (Stroop test (Stroop, 1935)) in 103 females (mean age 73 ± 6 years), identified inverse correlations between executive function and SDNN and RMSSD. In the publication entitled ‘Sometimes higher HRV is not better HRV’, 290 participants from the Cardiovascular Health Study with higher HRV indices had a significantly increased risk of mortality (mean age 71 ± 5 years, 53% male) (Stein et al., 2005). Stein et al. (2005) concluded that abnormal HR patterns elevate HRV parameters and are responsible for the increased risk of mortality.

Some studies have shown HRV decreases during cognitive activation (Wong et al., 2007, Sato and Miyake, 2004), which would account for the inverse correlations noted above. In particular, when a cognitive task is perceived as a stressor the PFC disinhibits the limbic structures (e.g. amygdala and hypothalamus) eliciting a stress response, which involves withdrawal of vagal input, cortisol release, and physiological responses (e.g. pupil dilation, increased HR, sweating etc.) (Lupien et al., 2005b). Those with reduced coping strategy for stressors (anxious/depressed individuals) tend to over-respond in this manner, leading to decreased abilities in PFC controlled tasks such as judgment/reasoning (executive function), working memory, attention and emotional response (Laborde et al., 2015, Maier and Watkins, 2010, Hansen et al., 2009, Malan et al., 2013). The technique of active neutral conversation, used during the active HRV state, explicitly avoids emotional or stressful stimuli in order to reduce the risk of eliciting a stress response.

4.2.3.2 Males (n=23)

In older aged males, mean HR significantly rose during active neutral conversation (accompanied by a corresponding fall in mean RR), as did LF, LF/HF, TP, SDNN and RMSSD. Rises in HR are expected with increased cognitive demand and increases in cardiac vagal tone during speaking tasks have been reported previously (Bernardi et al., 2000). In accordance with other research findings, positive correlations were found between baseline LF, TP, SDNN, and attention (Cognistat), baseline LF/HF and both comprehension (Cognistat) and judgment (Cognistat) (Lopez et al., 2015, Gillie et al., 2013). As previously discussed, the LF band has not received an agreeable clinical interpretation (Martelli et al., 2014, Reyes del Paso et al., 2013, Billman, 2013, Goldstein et al., 2011a). Literature states that increased vagal tone (as suggested by increased TP and SDNN) is beneficial to cognitive performance. Gillie et al. (2013), for example, found associations between higher HRV (HF) and better PFC inhibitory control. It was also found that attention (MMSE) was positively correlated to baseline mean RR (and correspondingly negatively correlated to baseline mean HR). The negative relationship to baseline mean HR was also found for attention (Cognistat) and total score (MMSE). Baseline HR is positively correlated with trait anxiety in previous research (the present study adjusted for this using scores from the stress coping section of the LAQ (LAQ part two) (Craig et al., 1996)) (Crowley et al., 2011, Friedman, 2007, Fisher and Newman). Chronic elevated HR (e.g. in chronic stress), due to vagal withdrawal and increased sympathetic control, has been linked with hypofunctioning of the PFC causing disinhibition of limbic structures, leading to deficits in attention, working memory, and fluid intelligence (Maier and Watkins, 2010, Critchley, 2009, Duschek et al., 2008, Beaumont et al., 2012). Furthermore, Karemaker and Lie (2000) report that RR intervals less than 67ms are an independent predictor for all-cause mortality.

CR of HF was negatively correlated to orientation (MMSE) and positively correlated to naming (Cognistat). These results appear contradictory as the orientation domain of the MMSE requires naming of the local surroundings. This incongruous finding may be attributed to the smaller sample size of this cohort and future research would benefit from investigating larger groups. CR of LF/HF was negatively correlated to recall skill (MMSE). As previously discussed, some researchers debate the use of the LF/HF ratio as a clinically informative measure (Heathers, 2012, Billman, 2013). Frewen's group (2013) assessed HRV and cognition in 4763 aging adults as part of the Irish Longitudinal Study

on Aging and also identified detrimental effects of low LF (and corresponding low LF/HF ratio) on recall, language, and overall Montreal Cognitive Assessment scores (Nasreddine et al., 2005), in both females and males (mean age 62 ± 8 years, 45% male). Frewen et al. (2013) explained their results by discussing studies showing lower HRV states were linked to increased inflammatory cytokines (interleukin-6 and C-reactive protein) (Sajadieh et al., 2004, Sloan et al., 2007, Trollor et al., 2012) and reductions in neurotransmitter levels (such as acetylcholine and noradrenaline) (Rountree et al., 2007), both of which increase the risk for cognitive impairment and provide further support for early cognitive impairment detection by HRV. Frewen et al. (2013) also supported research by Mielke et al. (2012) and Castle et al. (2005) suggesting that the fornix may be an anatomical crossover point between autonomic control and memory-related cognitive performance.

4.2.3.3 Comparison between females (n=42) and males (n=23) (51-65 years)

It is well documented that the sexes possess different cognitive strengths, yet on average the majority of cognitive skills are equal between females and males. In the older 51-65 year group, females had significantly higher naming (Cognistat), attention (Cognistat), and judgment (Cognistat) than males (however, it should be noted that the Cognistat attention and judgment domains are verbal tasks). This agrees with the literature, that females outperform males in verbal recall, naming, and judgment domains (Miller and Halpern, 2014, Weiss et al., 2003, Halpern, 2013). The Victoria Longitudinal Study by Wahlin et al. (2006) in support of these findings, showed that females had significantly higher verbal test scores than males (n=386, age range 61-95 years, 36% male). Similarly, van Hooren's team (2007) identified that females had significantly higher verbal memory performance than males in the Maastricht Aging Study (n=578, age range 64-81, 51% male).

Males scored significantly higher in the construction domain (Cognistat). This is supported in the longitudinal population-based Betula study by de Frias and colleagues (2006), who demonstrated that males excelled at visuospatial construction tasks, while women scored higher in verbal recall, recognition, and semantic fluency and that these differences remained stable over a lifetime (n=625, age range 35-90 years, 46% male).

These cognitive strengths do not suggest weakness in the other sex and are researched on the basis of group averages, not individual strengths, of which there are many exceptions.

As discussed previously, studies have attributed the majority of these cognitive disparities to hormonal differences. Male and female sex hormones bind to brain structures possessing respective hormonal receptors, leading to cognitive (and other) effects. For example, human studies have shown administration of oestrogen enhances verbal performance (Berent-Spillson et al., 2015, Ghidoni et al., 2006) and testosterone injections improve visuospatial tasks (Vangoozen et al., 1995, Janowsky et al., 1994, Cherrier et al., 2001a, Gómez-Gil et al., 2009), even in as little as a single dose in females (Aleman et al., 2004). Despite this, some research has found no effect of sex hormones on cognitive performance (principally post-menopausal females) (Bayer and Erdmann, 2008, Henderson, 2010, Rapp et al., 2003), and others have not detected significant differences between male and female cognitive domains entirely (particularly in younger years) (Evans and Hampson, 2015). The amygdala possesses strong sexual dimorphism due to its sex hormone receptor densities. As a key neural correlate in cardiac control and cognitive processes, it is suggested that the amygdala and its projections are the crossover point for cognitive as well as HRV differences between females and males. Based on these differences, sex (and sex hormones) ought to be taken into consideration when analysing HRV and cognition.

Baseline LF and TP were significantly higher in males than females. Cowan's laboratory (1994) reported similar results, identifying males had significantly higher time and frequency domain variables (except RMSSD) than females (n=111, mean age 54 ± 15 years, 36% male). Others demonstrated that females had increased vagal tone, measured by HF and RMSSD (n=614, aged 25-89 years (Fagard, 2001)), or that males had higher LF components (n=166, mean age 42 ± 15 years, 51% male (Bonnemeier et al., 2003)). Some studies showed that both of these relationships existed (males with increased sympathetic cardiac control and females with increased parasympathetic cardiac control) (n=188, mean age 50 ± 6 years, 50% male (Huikuri et al., 1996), n=1070, aged 40-79 years, 44% male (Kuo et al., 1999), n=653, mean age 40 ± 12 years, 45% male (Antelmi et al., 2004), n=28, mean age 21 ± 2 years, 50% male (Sato and Miyake, 2004)), or that neither of these relationships existed (HF, LF and RMSSD higher in males, n=22, mean age 32 ± 9 years, 68% male (Nugent et al., 2011b)). Further research, with standardised

HRV methodology, is required to understand HRV differences between sexes as data are inconsistent.

Baseline mean HR was positively correlated to total score (MMSE) in females, yet had an inverse relationship in males. Oestrogen levels in females have been shown to increase vagal tone, also linked to better cognitive performance (Sato and Miyake, 2004, Sullivan and Davison, 2001).

Generally, it is difficult to compare literature covering a similar age range to the present study (18-65 years). Age should be considered in future HRV analyses, as studies have identified that the disparity of HRV between sexes attenuates with increasing age (Kuo et al., 1999, Bonnemeier et al., 2003, Britton et al., 2007, Fagard, 2001). Additionally, literature more commonly examines RSA reactivity, HR reactivity, or HRV recovery and cognition; hence it is difficult to compare the present results to others in the novel area of HRV reactivity. Furthermore, methodological differences can influence the data, as the degree of CR is dependent on the type of stressor/cognitive intervention. Despite the disparities, further research is required to explore HRV reactivity, as it is understood that cardiac responsivity is aligned with better health, where less reactive hearts are a marker for cardiac arrhythmias and mortality (Huikuri et al., 1996, Fisher and Newman, 2013). Although these sex differences in cognition and HRV are apparent, it has also been found that sex differences change with aging, particularly the effects of menopause on female cognition (Berent-Spillson et al., 2015). The sharp decline in oestrogen and progesterone has been linked to poorer verbal fluency and processing speed. These neuro-hormonal correlates illustrate that sex should be taken into consideration when assessing cognitive and autonomic activity.

4.2.4 Age group comparisons (18-35, 36-50, 51-65 years) in females and males

4.2.4.1 Females (18-35, 36-50, 51-65 years)

Cognitive changes naturally occur over a life span, with neuronal development improving global cognitive performance up to mid and late twenties, cognitively stable periods from late twenties to late thirties and customary moderate declines particularly in fluid intelligence skills thereafter (Raz and Rodrigue, 2006).

Aging has known effects on cognitive performance largely due to structural deterioration of brain tissue, typically affecting reasoning, working memory, executive processes and processing speed (Caserta et al., 2009). Interestingly, not all cognitive domains decline with aging. ‘Crystallised’ skills such as calculation, procedural memory, and word defining skills can increase with increasing age, where learned experience benefits cognitive performance (Singer et al., 2003) (although evidence shows these too deteriorate in those over 80 years of age (Giambra et al., 1995, Lindenberger and Baltes, 1997)).

In females, mean RR fell significantly in all groups whereas mean HR, LF, LF/HF, TP, and SDNN all significantly rose from baseline to active state. HF and RMSSD also significantly rose between baseline and active in the 36-50 and 51-65 year groups, yet were not significant in the youngest group. Comparisons of HRV values between female age groups showed baseline TP, SDNN, and active mean HR were significantly higher in the 18-35 year group than the 51-65 year group. Epidemiological research supports these findings showing cardiac vagal tone decreases with increasing age (particularly HF and RMSSD) in females. Voss et al.’s research (2015) also demonstrates these findings, showing both time and frequency HRV indices significantly decrease with aging (n=1906, aged 25-74 years, 59% male). Kuo and researchers (1999) identified similar results, showing a linear decrease in LF and HF with increasing age (n=1070, aged 40-79 years, 44% male). Many other studies support these findings (Cowan et al., 1994, Greiser et al., 2009, Agelink et al., 2001, Felber Dietrich et al., 2006, Beckers et al., 2006, Sloan et al., 2008, Britton et al., 2007). It is proposed that the decline in oestrogen and progesterone during menopause potentiate the autonomic differences between young and older age females (as previously discussed, there is a positive correlation between oestrogen levels and parasympathetic tone) (Saleh and Connell, 2007). Withdrawal of vagal tone seen in aging has been linked to increases in HR and BP (Mori et al., 2014). These increases have been postulated to support perfusion in a system with weakened arterial elasticity and reduced cerebral blood flow (Kennelly et al., 2009).

CR of TP was higher in 18-35 year olds than the 36-50 year old sample. However, other CR indices were seen to increase with increasing age. CR of pNN50 was higher in the middle age group than the youngest, and CR RMSSD was significantly higher in the eldest age group than the youngest. Further, the 36-50 year and 51-65 year group had significantly higher CR SDNN than the youngest group. These findings contribute new

knowledge to the field as there is a scarcity of research on CR changes with increasing age, particularly in female cohorts. Uchino's longitudinal study (2005) assessed 133 participants, aged 30 to 70 years, and found increased CR (parasympathetic withdrawal) in response to stress accompanied aging in both males and females (follow up 7 to 16 months, mean age 48 ± 11 years, 48% male). They proposed that the basal vagal withdrawal and increased sympathetic CR in response to a stressor may contribute to the age-related risk of an adverse cardiovascular event (risk of myocardial infarction and hypertension has been linked to sympathetic overdrive (Parati and Esler, 2012)).

Females undergo more abrupt cognitive performance changes due to the steep decline in oestrogen levels occurring in menopause (Berent-Spillson et al., 2015). Oestrogen is known to have cardiovascular and neuro-protective benefits, and reductions in these levels have been linked with confusion and reduction in executive function (as well as many other symptoms) (Sherwin and Henry, 2008). As expected, the orientation (Cognistat) and construction (Cognistat) scores were significantly higher in the 18-35 year old group than the 51-65 year old group.

Unexpectedly, older females, aged 51-65 years, significantly outperformed the 36-50 year old female sample for total score (MMSE). In addition, the 51-65 year old female group scored significantly higher for recall (MMSE) than the 36-50 and 18-35 year groups. These comparisons, however, may be negligible due to the degree of difference only being 0.5 out of 30, and could be attributed to the variance in the data. Working memory (e.g. recall) and global cognitive scores typically decrease with healthy aging, yet still remain within a normal range (Ziegler et al., 2010). Psychometric assessment tools account for this with customised cognitive guidelines depending upon the participant's age (as well as years of education).

4.2.4.2 Males (18-35, 36-50, 51-65 years)

In each male age group, mean RR fell significantly whereas mean HR, LF, TP, SDNN and RMSSD all significantly rose from the baseline to active state. HF significantly rose in the middle age group (36-50 years) yet was not found to be significantly different between baseline and active states in the youngest (18-35 years) or oldest groups (51-65 years). The 18-35 and 51-65 year groups both exhibited statistically significant increases in LF/HF from baseline to active states. Although there were no significant differences

found between HRV in males between the three age groups (18-35, 36-50, 51-65 years), research findings illustrate cardiac vagal withdrawal occurs with increasing age (to maintain circulatory homeostasis as blood vessels lose elasticity (Faust et al., 2013)), particularly affecting the HF bandwidth (Cowan et al., 1994).

Furthermore, testosterone gradually declines in aging males (albeit less than the degree of change of oestrogen in females), accompanied by alterations in autonomic control (hormone receptors in the neuronal central autonomic network), as well as reduced cognitive performance, particularly spatial reasoning tasks (Janowsky, 2006, Cherrier et al., 2001a). The present study identified naming (Cognistat) was higher in the younger age group (18-35 years) than the eldest sample (51-65 years), supporting the natural cognitive decline of aging. Cognitive declines in healthy aging have been linked to neuronal atrophy and white matter abnormalities (Abe et al., 2008). Madhavan et al. (2015) also observed significant declines in language skill with aging in 112 individuals, attributed to declining white matter integrity in the superior longitudinal fasciculus (age range 19-76 years, 40% male). Additionally, a collation of four large cognitive aging studies by Salthouse (2004) demonstrated that aging is accompanied by declines in multiple domains, such as working memory, processing speed and reasoning, yet verbal skills remain stable and even increase with older age (n=1424, age range 20-80 years). Reduced scores in multiple cognitive domains on a psychometric test reduces global cognitive scores considerably, thereby justifying the findings in the present study. These findings, along with previous research, strongly confirm that age should be taken into account when assessing cognitive performance.

4.2.4.3 Comparison between total females (n=120) and males (n=102)

In accordance with the literature, the total cohort of males had significantly higher Cognistat scores for orientation, calculation, and construction, whereas females had significantly higher attention (Cognistat) and language (MMSE) scores. A physiological basis for these differences has been attributed to the interaction between sex hormones and neurons, as previously discussed in sections 4.2.1.3, 4.2.2.3, and 4.2.3.3. It was also identified that females had significantly higher total Cognistat score than males, which has been disputed by others research, that females and males do not significantly differ in measures of global cognitive scores (Evans and Hampson, 2015, Weiss et al., 2003).

This significant difference may have been affected by the larger sample size of the female cohort (females n=120; males n=102).

Differences in HRV parameters identified the total female cohort had significantly higher baseline HF, SDNN, TP, and CR LF/HF. As previously detailed in section 4.2.1.3, 4.2.2.3, and 4.2.3.3, research exploring HRV differences between sexes have presented conflicting results, with some identifying males with increased HRV parameters (Cowan et al., 1994) and other finding females had higher vagal tone, as measured by increased HF and RMSSD indices (Fagard, 2001).

4.3 Conclusion: HRV and cognition (non-clinical groups)

Overall, the current study identified a number of associations between HRV activity and cognitive performance, partially supporting hypothesis 1, that there will be a significant direct relationship between HRV and cognitive function. Higher baseline vagal activity was significantly correlated to better cognitive performance in females aged 18-50 years and in males 51-65 years, which has been well supported by other studies (Lopez et al., 2015, Murtazina, 2015, Solernó et al., 2012). However, higher vagal activity was also linked to poorer cognitive scores in some of the older age groups (females aged 36-65 years and males aged 36-50 years). Some studies show that higher vagal tone supports attention and verbal reasoning while lower vagal tone supports spatial tasks (Solernó et al., 2012, Porges, 2009). An interesting shift occurred from the middle age group to the older age group where males displayed inverse correlations between HRV and cognitive domains and females showed positive correlations, yet in the older age group this was reversed and males showed positive correlations and females displayed negative correlations. This may be due to the natural process of vagal withdrawal with aging, and potentially the onset of menopause in females (Saleh and Connell, 2007, Cowan et al., 1994). Hypothesis 3 (HRV reactivity will be inversely correlated to cognition) was partially supported by the present study. It was identified that HRV reactivity was mostly positively correlated to cognitive function in females aged 18-35 years and 51-65 years yet the opposite relationship was found in the middle age group. Interestingly, this pattern was also seen in males with positive correlations between HRV reactivity and cognition in the younger age and middle age group yet negative correlations in the oldest aged group. Males and females aged 51-65 years displayed mixed results; inverse relationships were identified between HRV reactivity and orientation, recall and total score (MMSE) and positive correlations between HRV reactivity and the naming domain (Cognistat). HRV reactivity has not been well examined by others and the present research significantly contributes new knowledge into the relationships between HRV change and cognitive function. The present findings also identified certain HRV states as beneficial to particular cognitive domains per age and sex subgroupings; for example, memory skill was positively correlated to TP reactivity in males yet a negative correlation was identified in females (36-50 years), however, females (18-35 years) showed a positive correlation between SDNN and memory. The present research also partially supports the polyvagal theory (Porges, 1992), with higher HRV benefitting attention skill in older

males aged 51-65 years however the opposite relationship was identified in middle-aged 36-50 year old males. The mechanisms behind these differences (potentially hormonal, neuronal, and circulatory) should be considered in future research. Refer to Table 4.70, Table 4.71, and Table 4.72 for a summary of significant results across each age group.

Table 4.70 Summary of significant correlations between HRV and cognitive domains in females (n=41) and males (n=42) aged 18-35 years

	Cognitive domain	HRV parameter							
		Baseline				HRV reactivity			
		LF/HF	RMSSD	SDNN	LF	LF/HF	TP	SDNN	HR
Cognitive test: Cognistat	Orientation	-							
	Comprehension						+	+	
	Calculation								+
	Naming				-				
	Construction					+			
	Memory	-	+	+					+ -
	Similarity	-							
	Judgment							+	
	Total score	-							+

Table 4.70 displays significant correlations between HRV parameters and cognitive domains from the MMSE (Folstein et al., 1975) and Cognistat (Kiernan et al., 1987) in females (shown in red) (n=41) and males (shown in black) (n=42) aged 18-35 years. HRV reactivity refers to the active minus baseline HRV data.

Key: HR = Heart rate; HRV = Heart rate variability; LF = Low frequency; LF/HF = Low frequency divided by high frequency (sympathovagal balance); MMSE = Mini Mental State Examination; RMSSD = Square root of the mean squared differences of successive NN intervals; SDNN = SD of all NN intervals (the square root of variance); TP = Total power; + = Positive correlation; - = Negative correlation

Table 4.71 Summary of significant correlations between HRV and cognitive domains in females (n=37) and males (n=37) aged 36-50 years

Cognitive domain		HRV parameter							
		Baseline							
		LF	HF	LF/HF	TP	RMSSD	SDNN	pNN50	
Cognitive test: Cognistat	Attention							-	
	Comprehension					-		-	
	Naming	+			+		+		
	Similarity			+					
	Judgment	-	-		-	-	-		
	Total score			++					
			HRV reactivity						
			LF	HF	TP	RMSSD	SDNN	pNN50	HR
		Repetition		-	-				+
		Comprehension							+
		Naming	-	-	-		-		
		Memory			- +			-	
		Calculation		+		+			
		Judgment				+	+	+	
	Total score		-	-					

Table 4.71 displays significant correlations between HRV parameters and cognitive domains from the MMSE (Folstein et al., 1975) and Cognistat (Kiernan et al., 1987) in females (shown in red) (n=37) and males (shown in black) (n=37) aged 36-50 years. HRV reactivity refers to the active minus baseline HRV data.

Key: HF = High frequency; HR = Heart rate; HRV = Heart rate variability; LF = Low frequency; LF/HF = Low frequency divided by high frequency (sympathovagal balance); MMSE = Mini Mental State Examination; pNN50 = Total number of interval differences (greater than 50 milliseconds) of consecutive NN (beat to beat) intervals divided by the total number of NN intervals; RMSSD = Square root of the mean squared differences of successive NN intervals; SDNN = SD of all NN intervals (the square root of variance); TP = Total power; + = Positive correlation; - = Negative correlation

Table 4.72 Summary of significant correlations between HRV and cognitive domains in females (n=42) and males (n=23) aged 51-65 years

Cognitive test	Cognitive domain	HRV parameter						
		Baseline						
		LF	HF	LF/HF	TP	SDNN	pNN50	HR
MMSE	Orientation		-				-	+
	Recall							-
	Total score							+ -
Cognistat	Attention	+			+	+		-
	Comprehension			+				
	Similarity			+				
	Judgment			+				
	Total score						-	
		HRV reactivity						
		LF	HF	LF/HF	TP	SDNN	pNN50	HR
MMSE	Orientation		-					
	Recall			-		-		+
	Total score						-	
Cognistat	Naming	+	+	+	+			

Table 4.72 displays significant correlations between HRV parameters and cognitive domains from the MMSE (Folstein et al., 1975) and Cognistat (Kiernan et al., 1987) in females (shown in red) (n=42) and males (shown in black) (n=23) aged 51-65 years. HRV reactivity refers to the active minus baseline HRV data.

Key: HF = High frequency; HR = Heart rate; HRV = Heart rate variability; LF = Low frequency; LF/HF = Low frequency divided by high frequency (sympathovagal balance); MMSE = Mini Mental State Examination; pNN50 = Total number of interval differences (greater than 50 milliseconds) of consecutive NN (beat to beat) intervals divided by the total number of NN intervals; SDNN = SD of all NN intervals (the square root of variance); TP = Total power; + = Positive correlation; - = Negative correlation

5. HRV and cognition (clinical groups)

Few studies have been conducted assessing the relationship between HRV and cognitive function within clinical groups (depression, type 1 DM, type 2 DM and hypertension) with comparison to a control group. Assessing both a healthy and clinical sample allows for comparisons to be made between groups. The aforementioned clinical conditions have each been associated with vagal withdrawal and increased tonic (sympathetic) cardiac control (Vasudev et al., 2015, Lagi et al., 1994, Abubaker et al., 2014, Shehab and Abdulle, 2011). Interestingly, these same changes in autonomic activity are also risk factors for cognitive decline yet have not been well elucidated in clinical groups (Thayer et al., 2009). Most HRV and cognitive function studies suggest that further research should be undertaken in the area, and a select few have promoted the use of HRV as a powerful marker of cognitive decline (Collins et al., 2012, Kim et al., 2006, Thayer and Sternberg, 2006). In addition, studies suggest CR (such as HR, RSA, or HRV reactivity) is blunted due to autonomic changes seen in these clinical conditions, however, there is a lack of research addressing this effect on cognition in clinical groups (Phillips, 2011, Mathewson et al., 2010).

Therefore the following results and discussion chapters 5.1 and 5.2 explore specific aims 1, 4, 5 and 6 (as shown in section 2.1.2.1), to identify the relationship between HRV and cognitive function; to examine if clinical conditions, depression, type 1 DM, type 2 DM, hypertension, will affect the relationship between HRV and cognition; to identify the relationships between cardiac autonomic reactivity and cognition in clinical and control groups; and to identify significant relationships between HRV and different cognitive domains as a potential predictive marker for identifying those at higher risk of cognitive impairment.

5.1 Results: HRV and cognition (clinical groups)

A total of 74 participants with chronic illnesses, aged 18-80 years, were recruited for the present study in the Neuroscience Research Unit at UTS. Subjects with the following illnesses were included: depression (n=10), type 1 diabetes (n=9), type 2 diabetes (n=38),

and hypertension (n=39) (sample distribution compared to control groups shown in Figure 5.1). There was some overlap with participants exhibiting more than one chronic illness (Table 5.1). This was adjusted for as a covariate in the analysis as ‘number of chronic illnesses’. Also, there were individual volunteers with ‘other’ chronic illnesses (silicosis, gout, osteoporosis, and idiopathic peripheral neuropathy) which were not included in the data analysis due to small sample numbers (n=4) and relevance to the aims of the research. This chapter reports the results for HRV and cognitive function in the chronic illness (clinical) samples and separately compares each group to a sex and age matched non-clinical control group.

Figure 5.1 Sample distribution per clinical and control group

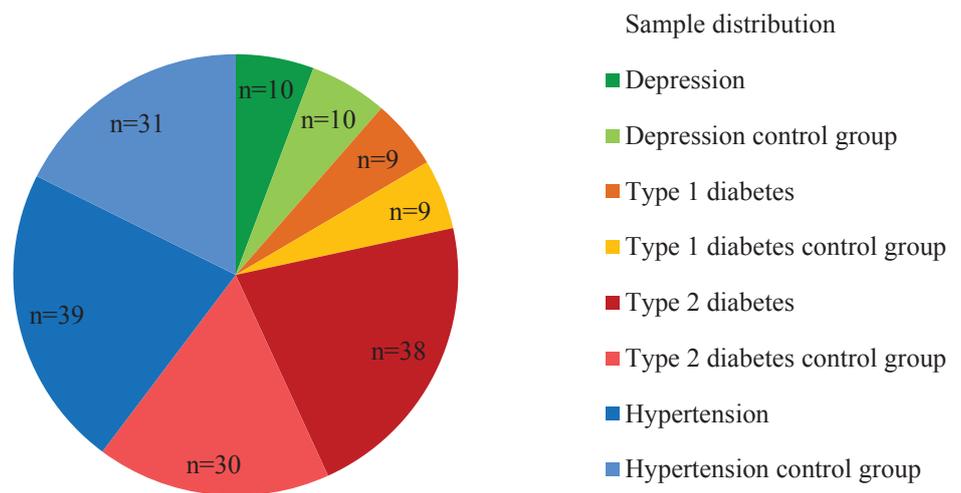


Figure 5.1 shows the sample distribution of clinical and control groups. Key: n = Sample size

Table 5.1 Distribution of participants with one or more chronic illnesses

	Depression (n=10)	Type 1 diabetes (n=9)	Type 2 diabetes (n=38)	Hypertension (n=39)
1 Illness	2	7	15	14
2 Illnesses	4	1	17	20
3 Illnesses	4	1	6	5
Depression	2	1	4	4
Type 1 diabetes	1	7	0	1
Type 2 diabetes	4	0	15	18
Hypertension	4	1	18	14

Table 5.1 shows the distribution of participants across the four clinical cohorts: depression (n=10), type 1 diabetes (n=9), type 2 diabetes (n=38), and hypertension (n=39). Seventy eight percent of participants in the present study had more than one chronic illness.

Key: n = Sample size

5.1.1 Depression (n=10)

Mean (\pm SD) demographics for the depression sample (n=10) are provided in Table 5.2.

Table 5.2 Mean sample demographics for subjects with depression (n=10)

Demographics		Value
Depression n=10	Years of age (mean \pm SD)	45.40 \pm 14.18
	Male (%)	40
	Years of education (mean \pm SD)	16.80 \pm 2.47
	BMI (mean \pm SD)	29.25 \pm 6.58
	Smoker (%)	0
	Medicated (%)	100
	LAQ part one (mean \pm SD)	17.90 \pm 3.72
	LAQ part two (mean \pm SD)	20.90 \pm 8.08

Table 5.2 shows mean demographic scores for subjects with depression (n=10). BMI normal reference range is 19-25 (Garrouste-Orgeas et al., 2004). All were medicated: 50% serotonin-selective reuptake inhibitors, 30% serotonin-noradrenaline reuptake inhibitors, 10% tricyclic antidepressants and 10% tricyclic antidepressants combined with monoamine oxidase inhibitors. The maximum score of LAQ part one (lifestyle risk factors) is 70 and LAQ part two (stress coping) is 75. Higher LAQ scores reflect increased risk for developing chronic illnesses (Craig et al., 1996).

Key: BMI = Body mass index; LAQ = Lifestyle Appraisal Questionnaire (Craig et al., 1996); n = Sample size; SD = Standard deviation

Mean (\pm SD) scores from the MMSE and Cognistat with reference to their respective maximum score and cognitive impairment thresholds are displayed in Table 5.3. All mean scores were above their respective cognitive impairment thresholds, although the lower end of the SD crossed those thresholds for the Cognistat domains of naming (7.60 ± 1.27), construction (4.90 ± 1.10), memory (10.70 ± 1.95), calculation (3.50 ± 0.71), and judgment (4.85 ± 0.94).

Mean (\pm SD) values for HRV frequency and time domain parameters for baseline and active states are provided in Table 5.4 and Table 5.5, respectively. CR refers to the active minus baseline HRV data. Large values are noted in the absolute values of frequency and time domain HRV data. Logarithmic transformation was applied to reduce the effect of skewed HRV data, as recommended by the literature (Tarkiainen et al., 2005, Macfarlane et al., 2011) (see methodology section 3.5). Logarithmically transformed HRV data were used for all further statistical analyses.

Table 5.3 Mean cognitive scores from the MMSE and Cognistat for subjects with depression (n=10)

		Cognitive assessment	Cognitive domain	Maximum possible score	Cognitive impairment threshold	Mean ± SD
Depression n=10	MMSE		Orientation	10	-	9.5 ± 0.71
			Registration	3	-	3.00 ± 0.00
			Attention	5	-	4.7 ± 0.95
			Recall	3	-	2.80 ± 0.42
			Language	9	-	8.65 ± 0.58
		Total MMSE		30	≤23	28.65 ± 1.97
	Cognistat		Orientation	12	<10	11.90 ± 0.32
			Attention	8	<6	7.50 ± 0.53
			Comprehension	6	<5	5.65 ± 0.47
			Repetition	12	<11	11.85 ± 0.47
			Naming	8	<7	7.60 ± 1.27
			Construction	6	<4	4.90 ± 1.10
			Memory	12	<10	10.70 ± 1.95
			Calculation	4	<3	3.50 ± 0.71
		Similarity	8	<5	7.30 ± 0.82	
	Judgment	6	<4	4.85 ± 0.94		
	Total Cognistat		82	<65	75.75 ± 5.34	

Table 5.3 shows mean cognitive scores from the MMSE (Folstein et al., 1975) and the Cognistat (Kiernan et al., 1987) for subjects with depression (n=10). The maximum score possible and the cognitive impairment threshold are provided for each cognitive domain. Scores below the cognitive impairment threshold indicate cognitive impairment. The Cognistat domains where the lower end of the SD crossed the cognitive impairment threshold are shown in **bold**.

Key: MMSE = Mini Mental State Examination; n = Sample size; SD = Standard deviation

Table 5.4 Mean frequency domain HRV values for subjects with depression (n=10)

HRV State		HRV frequency domain	Mean (\pm SD) ms ²
Depression n=10	Baseline	Low frequency (absolute)	1293.12 \pm 1803.18
		High frequency (absolute)	1010.92 \pm 1619.31
		LF/HF (absolute)	2.19 \pm 1.85
		Total power (absolute)	2286.23 \pm 3002.34
		Log low frequency	2.67 \pm 0.82
		Log high frequency	2.36 \pm 1.00
		Log LF/HF	0.31 \pm 0.51
		Log total power	3.19 \pm 0.96
	Active	Low frequency (absolute)	1356.34 \pm 1316.04
		High frequency (absolute)	1165.50 \pm 2215.26
		LF/HF (absolute)	3.13 \pm 2.58
		Total power (absolute)	3369.67 \pm 4425.02
		Log low frequency	2.88 \pm 0.56
		Log high frequency	2.54 \pm 0.72
		Log LF/HF	0.33 \pm 0.43
		Log total power	3.24 \pm 0.54
	Cardiac reactivity	Low frequency (absolute)	63.22 \pm 1811.37
		High frequency (absolute)	154.58 \pm 890.77
		LF/HF (absolute)	0.52 \pm 2.10
		Total power (absolute)	1264.11 \pm 1688.25
		Log low frequency	0.21 \pm 0.53
		Log high frequency	0.18 \pm 0.61
		Log LF/HF	0.03 \pm 0.36
		Log total power	0.26 \pm 0.34

Table 5.4 shows mean frequency domain HRV values for subjects with depression (n=10) during baseline and active states. Cardiac reactivity refers to the active minus baseline HRV data.

Key: HRV = Heart rate variability; LF/HF = Low frequency divided by high frequency (sympathovagal balance); ms² = Milliseconds squared; n = Sample size; SD = Standard deviation

Table 5.5 Mean time domain HRV values for subjects with depression (n=10)

HRV state		HRV time domain (unit)	Mean ± SD
Depression n=10	Baseline	Mean RR (ms)	782.86 ± 149.85
		SDNN (ms)	45.04 ± 27.56
		Mean heart rate (bpm)	79.72 ± 13.68
		RMSSD (ms)	44.08 ± 39.09
		pNN50 (%)	8.84 ± 10.60
		Log RMSSD (ms)	1.61 ± 0.57
		Log SDNN (ms)	1.56 ± 0.34
	Active	Mean RR (ms)	737.08 ± 121.61
		SDNN (ms)	51.72 ± 22.82
		Mean heart rate (bpm)	83.82 ± 13.59
		RMSSD (ms)	45.91 ± 29.99
		pNN50 (%)	5.60 ± 5.08
		Log RMSSD (ms)	1.60 ± 0.22
		Log SDNN (ms)	1.68 ± 0.17
	Cardiac reactivity	Mean RR (ms)	-45.78 ± 41.77
		SDNN (ms)	7.44 ± 10.86
		Mean heart rate (bpm)	4.09 ± 3.51
		RMSSD (ms)	3.03 ± 16.95
		pNN50 (%)	-3.24 ± 7.71
		Log RMSSD (ms)	0.13 ± 0.26
		Log SDNN (ms)	0.13 ± 0.21

Table 5.5 shows mean time domain HRV values for subjects with depression (n=10) during baseline and active states. Cardiac reactivity refers to the active minus baseline HRV data.

Key: bpm = Beats per minute; HRV = Heart rate variability; ms = Milliseconds; n = Sample size; pNN50 = Total number of interval differences (greater than 50 milliseconds) of consecutive NN (beat to beat) intervals divided by the total number of NN intervals; RMSSD = Square root of the mean squared differences of successive NN intervals; RR = Duration in milliseconds from one R peak to the next R peak of the electrocardiogram; SD = Standard deviation; SDNN = SD of all NN intervals (the square root of variance)

Wilcoxon signed rank tests were performed to determine significant differences between baseline and active (cognitive task) HRV measures (Table 5.6).

Table 5.6 Wilcoxon signed rank test between baseline and active HRV states in subjects with depression (n=10)

Depression n=10	Variable (unit)	Z	p	Median baseline (IQR)	Median active (IQR)	Median difference (active - baseline)
	Mean RR (ms)	-2.50	0.01	757.47 (141.44)	722.20 (139.59)	-35.27
	Mean heart rate (bpm)	-2.60	0.01	79.42 (16.41)	83.85 (17.43)	4.43
	Log SDNN (ms)	-2.07	0.04	1.60 (0.45)	1.69 (0.31)	0.09

Table 5.6 displays significant results from a Wilcoxon signed rank test between baseline and active HRV states in subjects with depression (n=10).

Key: bpm = Beats per minute; HRV = Heart rate variability; IQR = Interquartile range; ms = Milliseconds; n = Sample size; p = Level of statistical significance (p<<0.05); RR = Duration in milliseconds from one R peak to the next R peak of the electrocardiogram; SDNN = Standard deviation of all NN intervals (the square root of variance); Z = Z score

Spearman’s bivariate and partial correlations were performed between HRV and cognitive scores to address aims 1 and 5 (Table 5.7).

Table 5.7 Spearman’s correlation coefficients between cognitive scores and HRV in subjects with depression (n=10)

	Dependent variable	Independent variable	r	p
Depression n=10	Comprehension Cognistat	Log cardiac reactivity SDNN	-0.78	0.01
	Memory Cognistat	Log baseline LF	0.67	0.03
	Calculation Cognistat	Baseline mean RR	0.87	0.001
		Baseline mean heart rate	-0.87	0.001
		Cardiac reactivity mean RR	-0.66	0.04*

Table 5.7 displays significant results from a Spearman’s correlation between cognitive scores (MMSE (Folstein et al., 1975) and Cognistat (Kiernan et al., 1987)) and HRV in subjects with depression (n=10).

Key: HRV = Heart rate variability; LF = Low frequency; MMSE = Mini Mental State Examination; n = Sample size; p = Level of statistical significance (p<0.05); r = Correlation coefficient; RR = Duration in milliseconds from one R peak to the next R peak of the electrocardiogram; SDNN = Standard deviation of all NN intervals (the square root of variance); * = Bonferroni correction excludes this significant correlation

Partial Spearman’s correlations between cognitive scores and HRV values showed negative correlations between log CR LF/HF and the Cognistat scores of comprehension (r=-0.74, p=0.03) and construction (r=-0.87, p=0.01) (controlled for LAQ part one, part two and duration of depression (years)).

5.1.2 Control group without depression (n=10)

Mean (\pm SD) demographic data for the control group without depression (n=10) is provided in Table 5.8.

Table 5.8 Mean sample demographics for the control group without depression (n=10)

Control group without depression n=10	Demographics	Value
	Years of age (mean \pm SD)	45.80 \pm 14.03
	Male (%)	40
	Years of education (mean \pm SD)	19.00 \pm 4.06
	BMI (mean \pm SD)	26.29 \pm 3.97
	Smoker (%)	10
	LAQ part one (mean \pm SD)	13.40 \pm 7.59
	LAQ part two (mean \pm SD)	18.80 \pm 11.43

Table 5.8 shows mean demographic scores for the control group without depression (n=10). BMI normal reference range is 19-25 (Garrouste-Orgeas et al., 2004). The maximum score of LAQ part one (lifestyle risk factors) is 70 and LAQ part two (stress coping) is 75. Higher LAQ scores reflect increased risk for developing chronic illnesses (Craig et al., 1996).

Key: BMI = Body mass index; LAQ = Lifestyle Appraisal Questionnaire (Craig et al., 1996); n = Sample size; SD = Standard deviation

Mean (\pm SD) scores from the MMSE and Cognistat with reference to their respective maximum score and cognitive impairment thresholds are displayed in Table 5.9. All mean scores were above their respective cognitive impairment thresholds, although the lower end of the SD crossed that threshold for the Cognistat domain of judgment (4.75 \pm 1.81) only.

Mean (\pm SD) values for HRV frequency and time domain parameters for baseline and active states are provided in Table 5.10 and Table 5.11, respectively.

Table 5.9 Mean cognitive scores from the MMSE and Cognistat for the control group without depression (n=10)

		Cognitive assessment	Cognitive domain	Maximum possible score	Cognitive impairment threshold	Mean ± SD
Control group without depression n=10	MMSE		Orientation	10	-	9.90 ± 0.32
			Registration	3	-	3.00 ± 0.00
			Attention	5	-	5.00 ± 0.00
			Recall	3	-	2.70 ± 0.48
			Language	9	-	8.65 ± 0.47
		Total MMSE		30	≤23	29.25 ± 0.86
	Cognistat		Orientation	12	<10	11.90 ± 0.32
			Attention	8	<6	7.70 ± 0.67
			Comprehension	6	<5	5.75 ± 0.42
			Repetition	12	<11	11.80 ± 0.42
			Naming	8	<7	7.80 ± 0.42
			Construction	6	<4	5.20 ± 0.79
			Memory	12	<10	11.50 ± 1.27
			Calculation	4	<3	3.90 ± 0.32
		Similarity	8	<5	7.70 ± 0.67	
		Judgment	6	<4	4.75 ± 1.81	
	Total Cognistat		82	<65	78.00 ± 3.31	

Table 5.9 shows mean cognitive scores from the MMSE (Folstein et al., 1975) and the Cognistat (Kiernan et al., 1987) for the control group without depression (n=10). The maximum score possible and the cognitive impairment threshold are provided for each cognitive domain. Scores below the cognitive impairment threshold indicate cognitive impairment. The Cognistat domains where the lower end of the SD crossed the cognitive impairment threshold are shown in **bold**.

Key: MMSE = Mini Mental State Examination; n = Sample size; SD = Standard deviation

Table 5.10 Mean frequency domain HRV values for the control group without depression (n=10)

HRV State		HRV frequency domain	Mean (\pm SD) ms ²
Control group without depression n=10	Baseline	Low frequency (absolute)	1306.93 \pm 1635.90
		High frequency (absolute)	2039.99 \pm 3863.47
		LF/HF (absolute)	0.94 \pm 0.51
		Total power (absolute)	4617.76 \pm 6347.22
		Log low frequency	2.81 \pm 0.56
		Log high frequency	2.91 \pm 0.55
		Log LF/HF	-0.10 \pm 0.29
		Log total power	3.41 \pm 0.47
	Active	Low frequency (absolute)	2266.59 \pm 1495.14
		High frequency (absolute)	1555.80 \pm 1659.22
		LF/HF (absolute)	2.44 \pm 1.39
		Total power (absolute)	6175.63 \pm 5122.99
		Log low frequency	3.25 \pm 0.33
		Log high frequency	2.94 \pm 0.53
		Log LF/HF	0.32 \pm 0.27
		Log total power	3.67 \pm 0.35
	Cardiac reactivity	Low frequency (absolute)	922.77 \pm 1690.30
		High frequency (absolute)	-625.52 \pm 3192.82
		LF/HF (absolute)	1.62 \pm 1.31
		Total power (absolute)	1540.68 \pm 6178.64
		Log low frequency	0.45 \pm 0.51
		Log high frequency	0.03 \pm 0.53
		Log LF/HF	0.42 \pm 0.25
		Log total power	0.26 \pm 0.39

Table 5.10 shows mean frequency domain HRV values of the control group without depression (n=10) during baseline and active states. Cardiac reactivity refers to the active minus baseline HRV data.

Key: HRV = Heart rate variability; LF/HF = Low frequency divided by high frequency (sympathovagal balance); ms² = Milliseconds squared; n = Sample size; SD = Standard deviation

Table 5.11 Mean time domain HRV values for the control group without depression (n=10)

HRV state		HRV time domain (unit)	Mean ± SD
Control group without depression n=10	Baseline	Mean RR (ms)	914.13 ± 170.25
		SDNN (ms)	60.88 ± 36.59
		Mean heart rate (bpm)	67.92 ± 11.55
		RMSSD (ms)	56.49 ± 49.20
		pNN50 (%)	12.93 ± 16.63
		Log RMSSD (ms)	1.65 ± 0.28
		Log SDNN (ms)	1.73 ± 0.22
	Active	Mean RR (ms)	860.60 ± 152.72
		SDNN (ms)	73.59 ± 29.77
		Mean heart rate (bpm)	72.01 ± 11.28
		RMSSD (ms)	58.46 ± 32.12
		pNN50 (%)	12.17 ± 11.02
		Log RMSSD (ms)	1.71 ± 0.25
		Log SDNN (ms)	1.84 ± 0.16
	Cardiac reactivity	Mean RR (ms)	-53.54 ± 37.40
		SDNN (ms)	12.72 ± 29.36
		Mean heart rate (bpm)	4.09 ± 2.64
		RMSSD (ms)	1.97 ± 35.24
		pNN50 (%)	-1.98 ± 8.09
		Log RMSSD (ms)	0.05 ± 0.20
		Log SDNN (ms)	0.11 ± 0.17

Table 5.11 shows mean time domain HRV values for the control group without depression (n=10) during baseline and active states. Cardiac reactivity refers to the active minus baseline HRV data.

Key: bpm = Beats per minute; HRV = Heart rate variability; ms = Milliseconds; n = Sample size; pNN50 = Total number of interval differences (greater than 50 milliseconds) of consecutive NN (beat to beat) intervals divided by the total number of NN intervals; RMSSD = Square root of the mean squared differences of successive NN intervals; RR = Duration in milliseconds from one R peak to the next R peak of the electrocardiogram; SD = Standard deviation; SDNN = SD of all NN intervals (the square root of variance)

Wilcoxon signed rank tests were performed to determine significant differences between baseline and active (cognitive task) HRV states (Table 5.12).

Table 5.12 Wilcoxon signed rank test between baseline and active HRV states in the control group without depression (n=10)

Control group without depression n=10	Variable (unit)	Z	p	Median baseline (IQR)	Median active (IQR)	Median difference (active – baseline)
	Mean RR (ms)	-2.80	0.01	876.48 (286.78)	808.82 (228.71)	-67.66
	Mean heart rate (bpm)	-2.80	0.01	68.89 (22.24)	74.59 (19.46)	5.70
	Log LF (ms ²)	-2.19	0.03	2.69 (0.83)	3.29 (0.67)	0.60
	Log LF/HF (ms ²)	-2.80	0.01	-0.06 (0.42)	0.29 (0.44)	0.23

Table 5.12 displays significant results from a Wilcoxon signed rank test between baseline and active HRV states in the control group without depression (n=10).

Key: bpm = Beats per minute; HRV = Heart rate variability; IQR = Interquartile range; LF = Low frequency; LF/HF = Low frequency divided by high frequency (sympathovagal balance); ms = Milliseconds; ms² = Milliseconds squared; n = Sample size; p = Level of statistical significance (p<0.05); RR = Duration in milliseconds from one R peak to the next R peak of the electrocardiogram; Z = Z score

Spearman’s bivariate and partial correlations were performed between HRV and cognitive scores to address aims 1 and 5. CR pNN50 and judgment (Cognistat) were positively correlated (r=0.65, p=0.04). Partial Spearman’s correlations are shown in Table 5.13.

Table 5.13 Partial Spearman’s correlation coefficients between HRV and cognitive scores in the control group without depression (n=10)

	Covariate	Dependent variable	Independent variable	r	p
Control group without depression n=10	Age	Construction Cognistat	Log cardiac reactivity LF/HF	-0.82	0.01
		Calculation Cognistat		-0.67	0.03
		Similarity Cognistat		-0.67	0.03
	Sex	Memory Cognistat	Baseline pNN50	0.73	0.02
		Language MMSE	Log cardiac reactivity LF	0.73	0.03
			Log cardiac reactivity SDNN	0.85	0.01
	Sex and LAQ part one (lifestyle risk factors)	Judgment Cognistat	Log baseline LF/HF	0.69	0.03
		Construction Cognistat	Log baseline LF/HF	0.80	0.01
	LAQ part two (stress coping)	Total MMSE	Log baseline LF/HF	-0.71	0.04*
			Log cardiac reactivity LF	0.96	<0.001
			Log cardiac reactivity HF	0.80	0.02*
Log cardiac reactivity total power			0.96	<0.001	
Log cardiac reactivity SDNN			0.99	<0.001	
Log cardiac reactivity RMSSD			0.71	0.04*	

Table 5.13 displays significant results from a partial Spearman’s correlation between HRV and cognitive scores (MMSE (Folstein et al., 1975) and Cognistat (Kiernan et al., 1987)) in the control group without depression (n=10).

Key: HF = High frequency; HRV = Heart rate variability; LAQ = Lifestyle Appraisal Questionnaire (Craig et al., 1996); LF = Low frequency; LF/HF = Low frequency divided by high frequency (sympathovagal balance); MMSE = Mini Mental State Examination; n = Sample size; p = Level of statistical significance (p<=0.05); pNN50 = Total number of interval differences (greater than 50 milliseconds) of consecutive NN (beat to beat) intervals divided by the total number of NN intervals; r = Correlation coefficient; RMSSD = Square root of the mean squared differences of successive NN intervals; SDNN = Standard deviation of all NN intervals (the square root of variance); * = Bonferroni correction excludes this significant correlation

5.1.2.1 Depression (n=10) and the control group (n=10)

Mean cognitive scores (Cognistat and MMSE) for the depression and control group without depression are displayed in Figure 5.2.

Figure 5.2 Mean cognitive scores (Cognistat and MMSE) for the depression (n=10) and control group without depression (n=10)

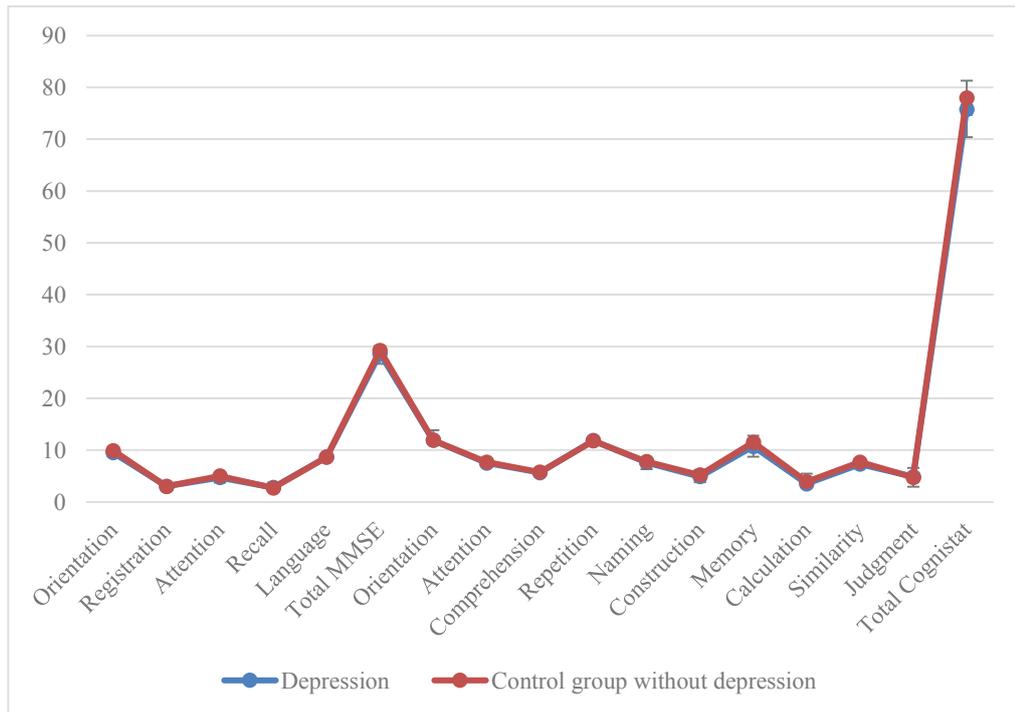


Figure 5.2 displays mean cognitive scores (Cognistat (Kiernan et al., 1987) and MMSE (Folstein et al., 1975)) for the depression (n=39) and control group without depression (n=31).

MMSE = Mini Mental State Examination

Wilcoxon signed rank tests were used to compare the baseline and active HRV states in the depression and control groups (Table 5.6 and Table 5.12). It was observed that mean HR increased and mean RR decreased significantly in both groups. Log SDNN significantly rose in the depression group and log LF/HF and log LF significantly rose from the baseline to the active state in the control group.

A Mann-Whitney U test compared cognitive scores between depression and the control group, yet without significant results. On the other hand, comparison of HRV values between the depression group and control group showed log CR LF/HF was significantly lower in the depression sample than the control (median (IQR) 0.06 (0.64), 0.39 (0.41),

respectively) ($p=0.03$, $Z=-2.19$, $U=21$). A Mann-Whitney U test with covariance were not performed due to low sample size.

Observed correlations found between the same variables (cognitive scores and HRV) in both the depression and control groups were compared using Z scores to address aim 4, however did not yield significant results ($p<0.05$).

5.1.3 Type 1 DM (n=9)

Mean (\pm SD) demographics for subjects with type 1 diabetes (n=9) are provided in Table 5.14.

Table 5.14 Mean sample demographics for subjects with type 1 diabetes (n=9)

Demographics		Value
Type 1 diabetes n=9	Years of age (mean \pm SD)	44.67 \pm 19.44
	Male (%)	11.11
	Years of education (mean \pm SD)	15.44 \pm 3.14
	BMI (mean \pm SD)	23.87 \pm 3.09
	Smoker (%)	22.22
	LAQ part one (mean \pm SD)	100
	LAQ part two (mean \pm SD)	15.44 \pm 4.75

Table 5.14 shows mean demographic scores for subjects with type 1 diabetes (n=9). BMI normal reference range is 19-25 (Garrouste-Orgeas et al., 2004). The maximum score of LAQ part one (lifestyle risk factors) is 70 and LAQ part two (stress coping) is 75. Higher LAQ scores reflect increased risk for developing chronic illnesses (Craig et al., 1996).

Key: BMI = Body mass index; LAQ = Lifestyle Appraisal Questionnaire (Craig et al., 1996); n = Sample size; SD = Standard deviation

Mean (\pm SD) scores from the MMSE and Cognistat with reference to their respective maximum score and cognitive impairment thresholds are displayed in Table 5.15. All mean scores were above their respective cognitive impairment thresholds, although the lower end of the SD crossed those thresholds for the Cognistat domains of construction (4.78 ± 1.30) and memory (10.22 ± 1.39).

Mean (\pm SD) values for HRV frequency and time domain parameters for baseline and active states are provided in Table 5.16 and Table 5.17, respectively.

Table 5.15 Mean cognitive scores from the MMSE and Cognistat for subjects with type 1 diabetes (n=9)

		Cognitive assessment	Cognitive domain	Maximum possible score	Cognitive impairment threshold	Mean \pm SD
Type 1 diabetes n=9	MMSE		Orientation	10	-	9.67 \pm 0.50
			Registration	3	-	3.00 \pm 0.00
			Attention	5	-	3.89 \pm 1.54
			Recall	3	-	2.78 \pm 0.44
			Language	9	-	8.89 \pm 0.22
		Total MMSE		30	\leq 23	28.22 \pm 2.09
	Cognistat		Orientation	12	<10	11.89 \pm 0.33
			Attention	8	<6	7.67 \pm 0.71
			Comprehension	6	<5	5.56 \pm 0.53
			Repetition	12	<11	11.89 \pm 0.33
			Naming	8	<7	8.00 \pm 0.00
			Construction	6	<4	4.78 \pm 1.30
			Memory	12	<10	10.22 \pm 1.39
			Calculation	4	<3	3.67 \pm 0.50
		Similarity	8	<5	7.56 \pm 1.01	
		Judgment	6	<4	5.00 \pm 0.83	
	Total Cognistat		82	<65	76.22 \pm 3.61	

Table 5.15 shows mean cognitive scores from the MMSE (Folstein et al., 1975) and the Cognistat (Kiernan et al., 1987) for subjects with type 1 diabetes (n=9). The maximum score possible and the cognitive impairment threshold are provided for each cognitive domain. Scores below the cognitive impairment threshold indicate cognitive impairment. The Cognistat domains where the lower end of the SD crossed the cognitive impairment threshold are shown in **bold**.

Key: MMSE = Mini Mental State Examination; n = Sample size; SD = Standard deviation

Table 5.16 Mean frequency domain HRV values for subjects with type 1 diabetes (n=9)

HRV State		HRV frequency domain	Mean (\pm SD) ms ²
Type 1 diabetes n=9	Baseline	Low frequency (absolute)	1086.83 \pm 2127.23
		High frequency (absolute)	1741.18 \pm 4052.92
		LF/HF (absolute)	1.77 \pm 1.92
		Total power (absolute)	3803.46 \pm 7344.61
		Log low frequency	2.61 \pm 0.60
		Log high frequency	2.57 \pm 0.72
		Log LF/HF	0.04 \pm 0.45
		Log total power	3.18 \pm 0.55
	Active	Low frequency (absolute)	2475.23 \pm 2644.06
		High frequency (absolute)	1389.74 \pm 1265.94
		LF/HF (absolute)	1.65 \pm 1.12
		Total power (absolute)	7921.40 \pm 10972.62
		Log low frequency	3.20 \pm 0.47
		Log high frequency	3.07 \pm 0.72
		Log LF/HF	0.13 \pm 0.31
		Log total power	3.64 \pm 0.51
	Cardiac reactivity	Low frequency (absolute)	1388.40 \pm 1161.77
		High frequency (absolute)	1840.20 \pm 2768.42
		LF/HF (absolute)	-0.12 \pm 1.07
		Total power (absolute)	4117.94 \pm 4130.79
		Log low frequency	0.58 \pm 0.60
		Log high frequency	0.50 \pm 0.44
		Log LF/HF	0.08 \pm 0.28
		Log total power	0.46 \pm 0.41

Table 5.16 shows mean frequency domain HRV values for subjects with type 1 diabetes (n=9) during baseline and active states. Cardiac reactivity refers to the active minus baseline HRV data.

Key: HRV = Heart rate variability; LF/HF = Low frequency divided by high frequency (sympathovagal balance); ms² = Milliseconds squared; n = Sample size; SD = Standard deviation

Table 5.17 Mean time domain HRV values for subjects with type 1 diabetes (n=9)

HRV state		HRV time domain (unit)	Mean ± SD
Type 1 diabetes n=9	Baseline	Mean RR (ms)	837.54 ± 106.46
		SDNN (ms)	47.78 ± 34.44
		Mean heart rate (bpm)	73.11 ± 10.89
		RMSSD (ms)	48.07 ± 53.56
		pNN50 (%)	7.76 ± 15.31
		Log RMSSD (ms)	1.53 ± 0.34
		Log SDNN (ms)	1.61 ± 0.25
	Active	Mean RR (ms)	780.89 ± 102.64
		SDNN (ms)	81.98 ± 40.74
		Mean heart rate (bpm)	79.03 ± 11.87
		RMSSD (ms)	91.20 ± 61.73
		pNN50 (%)	8.92 ± 9.66
		Log RMSSD (ms)	1.89 ± 0.26
		Log SDNN (ms)	1.87 ± 0.22
	Cardiac reactivity	Mean RR (ms)	-56.65 ± 39.94
		SDNN (ms)	34.20 ± 22.45
		Mean heart rate (bpm)	5.92 ± 3.93
		RMSSD (ms)	43.14 ± 31.31
		pNN50 (%)	1.15 ± 7.03
		Log RMSSD (ms)	0.36 ± 0.26
		Log SDNN (ms)	0.26 ± 0.19

Table 5.17 shows mean time domain HRV values for subjects with type 1 diabetes (n=9) during baseline and active states. Cardiac reactivity refers to the active minus baseline HRV data.

Key: bpm = Beats per minute; HRV = Heart rate variability; ms = Milliseconds; n = Sample size; pNN50 = Total number of interval differences (greater than 50 milliseconds) of consecutive NN (beat to beat) intervals divided by the total number of NN intervals; RMSSD = Square root of the mean squared differences of successive NN intervals; RR = Duration in milliseconds from one R peak to the next R peak of the electrocardiogram; SD = Standard deviation; SDNN = SD of all NN intervals (the square root of variance)

Wilcoxon signed rank tests were performed to determine significant differences between HRV data in the baseline and active (cognitive task) states (Table 5.18).

Table 5.18 Wilcoxon signed rank test between baseline and active HRV states in subjects with type 1 diabetes (n=9)

	Variable (unit)	Z	p	Median baseline (IQR)	Median active (IQR)	Median difference (active – baseline)
Type 1 diabetes n=9	Mean RR (ms)	-2.55	0.01	832.27 (88.01)	795.32 (141.72)	-36.95
	Mean heart rate (bpm)	-2.55	0.01	72.95 (7.03)	75.85 (13.33)	2.90
	Log LF (ms ²)	-2.31	0.02	2.61 (0.51)	3.14 (0.50)	0.53
	Log HF (ms ²)	-2.55	0.01	2.33 (0.90)	3.09 (0.79)	0.76
	Log total power (ms ²)	-2.67	0.01	3.23 (0.68)	3.59 (0.45)	0.36
	Log SDNN (ms)	-2.67	0.01	1.59 (0.34)	1.88 (0.27)	0.29
	Log RMSSD (ms)	-2.55	0.01	1.41 (0.48)	1.87 (0.29)	0.46

Table 5.18 displays significant results from a Wilcoxon signed rank test between baseline and active HRV states in subjects with type 1 diabetes (n=9).

Key: bpm = Beats per minute; HF = High frequency; HRV = Heart rate variability; IQR = Interquartile range; LF = Low frequency; ms = Milliseconds; ms² = Milliseconds squared; n = Sample size; p = Level of statistical significance (p<0.05); RMSSD = Square root of the mean squared differences of successive NN intervals; RR = Duration in milliseconds from one R peak to the next R peak of the electrocardiogram; SDNN = Standard deviation of all NN intervals (the square root of variance); Z = Z score

Spearman’s bivariate and partial correlations were performed between HRV and cognitive scores to address aims 1 and 5 (Table 5.19 and Table 5.20, respectively).

Table 5.19 Spearman’s correlation coefficients between cognitive scores and HRV in subjects with type 1 diabetes (n=9)

	Dependent variable	Independent variable	r	p
Type 1 diabetes n=9	Total MMSE	Baseline mean heart rate	0.67	0.047
	Attention Cognistat	Log baseline total power	0.73	0.03
		Log baseline SDNN	0.71	0.03
	Construction Cognistat	Baseline mean RR	-0.83	0.01
		Baseline mean heart rate	0.88	0.002
		Log cardiac reactivity LF	-0.69	0.04*
		Log cardiac reactivity total power	-0.75	0.02*

Table 5.19 displays significant results from a Spearman’s correlation between cognitive scores (MMSE (Folstein et al., 1975) and Cognistat (Kiernan et al., 1987)) and HRV in subjects with type 1 diabetes (n=9).

Key: HRV = Heart rate variability; LF = Low frequency; MMSE = Mini Mental State Examination; n = Sample size; p = Level of statistical significance (p<0.05); r = Correlation coefficient; RR = Duration in milliseconds from one R peak to the next R peak of the electrocardiogram; SDNN = Standard deviation of all NN intervals (the square root of variance); * = Bonferroni correction excludes this significant correlation

Table 5.20 Partial Spearman’s correlation coefficients between cognitive scores and HRV in subjects with type 1 diabetes (n=9)

	Covariate	Dependent variable	Independent variable	r	p
Type 1 diabetes n=9	LAQ part two (stress coping)	Memory Cognistat	Cardiac reactivity pNN50	0.80	0.01
		Total Cognistat		0.72	0.02
	Age	Orientation Cognistat	Baseline pNN50	0.88	0.002
	LAQ part one (lifestyle risk factors) and number of illnesses	Similarity Cognistat	Log baseline HF	0.70	0.04
		Construction Cognistat	Log baseline HF	0.71	0.04
		Comprehension Cognistat	Log baseline HF	0.86	0.01
			Log baseline RMSSD	0.84	0.01
	Repetition Cognistat	Log baseline HF	-0.71	0.04	
		Log baseline RMSSD	-0.72	0.03	
	Smoking status	Total Cognistat	Log baseline total power	0.72	0.03*
			Log baseline SDNN	0.86	0.01
	LAQ part one (lifestyle risk factors)	Comprehension Cognistat	Log baseline LF	0.94	0.001
			Log baseline total power	0.79	0.02*
			Log cardiac reactivity LF	-0.73	0.03*
			Log cardiac reactivity HF	-0.80	0.02*
			Log cardiac reactivity total power	-0.94	0.001
			Log cardiac reactivity SDNN	-0.92	0.002
	Number of illnesses	Calculation Cognistat	Log baseline SDNN	-0.67	0.049
	BMI	Judgment Cognistat	Log baseline HF	0.70	0.04*
Log baseline total power			0.77	0.02	
Log baseline RMSSD			0.73	0.03*	
Language MMSE		Log baseline HF	-0.68	0.047*	
Age	Orientation MMSE	Cardiac reactivity pNN50	0.71	0.04*	
		Cardiac reactivity mean heart rate	0.68	0.048	

Table 5.20 displays significant results from a partial Spearman’s correlation between cognitive scores (MMSE (Folstein et al., 1975) and Cognistat (Kiernan et al., 1987)) and HRV in subjects with type 1 diabetes (n=9).

Key: BMI = Body mass index; HF = High frequency; HRV = Heart rate variability; LAQ = Lifestyle Appraisal Questionnaire (Craig et al., 1996); LF = Low frequency; MMSE = Mini Mental State Examination; n = Sample size; p = Level of statistical significance (p<0.05); pNN50 = Total number of

(continued from previous page) interval differences (greater than 50 milliseconds) of consecutive NN (beat to beat) intervals divided by the total number of NN intervals; r = Correlation coefficient; RMSSD = Square root of the mean squared differences of successive NN intervals; SDNN = Standard deviation of all NN intervals (the square root of variance); * = Bonferroni correction excludes this significant correlation

5.1.4 Control group without type 1 DM (n=9)

Mean (± SD) demographics for the control group without type 1 diabetes (n=9) are provided in Table 5.21.

Table 5.21 Mean sample demographics for the control group without type 1 diabetes (n=9)

Control group without type 1 diabetes (n=9)	Demographics	Value
	Years of age (mean ± SD)	43.11 ± 17.42
	Male (%)	11
	Years of education (mean ± SD)	19.17 ± 6.71
	BMI (mean ± SD)	25.58 ± 4.47
	Smoker (%)	0
	LAQ part one (mean ± SD)	12.22 ± 5.21
	LAQ part two (mean ± SD)	14.78 ± 9.97

Table 5.21 shows mean demographic scores for the control group without type 1 diabetes (n=9). BMI normal reference range is 19-25 (Garrouste-Orgeas et al., 2004). The maximum score of LAQ part one (lifestyle risk factors) is 70 and LAQ part two (stress coping) is 75. Higher LAQ scores reflect increased risk for developing chronic illnesses (Craig et al., 1996).

Key: BMI = Body mass index; LAQ = Lifestyle Appraisal Questionnaire (Craig et al., 1996); n = Sample size; SD = Standard deviation

Mean (\pm SD) scores from the MMSE and Cognistat with reference to their respective maximum score and cognitive impairment thresholds are displayed in Table 5.15. All mean scores were above their respective cognitive impairment thresholds, although the lower end of the SD crossed those thresholds for the Cognistat domains of comprehension (5.33 ± 0.71), repetition (11.56 ± 1.33), naming (7.56 ± 0.73), construction (4.89 ± 1.05), memory (11.11 ± 1.36), similarity (6.11 ± 1.96), and judgment (4.33 ± 1.22).

Mean (\pm SD) values for HRV frequency and time domain parameters for baseline and active states are provided in Table 5.16 and Table 5.17, respectively.

Table 5.22 Mean cognitive scores from the MMSE and Cognistat for the control group without type 1 diabetes (n=9)

		Cognitive assessment	Cognitive domain	Maximum possible score	Cognitive impairment threshold	Mean \pm SD
Control group without type 1 diabetes (n=9)	MMSE		Orientation	10	-	9.78 \pm 0.44
			Registration	3	-	3.00 \pm 0.00
			Attention	5	-	5.00 \pm 0.00
			Recall	3	-	2.89 \pm 0.33
			Language	9	-	8.44 \pm 0.73
		Total MMSE		30	≤ 23	29.11 \pm 1.17
	Cognistat		Orientation	12	<10	11.78 \pm 0.67
			Attention	8	<6	7.44 \pm 0.73
			Comprehension	6	<5	5.33 \pm 0.71
			Repetition	12	<11	11.56 \pm 1.33
			Naming	8	<7	7.56 \pm 0.73
			Construction	6	<4	4.89 \pm 1.05
			Memory	12	<10	11.11 \pm 1.36
			Calculation	4	<3	3.89 \pm 0.33
		Similarity	8	<5	6.11 \pm 1.96	
		Judgment	6	<4	4.33 \pm 1.22	
	Total Cognistat		82	<65	74.00 \pm 5.17	

Table 5.22 shows mean cognitive scores from the MMSE (Folstein et al., 1975) and the Cognistat (Kiernan et al., 1987) for the control group without type 1 diabetes (n=9). The maximum score possible and the cognitive impairment threshold are provided for each cognitive domain. Scores below the cognitive impairment threshold indicate cognitive impairment. The Cognistat domains where the lower end of the SD crossed the cognitive impairment threshold are shown in **bold**.

Key: MMSE = Mini Mental State Examination; n = Sample size; SD = Standard deviation

Table 5.23 Mean frequency domain HRV values for the control group without type 1 diabetes (n=9)

HRV State		HRV frequency domain	Mean (\pm SD) ms ²
Control group without type 1 diabetes (n=9)	Baseline	Low frequency (absolute)	1253.97 \pm 1380.74
		High frequency (absolute)	993.06 \pm 1054.09
		LF/HF (absolute)	1.63 \pm 1.77
		Total power (absolute)	3808.50 \pm 3339.23
		Log low frequency	3.03 \pm 0.74
		Log high frequency	2.77 \pm 0.53
		Log LF/HF	0.00 \pm 0.46
		Log total power	3.40 \pm 0.44
	Active	Low frequency (absolute)	2466.77 \pm 2118.70
		High frequency (absolute)	1301.66 \pm 1840.18
		LF/HF (absolute)	2.78 \pm 1.59
		Total power (absolute)	5410.41 \pm 4561.86
		Log low frequency	3.20 \pm 0.47
		Log high frequency	2.85 \pm 0.49
		Log LF/HF	0.35 \pm 0.34
		Log total power	3.60 \pm 0.37
	Cardiac reactivity	Low frequency (absolute)	835.68 \pm 657.00
		High frequency (absolute)	288.36 \pm 1030.01
		LF/HF (absolute)	1.15 \pm 1.74
		Total power (absolute)	1244.00 \pm 2185.70
		Log low frequency	0.17 \pm 0.39
		Log high frequency	0.05 \pm 0.31
		Log LF/HF	0.35 \pm 0.43
		Log total power	0.15 \pm 0.16

Table 5.23 shows mean frequency domain HRV values of the control group without type 1 diabetes (n=9) during baseline and active states. Cardiac reactivity refers to the active minus baseline HRV data.

Key: HRV = Heart rate variability; LF/HF = Low frequency divided by high frequency (sympathovagal balance); ms² = Milliseconds squared; n = Sample size; SD = Standard deviation

Table 5.24 Mean time domain HRV values for the control group without type 1 diabetes (n=9)

HRV state		HRV time domain (unit)	Mean ± SD
Control group without type 1 diabetes (n=9)	Baseline	Mean RR (ms)	882.24 ± 122.93
		SDNN (ms)	58.65 ± 25.97
		Mean heart rate (bpm)	70.01 ± 11.02
		RMSSD (ms)	48.30 ± 24.36
		pNN50 (%)	20.91 ± 14.85
		Log RMSSD (ms)	1.72 ± 0.34
		Log SDNN (ms)	1.79 ± 0.26
	Active	Mean RR (ms)	848.59 ± 112.94
		SDNN (ms)	68.50 ± 22.11
		Mean heart rate (bpm)	72.35 ± 10.07
		RMSSD (ms)	58.64 ± 32.86
		pNN50 (%)	24.66 ± 14.85
		Log RMSSD (ms)	1.71 ± 0.23
		Log SDNN (ms)	1.82 ± 0.14
	Cardiac reactivity	Mean RR (ms)	-33.65 ± 56.87
		SDNN (ms)	7.85 ± 9.82
		Mean heart rate (bpm)	2.35 ± 4.79
		RMSSD (ms)	8.53 ± 17.56
		pNN50 (%)	3.75 ± 9.87
		Log RMSSD (ms)	0.00 ± 0.22
		Log SDNN (ms)	0.02 ± 0.16

Table 5.24 shows mean time domain HRV values for the control group without type 1 diabetes (n=9) during baseline and active states. Cardiac reactivity refers to the active minus baseline HRV data.

Key: bpm = Beats per minute; HRV = Heart rate variability; ms = Milliseconds; n = Sample size; pNN50 = Total number of interval differences (greater than 50 milliseconds) of consecutive NN (beat to beat) intervals divided by the total number of NN intervals; RMSSD = Square root of the mean squared differences of successive NN intervals; RR = Duration in milliseconds from one R peak to the next R peak of the electrocardiogram; SD = Standard deviation; SDNN = SD of all NN intervals (the square root of variance)

Wilcoxon signed rank tests were performed to determine significant differences between baseline and active (cognitive task) HRV states. Only log TP significantly rose from baseline to the active state ($p=0.04$, $Z=-2.10$) (median (IQR) 3.37 (0.83), 3.69 (0.67), respectively).

Spearman’s bivariate and partial correlations were performed between HRV and cognitive scores to address aims 1 and 5 (Table 5.25 and Table 5.26, respectively).

Table 5.25 Spearman’s correlation coefficients between cognitive scores and HRV in the control group without type 1 diabetes ($n=9$)

	Dependent variable	Independent variable	r	p
Control group without type 1 diabetes ($n=9$)	Language MMSE	Log baseline LF/HF	0.71	0.03
	Attention Cognistat	Log cardiac reactivity LF	0.78	0.01
	Comprehension Cognistat	Baseline mean RR	0.91	0.001
		Baseline mean heart rate	-0.91	0.001
	Construction Cognistat	Log cardiac reactivity LF	0.75	0.02

Table 5.25 displays significant results from a partial Spearman’s correlation between cognitive scores (MMSE (Folstein et al., 1975) and Cognistat (Kiernan et al., 1987)) and HRV in the control group without type 1 diabetes ($n=9$).

Key: HRV = Heart rate variability; LAQ = Lifestyle Appraisal Questionnaire (Craig et al., 1996); LF = Low frequency; LF/HF = Low frequency divided by high frequency (sympathovagal balance); MMSE = Mini Mental State Examination; n = Sample size; p = Level of statistical significance ($p<0.05$); r = Correlation coefficient; RR = Duration in milliseconds from one R peak to the next R peak of the electrocardiogram

Table 5.26 Partial Spearman’s correlation coefficients between cognitive scores and HRV in the control group without type 1 diabetes (n=9)

	Covariate	Dependent variable	Independent variable	r	p
Control group without type 1 diabetes (n=9)	BMI	Naming Cognistat	Log baseline LF/HF	0.80	0.02*
			Cardiac reactivity mean RR	0.68	0.047*
			Cardiac reactivity mean heart rate	-0.68	0.047*
			Log cardiac reactivity HF	0.76	0.02*
			Log cardiac reactivity RMSSD	0.71	0.04*
	LAQ part one (lifestyle risk factors)	Attention Cognistat	Log cardiac reactivity total power	0.70	0.04

Table 5.26 displays significant results from a partial Spearman’s correlation between cognitive scores (MMSE (Folstein et al., 1975) and Cognistat (Kiernan et al., 1987)) and HRV in the control group without type 1 diabetes (n=9).

Key: BMI = Body mass index; HF = High frequency; HRV = Heart rate variability; LAQ = Lifestyle Appraisal Questionnaire (Craig et al., 1996); LF/HF = Low frequency divided by high frequency (sympathovagal balance); MMSE = Mini Mental State Examination; n = Sample size; p = Level of statistical significance (p=<0.05); r = Correlation coefficient; RMSSD = Square root of the mean squared differences of successive NN intervals; RR = Duration in milliseconds from one R peak to the next R peak of the electrocardiogram; * = Bonferroni correction excludes this significant correlation

5.1.4.1 Type 1 DM (n=9) and the control group (n=9)

Mean cognitive scores (Cognistat and MMSE) for the type 1 diabetes and control group without type 1 diabetes are displayed in Figure 5.3.

Figure 5.3 Mean cognitive scores (Cognistat and MMSE) for the type 1 diabetes (n=9) and control group without type 1 diabetes (n=9)

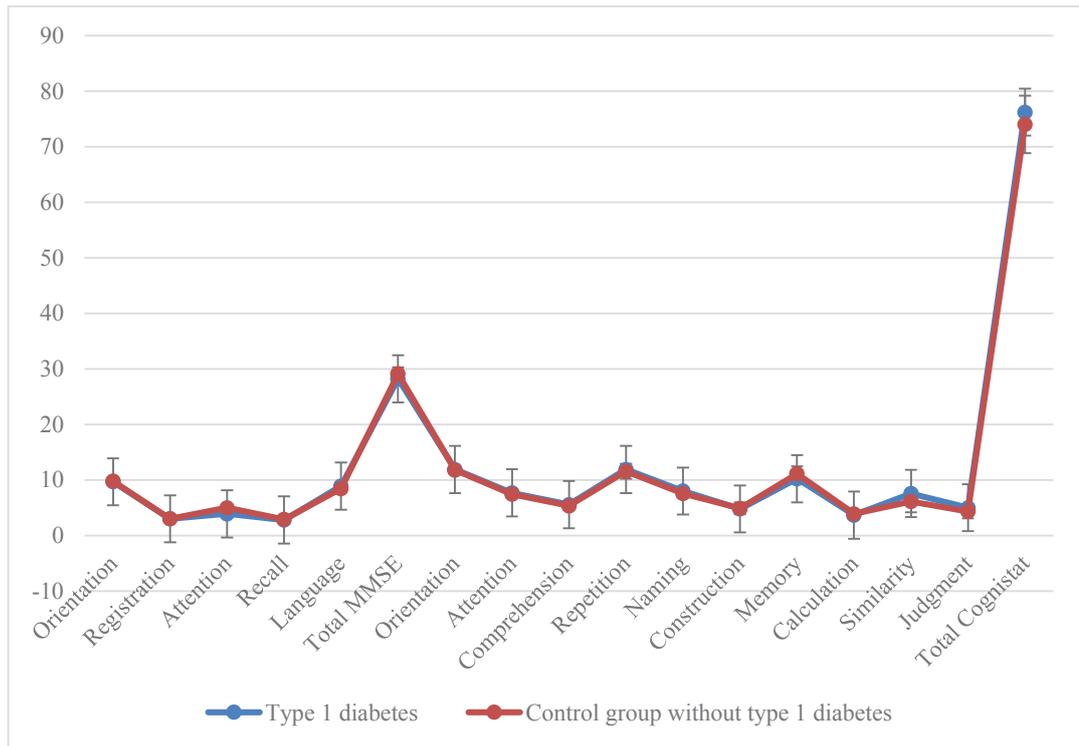


Figure 5.3 displays mean cognitive scores (Cognistat (Kiernan et al., 1987) and MMSE (Folstein et al., 1975)) for the type 1 diabetes (n=39) and control group without type 1 diabetes (n=31).

MMSE = Mini Mental State Examination

Wilcoxon signed rank tests were applied to compare the baseline and active HRV states in subjects with type 1 diabetes and the control group. It was observed that log TP increased significantly from baseline to active states in both groups. The type 1 DM cohort had a significant decrease in mean RR, and significant increases in mean HR, log LF, log HF, log SDNN, and log RMSSD from baseline to active states.

Mann-Whitney U tests compared cognitive scores between subjects with type 1 diabetes and the control group, yet did not show significant results. A Mann-Whitney U test

compared HRV values between the type 1 DM group and the control (Table 5.27). Mann-Whitney U test with covariance was not performed due to low sample size.

Table 5.27 Mann-Whitney U test comparing HRV values between subjects with type 1 diabetes and the control group

	Variable (unit)	U	Z	p	Median control (IQR)	Median clinical (IQR)	Median difference (clinical – control)
Type 1 diabetes and control group	Baseline pNN50 (%)	17	-2.08	0.04	3.67 (5.62)	24.20 (28.23)	20.53
	Log cardiac reactivity HF (ms ²)	59	2.21	0.03	-0.05 (0.39)	-0.05 (0.39)	0.00
	Log cardiac reactivity SDNN (ms)	71	2.69	0.01	0.08 (0.16)	0.22 (0.31)	0.14
	Log cardiac reactivity RMSSD (ms)	69	2.52	0.01	0.02 (0.19)	0.34 (0.50)	0.32

Table 5.27 displays significant results from a Mann-Whitney U test of HRV values between subjects with type 1 diabetes (n=9) and the control group (n=9).

Key: DM = Diabetes mellitus; HRV = Heart rate variability; HF = High frequency; IQR = Interquartile range; ms = Milliseconds; ms² = Milliseconds squared; n = Sample size; p = Level of statistical significance (p<0.05); pNN50 = Total number of interval differences (greater than 50 milliseconds) of consecutive NN (beat to beat) intervals divided by the total number of NN intervals; RMSSD = Square root of the mean squared differences of successive NN intervals; SDNN = SD of all NN intervals (the square root of variance); U = U test statistic; Z = Z score

Significant correlations in subjects with type 1 diabetes and the control group were compared using Z scores to address aim 4. The log CR LF correlation with construction (Cognistat) was significantly different between the clinical and the control group (p=0.001, Z=3.15) (r=-0.69, p=0.04; r=0.75, p=0.02, respectively).

5.1.5 Type 2 DM (n=38)

Mean (\pm SD) demographics for subjects with type 2 diabetes (n=38) are provided in Table 5.28.

Table 5.28 Mean sample demographics for subjects with type 2 diabetes (n=38)

Demographics		Value
Type 2 diabetes (n=38)	Years of age (mean \pm SD)	64.58 \pm 12.64
	Male (%)	63.16
	Years of education (mean \pm SD)	15.36 \pm 3.24
	BMI (mean \pm SD)	28.06 \pm 6.23
	Smoker (%)	2.63
	Medicated (%)	87
	LAQ part one (mean \pm SD)	20.25 \pm 5.57
	LAQ part two (mean \pm SD)	18.79 \pm 12.68

Table 5.28 shows mean demographic scores for subjects with type 2 diabetes (n=38). BMI normal reference range is 19-25 (Garrouste-Orgeas et al., 2004). The maximum score of LAQ part one (lifestyle risk factors) is 70 and LAQ part two (stress coping) is 75. Higher LAQ scores reflect increased risk for developing chronic illnesses (Craig et al., 1996).

Key: BMI = Body mass index; LAQ = Lifestyle Appraisal Questionnaire (Craig et al., 1996); n = Sample size; SD = Standard deviation

Mean (\pm SD) scores from the MMSE and Cognistat with reference to their respective maximum score and cognitive impairment thresholds are displayed in Table 5.29. All mean scores were above their respective cognitive impairment thresholds, although the lower end of the SD crossed those thresholds for the Cognistat domains of comprehension (5.37 \pm 1.12), repetition (11.33 \pm 1.44), naming (7.53 \pm 1.03), construction (4.34 \pm 1.22), and memory (10.00 \pm 2.01).

Mean (\pm SD) values for HRV frequency and time domain parameters for baseline and active states are provided in Table 5.30 and Table 5.31, respectively.

Table 5.29 Mean cognitive scores from the MMSE and Cognistat for subjects with type 2 diabetes (n=38)

		Cognitive assessment	Cognitive domain	Maximum possible score	Cognitive impairment threshold	Mean ± SD
Type 2 diabetes n=38	MMSE		Orientation	10	-	9.63 ± 0.59
			Registration	3	-	3.00 ± 0.00
			Attention	5	-	4.18 ± 1.00
			Recall	3	-	2.24 ± 0.75
			Language	9	-	8.45 ± 0.69
		Total MMSE		30	≤23	27.50 ± 1.76
	Cognistat		Orientation	12	<10	11.92 ± 0.27
			Attention	8	<6	7.34 ± 1.19
			Comprehension	6	<5	5.37 ± 1.12
			Repetition	12	<11	11.33 ± 1.44
			Naming	8	<7	7.53 ± 1.03
			Construction	6	<4	4.34 ± 1.22
			Memory	12	<10	10.00 ± 2.01
			Calculation	4	<3	3.71 ± 0.65
		Similarity	8	<5	6.72 ± 1.33	
		Judgment	6	<4	4.80 ± 0.68	
	Total Cognistat		82	<65	73.07 ± 6.08	

Table 5.29 shows mean cognitive scores from the MMSE (Folstein et al., 1975) and the Cognistat (Kiernan et al., 1987) for subjects with type 2 diabetes (n=38). The maximum score possible and the cognitive impairment threshold are provided for each cognitive domain. Scores below the cognitive impairment threshold indicate cognitive impairment. The Cognistat domains where the lower end of the SD crossed the cognitive impairment threshold are shown in **bold**.

Key: MMSE = Mini Mental State Examination; n = Sample size; SD = Standard deviation

Table 5.30 Mean frequency domain HRV values for subjects with type 2 diabetes (n=38)

HRV State		HRV frequency domain	Mean (\pm SD) ms ²
Type 2 diabetes n=38	Baseline	Low frequency (absolute)	1353.89 \pm 1931.11
		High frequency (absolute)	2232.91 \pm 3867.24
		LF/HF (absolute)	0.97 \pm 0.85
		Total power (absolute)	5548.88 \pm 10256.88
		Log low frequency	2.65 \pm 0.75
		Log high frequency	2.77 \pm 0.93
		Log LF/HF	-0.12 \pm 0.44
		Log total power	3.24 \pm 0.73
	Active	Low frequency (absolute)	2230.77 \pm 2983.77
		High frequency (absolute)	2815.43 \pm 3884.04
		LF/HF (absolute)	1.65 \pm 1.65
		Total power (absolute)	5871.56 \pm 7577.34
		Log low frequency	2.93 \pm 0.66
		Log high frequency	2.92 \pm 0.86
		Log LF/HF	0.01 \pm 0.43
		Log total power	3.49 \pm 0.63
	Cardiac reactivity	Low frequency (absolute)	585.43 \pm 2078.93
		High frequency (absolute)	312.36 \pm 2663.58
		LF/HF (absolute)	0.54 \pm 1.41
		Total power (absolute)	2485.65 \pm 9571.76
		Log low frequency	0.29 \pm 0.59
		Log high frequency	0.16 \pm 0.62
		Log LF/HF	0.17 \pm 0.34
		Log total power	0.25 \pm 0.51

Table 5.30 shows mean frequency domain HRV values for subjects with type 2 diabetes (n=38) during baseline and active states. Cardiac reactivity refers to the active minus baseline HRV data.

Key: HRV = Heart rate variability; LF/HF = Low frequency divided by high frequency (sympathovagal balance); ms² = Milliseconds squared; n = Sample size; SD = Standard deviation

Table 5.31 Mean time domain HRV values for subjects with type 2 diabetes (n=38)

HRV state		HRV time domain (unit)	Mean ± SD
Type 2 diabetes n=38	Baseline	Mean RR (ms)	811.03 ± 94.81
		SDNN (ms)	62.30 ± 46.83
		Mean heart rate (bpm)	75.64 ± 9.13
		RMSSD (ms)	78.79 ± 73.68
		pNN50 (%)	7.66 ± 12.09
		Log RMSSD (ms)	1.72 ± 0.42
		Log SDNN (ms)	1.68 ± 0.33
	Active	Mean RR (ms)	783.59 ± 96.15
		SDNN (ms)	68.91 ± 39.92
		Mean heart rate (bpm)	78.64 ± 10.11
		RMSSD (ms)	79.25 ± 59.92
		pNN50 (%)	8.73 ± 12.50
		Log RMSSD (ms)	1.80 ± 0.35
		Log SDNN (ms)	1.79 ± 0.25
	Cardiac reactivity	Mean RR (ms)	-27.44 ± 30.11
		SDNN (ms)	10.90 ± 29.85
		Mean heart rate (bpm)	2.58 ± 2.46
		RMSSD (ms)	7.57 ± 33.36
		pNN50 (%)	1.00 ± 4.89
		Log RMSSD (ms)	0.08 ± 0.24
		Log SDNN (ms)	0.11 ± 0.22

Table 5.31 shows mean time domain HRV values for subjects with type 2 diabetes (n=38) during baseline and active states. Cardiac reactivity refers to the active minus baseline HRV data.

Key: bpm = Beats per minute; HRV = Heart rate variability; ms = Milliseconds; n = Sample size; pNN50 = Total number of interval differences (greater than 50 milliseconds) of consecutive NN (beat to beat) intervals divided by the total number of NN intervals; RMSSD = Square root of the mean squared differences of successive NN intervals; RR = Duration in milliseconds from one R peak to the next R peak of the electrocardiogram; SD = Standard deviation; SDNN = SD of all NN intervals (the square root of variance)

Dependent sample t-tests were performed to determine significant differences between HRV data in the baseline and active (cognitive task) states (Table 5.32).

Table 5.32 Dependent sample t-test between baseline and active HRV states for subjects with type 2 diabetes (n=38)

	Variable (unit)	t	df	p	Baseline mean ± SD	Active mean ± SD	Mean difference (active – baseline)
Type 2 diabetes n=38	Mean RR (ms)	5.62	37	<0.001	811.03 ± 94.81	783.59 ± 96.15	-27.44
	Mean heart rate (bpm)	-5.19	37	<0.001	75.64 ± 9.13	78.64 ± 10.11	3.00
	Log total power (ms ²)	-3.07	37	0.004	3.24 ± 0.73	3.49 ± 0.63	0.25
	Log SDNN (ms)	-2.93	37	0.01	1.68 ± 0.33	1.79 ± 0.25	0.11
	Log RMSSD (ms)	-2.06	37	0.046	1.72 ± 0.42	1.80 ± 0.35	0.08

Table 5.32 displays significant results from a dependent sample t-test between baseline and active HRV states for subjects with type 2 diabetes (n=38).

Key: bpm = Beats per minute; df = Degrees of freedom; HRV = Heart rate variability; ms = Milliseconds; ms² = Milliseconds squared; n = Sample size; p = Level of statistical significance (p<0.05); RMSSD = Square root of the mean squared differences of successive NN intervals; RR = Duration in milliseconds from one R peak to the next R peak of the electrocardiogram; SD = Standard deviation; SDNN = Standard deviation of all NN intervals (the square root of variance); t = T statistic

Pearson’s bivariate and partial correlations were performed between HRV and cognitive scores to address aims 1 and 5 (Table 5.33). Only one statistically significantly negative correlation was identified between orientation (Cognistat) and log CR LF/HF (r=-0.36, p=0.03) in the type 2 diabetes group. After Bonferroni correction on HRV p-values from Table 5.33, there were insufficient variables (≤3) to perform a multiple regression.

Table 5.33 Partial Pearson’s correlation coefficients between cognitive scores and HRV in subjects with type 2 diabetes (n=38)

	Covariate	Dependent variable	Independent variable	r	p
Type 2 diabetes n=38	Age and smoking status	Orientation MMSE	Log baseline LF	0.36	0.03
	Sex	Naming Cognistat	Log baseline SDNN	0.33	0.045
	Age	Memory Cognistat	Log baseline LF	0.42	0.01
			Log baseline HF	0.38	0.02*
			Log baseline total power	0.42	0.01
			Log baseline SDNN	0.38	0.02*
			Log baseline RMSSD	0.37	0.02*
			Log cardiac reactivity total power	-0.37	0.03*
			Log cardiac reactivity SDNN	-0.37	0.03*
	Years of education	Memory Cognistat	Log cardiac reactivity RMSSD	-0.38	0.02*
BMI, LAQ part two (stress coping) and number of illnesses	Similarity Cognistat	Log cardiac reactivity total power	0.34	0.045	

Table 5.33 displays significant results from a partial Pearson’s correlation between cognitive scores (MMSE (Folstein et al., 1975) and Cognistat (Kiernan et al., 1987)) and HRV in subjects with type 2 diabetes (n=38).

Key: BMI = Body mass index; HF = High frequency; HRV = Heart rate variability; LAQ = Lifestyle Appraisal Questionnaire (Craig et al., 1996); LF = Low frequency; MMSE = Mini Mental State Examination; n = Sample size; p = Level of statistical significance (p<0.05); r = Correlation coefficient; RMSSD = Square root of the mean squared differences of successive NN (beat to beat) intervals; SDNN = Standard deviation of all NN intervals (the square root of variance); * = Bonferroni correction excludes this significant correlation

5.1.6 Control group without type 2 DM (n=30)

Mean (\pm SD) demographics for the control group without type 2 diabetes (n=30) are provided in Table 5.34.

Table 5.34 Mean sample demographics for the control group without type 2 diabetes (n=30)

Control group without type 2 diabetes (n=30)	Demographics	Value
	Years of age (mean \pm SD)	56.13 \pm 9.28
	Male (%)	57
	Years of education (mean \pm SD)	19.93 \pm 4.60
	BMI (mean \pm SD)	26.16 \pm 3.70
	Smoker (%)	10
	LAQ part one (mean \pm SD)	15.30 \pm 7.76
	LAQ part two (mean \pm SD)	19.83 \pm 10.85

Table 5.34 shows mean demographic scores for the control group without type 2 diabetes (n=30). BMI normal reference range is 19-25 (Garrouste-Orgeas et al., 2004). The maximum score of LAQ part one (lifestyle risk factors) is 70 and LAQ part two (stress coping) is 75. Higher LAQ scores reflect increased risk for developing chronic illnesses (Craig et al., 1996).

Key: BMI = Body mass index; LAQ = Lifestyle Appraisal Questionnaire (Craig et al., 1996); n = Sample size; SD = Standard deviation

Mean (\pm SD) scores from the MMSE and Cognistat with reference to their respective maximum score and cognitive impairment thresholds are displayed in Table 5.35. All mean scores were above their respective cognitive impairment thresholds, although the lower end of the SD crossed those thresholds for the Cognistat domains of comprehension (5.38 \pm 0.78), repetition (11.40 \pm 1.28), memory (10.67 \pm 1.92), and judgment (4.47 \pm 1.28).

Mean (\pm SD) values for HRV frequency and time domain parameters for the baseline and active states are provided in Table 5.36 and Table 5.37, respectively.

Table 5.35 Mean cognitive scores from the MMSE and Cognistat for the control group without type 2 diabetes (n=30)

		Cognitive assessment	Cognitive domain	Maximum possible score	Cognitive impairment threshold	Mean \pm SD
Control group without type 2 diabetes (n=30)	MMSE		Orientation	10	-	9.93 \pm 0.25
			Registration	3	-	3.00 \pm 0.00
			Attention	5	-	4.20 \pm 1.40
			Recall	3	-	2.80 \pm 0.41
			Language	9	-	8.13 \pm 0.97
		Total MMSE		30	≤ 23	28.07 \pm 1.98
	Cognistat		Orientation	12	<10	11.87 \pm 0.35
			Attention	8	<6	7.50 \pm 1.14
			Comprehension	6	<5	5.38 \pm 0.78
			Repetition	12	<11	11.40 \pm 1.28
			Naming	8	<7	7.63 \pm 0.61
			Construction	6	<4	5.40 \pm 0.81
			Memory	12	<10	10.67 \pm 1.92
			Calculation	4	<3	3.70 \pm 0.60
		Similarity	8	<5	7.40 \pm 1.13	
		Judgment	6	<4	4.47 \pm 1.28	
	Total Cognistat		82	<65	75.42 \pm 5.06	

Table 5.35 shows mean cognitive scores from the MMSE (Folstein et al., 1975) and the Cognistat (Kiernan et al., 1987) for the control group without type 2 diabetes (n=30). The maximum score possible and the cognitive impairment threshold are provided for each cognitive domain. Scores below the cognitive impairment threshold indicate cognitive impairment. The Cognistat domains where the lower end of the SD crossed the cognitive impairment threshold are shown in **bold**.

Key: MMSE = Mini Mental State Examination; n = Sample size; SD = Standard deviation

Table 5.36 Mean frequency domain HRV values for the control group without type 2 diabetes (n=30)

	HRV State	HRV frequency domain	Mean (\pm SD) ms ²
Control group without type 2 diabetes (n=30)	Baseline	Low frequency (absolute)	1097.28 \pm 1105.76
		High frequency (absolute)	1321.72 \pm 2515.73
		LF/HF (absolute)	1.57 \pm 1.47
		Total power (absolute)	3606.27 \pm 3595.61
		Log low frequency	2.81 \pm 0.48
		Log high frequency	2.68 \pm 0.66
		Log LF/HF	0.13 \pm 0.47
		Log total power	3.36 \pm 0.43
	Active	Low frequency (absolute)	2423.50 \pm 2096.78
		High frequency (absolute)	2191.85 \pm 3927.81
		LF/HF (absolute)	3.50 \pm 3.55
		Total power (absolute)	6583.83 \pm 7061.12
		Log low frequency	3.22 \pm 0.40
		Log high frequency	2.89 \pm 0.63
		Log LF/HF	0.34 \pm 0.44
		Log total power	3.63 \pm 0.40
	Cardiac reactivity	Low frequency (absolute)	1326.22 \pm 2054.52
		High frequency (absolute)	870.12 \pm 2747.63
		LF/HF (absolute)	1.48 \pm 3.31
		Total power (absolute)	2977.56 \pm 5819.76
		Log low frequency	0.41 \pm 0.38
		Log high frequency	0.21 \pm 0.54
		Log LF/HF	0.26 \pm 0.42
		Log total power	0.27 \pm 0.34

Table 5.36 shows mean frequency domain HRV values of the control group without type 2 diabetes (n=30) during baseline and active states. Cardiac reactivity refers to the active minus baseline HRV data.

Key: HRV = Heart rate variability; LF/HF = Low frequency divided by high frequency (sympathovagal balance); ms² = Milliseconds squared; n = Sample size; SD = Standard deviation

Table 5.37 Mean time domain HRV values for the control group without type 2 diabetes (n=30)

HRV state		HRV time domain (unit)	Mean ± SD
Control group without type 2 diabetes (n=30)	Baseline	Mean RR (ms)	888.14 ± 150.09
		SDNN (ms)	54.26 ± 21.56
		Mean heart rate (bpm)	69.64 ± 10.33
		RMSSD (ms)	46.64 ± 29.09
		pNN50 (%)	13.15 ± 17.71
		Log RMSSD (ms)	1.61 ± 0.33
		Log SDNN (ms)	1.72 ± 0.21
	Active	Mean RR (ms)	860.31 ± 137.43
		SDNN (ms)	71.15 ± 31.58
		Mean heart rate (bpm)	71.88 ± 10.04
		RMSSD (ms)	63.95 ± 47.43
		pNN50 (%)	14.05 ± 14.29
		Log RMSSD (ms)	1.74 ± 0.30
		Log SDNN (ms)	1.83 ± 0.20
	Cardiac reactivity	Mean RR (ms)	-27.83 ± 35.64
		SDNN (ms)	16.35 ± 27.00
		Mean heart rate (bpm)	2.24 ± 3.00
		RMSSD (ms)	16.38 ± 37.62
		pNN50 (%)	-0.40 ± 7.04
		Log RMSSD (ms)	0.13 ± 0.25
		Log SDNN (ms)	0.11 ± 0.16

Table 5.37 shows mean time domain HRV values for the control group without type 2 diabetes (n=30) during baseline and active states. Cardiac reactivity refers to the active minus baseline HRV data.

Key: bpm = Beats per minute; HRV = Heart rate variability; ms = Milliseconds; n = Sample size; pNN50 = Total number of interval differences (greater than 50 milliseconds) of consecutive NN (beat to beat) intervals divided by the total number of NN intervals; RMSSD = Square root of the mean squared differences of successive NN intervals; RR = Duration in milliseconds from one R peak to the next R peak of the electrocardiogram; SD = Standard deviation; SDNN = SD of all NN intervals (the square root of variance)

Dependent sample t-tests were performed to determine significant differences in HRV data between the baseline and active (cognitive task) states (Table 5.38).

Table 5.38 Dependent sample t-test between baseline and active HRV states for the control group without type 2 diabetes (n=30)

	Variable (unit)	t	df	p	Baseline mean ± SD	Active mean ± SD	Mean difference (active – baseline)
Control group without type 2 diabetes (n=30)	Mean RR (ms)	4.28	29	<0.001	888.14 ± 150.09	860.31 ± 137.43	-27.83
	Mean heart rate (bpm)	-4.09	29	<0.001	69.64 ± 10.33	71.88 ± 10.04	2.24
	Log LF (ms ²)	-5.91	29	<0.001	2.81 ± 0.48	3.22 ± 0.40	0.41
	Log HF (ms ²)	-2.09	29	0.045	2.68 ± 0.66	2.89 ± 0.63	0.21
	Log LF/HF	-2.36	29	0.03	0.13 ± 0.47	0.34 ± 0.44	0.21
	Log total power (ms ²)	-4.28	29	<0.001	3.36 ± 0.43	3.63 ± 0.40	0.27
	Log SDNN (ms)	-3.78	29	0.001	1.72 ± 0.21	1.83 ± 0.20	0.11
	Log RMSSD (ms)	-2.91	29	0.01	1.61 ± 0.33	1.74 ± 0.30	0.13

Table 5.38 displays significant results from a dependent sample t-test between baseline and active HRV states for the control group without type 2 diabetes (n=30).

Key: bpm = Beats per minute; df= Degrees of freedom; HF = High frequency; HRV = Heart rate variability; LF = Low frequency; LF/HF = Low frequency divided by high frequency (sympathovagal balance); ms = Milliseconds; ms² = Milliseconds squared; n = Sample size; p = Level of statistical significance (p<0.05); RMSSD = Square root of the mean squared differences of successive NN intervals; RR = Duration in milliseconds from one R peak to the next R peak of the electrocardiogram; SD = Standard deviation; SDNN = Standard deviation of all NN intervals (the square root of variance); t = T statistic

Pearson’s bivariate and partial correlations were performed between HRV and cognitive scores to address aims 1 and 5. A negative correlation was identified between total MMSE score and baseline mean HR (r=-0.38, p=0.04).

A positive partial correlation was identified between calculation (Cognistat) and log baseline LF/HF (r=0.40, p=0.04), yet negatively correlated between judgment (Cognistat)

and log baseline LF/HF ($r=-0.53$, $p=0.004$), when controlled for LAQ part one and part two.

5.1.6.1 Type 2 DM (n=38) and the control group (n=30)

Mean cognitive scores (Cognistat and MMSE) for the type 2 diabetes and control group without type 2 diabetes are displayed in Figure 5.4

Figure 5.4 Mean cognitive scores (Cognistat and MMSE) for the type 2 diabetes (n=38) and control group without type 2 diabetes (n=30)

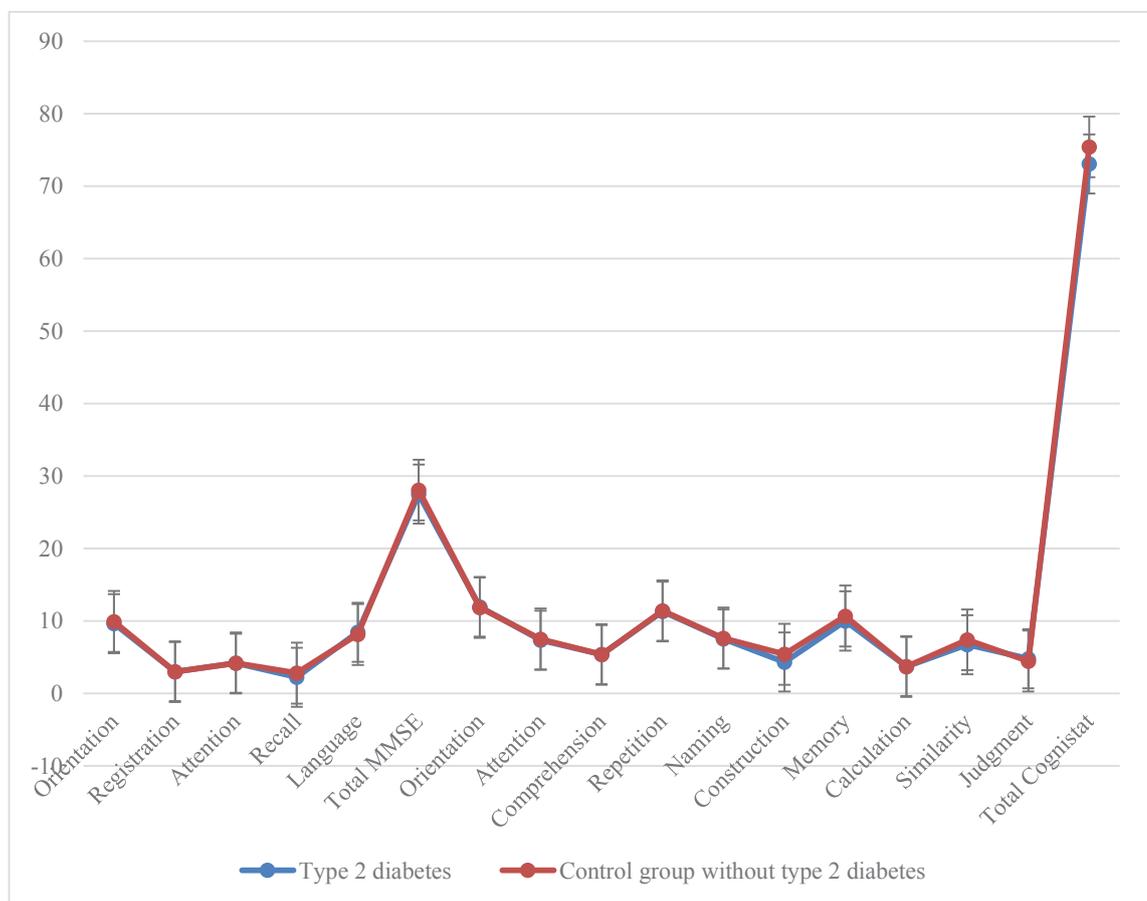


Figure 5.4 displays mean cognitive scores (Cognistat (Kiernan et al., 1987) and MMSE (Folstein et al., 1975)) for the type 2 diabetes (n=38) and control group without type 2 diabetes (n=30).

MMSE = Mini Mental State Examination

Observations were made to compare the previously conducted dependent sample t-tests between baseline and active HRV states in the type 2 DM group and control group (Table 5.32 and Table 5.38). It was observed that mean RR fell significantly across both groups

whereas mean HR, log TP, log SDNN and log RMSSD all increased significantly within the type 2 diabetes group and the control group. Log LF, log HF and log LF/HF all significantly rose in the control group yet were not found to be statistically significantly different between baseline and active states in subjects with type 2 diabetes.

An independent sample t-test was used to compare cognitive scores between subjects with type 2 DM and the control group. Orientation (MMSE) was significantly higher in the control group (9.93 ± 0.25) than the clinical sample (9.63 ± 0.59) ($t=2.62$, $df=66$, $p=0.01$, Levene's test $p<0.001$ (equal variances not assumed)).

An independent sample t-test with covariates was used to compare cognitive scores between subjects with the type 2 diabetes sample and the control group (Table 5.39).

Table 5.39 Independent sample t-test with covariates of cognitive scores between the subjects with type 2 diabetes and the control group

	Covariate	Variable	F	df	p	Control mean ± SD	Clinical mean ± SD	Mean difference (clinical - control)
Type 2 diabetes and control	Years of education, age and LAQ part one (lifestyle risk factors)	Recall MMSE	5.67	2, 56	0.003	2.80 ± 0.41	2.24 ± 0.75	-0.56
		Construction Cognistat	6.21	2, 56	0.003	5.40 ± 0.81	4.34 ± 1.22	-1.06
	Years of education and smoking status	Total MMSE	8.66	2, 56	<0.001	28.07 ± 1.98	27.50 ± 1.76	-0.57
	Smoking status	Language MMSE	4.76	2, 62	0.03	8.13 ± 0.97	8.45 ± 0.69	0.32
	BMI	Similarity Cognistat	7.04	2, 64	0.01	6.72 ± 1.33	7.40 ± 1.13	0.68

Table 5.39 displays significant results from independent sample t-tests with covariates of cognitive scores (from the MMSE (Folstein et al., 1975) and Cognistat (Kiernan et al., 1987)) between subjects with type 2 diabetes (n=38) and the control group (n=30).

Key: BMI = Body mass index; df = Degrees of freedom; F = F statistic; LAQ = Lifestyle Appraisal Questionnaire (Craig et al., 1996); MMSE = Mini Mental State Examination; n = Sample size; p = Level of statistical significance (p<0.05); SD = Standard deviation

Independent sample t-tests were used to compare HRV values between subjects with type 2 diabetes and the control group (Table 5.40).

Table 5.40 Independent sample t-test of HRV values between subjects with type 2 diabetes and the control group

	Variable (unit)	t	df	p	Control mean ± SD	Clinical mean ± SD	Mean difference (clinical – control)
Type 2 diabetes and control	Baseline mean RR (ms)	2.58	66	0.01	888.14 ± 150.09	811.03 ± 94.81	-77.11
	Baseline mean heart rate (bpm)	-2.54	66	0.01	69.64 ± 10.33	75.64 ± 9.13	6.00
	Log baseline LF/HF	2.24	66	0.03	0.13 ± 0.47	-0.12 ± 0.44	0.01
	Active mean RR (ms)	2.71	66	0.01	860.31 ± 137.43	783.59 ± 96.15	-76.72
	Active mean heart rate (bpm)	-2.74	66	0.01	71.88 ± 10.04	78.64 ± 10.11	6.76

Table 5.40 displays significant results from independent sample t-tests of HRV values between subjects with type 2 diabetes (n=38) and the control group (n=30).

Key: bpm = Beats per minute; df = Degrees of freedom; HRV = Heart rate variability; LF/HF = Low frequency divided by high frequency (sympathovagal balance); ms = Milliseconds; n = Sample size; p = Level of statistical significance (p<0.05); RR = Duration in milliseconds from one R peak to the next R peak of the electrocardiogram; SD = Standard deviation; t = T statistic

An independent sample t-test with covariates was used to compare HRV values between subjects with type 2 DM and the control group (Table 5.41).

Table 5.41 Independent sample t-test with covariates of HRV values between subjects with type 2 diabetes and the control group

	Covariate	Variable (unit)	F	df	p	Control mean ± SD	Clinical mean ± SD	Mean difference (clinical – control)
Type 2 diabetes and control	Smoking status	Active pNN50 (%)	13.64	2, 62	0.03	14.05 ± 14.29	8.73 ± 12.50	-5.32
	Age	Log active LF/HF	6.73	2, 65	0.03	0.34 ± 0.44	0.01 ± 0.43	-0.33
	Sex	CR pNN50 (%)	6.20	2, 62	0.02	-0.40 ± 7.04	1.00 ± 4.89	0.60

Table 5.41 displays significant results from independent sample t-tests with covariates of HRV values between subjects with type 2 diabetes (n=38) and the control group (n=30).

Key: CR = Cardiac reactivity; df = Degrees of freedom; F = F statistic; HRV = Heart rate variability; LF/HF = Low frequency divided by high frequency (sympathovagal balance); n = Sample size; p = Level of statistical significance (p<0.05); pNN50 = Total number of interval differences (greater than 50 milliseconds) of consecutive NN (beat to beat) intervals divided by the total number of NN intervals

No matching correlations were found between the same variables in the type 2 diabetes and control groups to perform a Z score comparison.

5.1.7 Hypertension (n=39)

Mean (\pm SD) demographics for the subjects with hypertension (n=39) are provided in Table 5.42.

Table 5.42 Mean sample demographics for subjects with hypertension (n=39)

Demographics		Value
Hypertension (n=39)	Years of age (mean \pm SD)	59.88 \pm 14.94
	Male (%)	67.50
	Years of education (mean \pm SD)	16.53 \pm 3.42
	BMI (mean \pm SD)	28.01 \pm 5.86
	Smoker (%)	2.50
	Medicated (%)	92
	LAQ part one (mean \pm SD)	19.30 \pm 5.63
	LAQ part two (mean \pm SD)	18.62 \pm 11.47

Table 5.42 shows mean demographic scores for subjects with hypertension (n=39). BMI normal reference range is 19-25 (Garrouste-Orgeas et al., 2004). 92% were taking antihypertensive medications. The maximum score of LAQ part one (lifestyle risk factors) is 70 and LAQ part two (stress coping) is 75. Higher LAQ scores reflect increased risk for developing chronic illnesses (Craig et al., 1996).

Key: BMI = Body mass index; LAQ = Lifestyle Appraisal Questionnaire (Craig et al., 1996); n = Sample size; SD = Standard deviation

Mean (\pm SD) scores from the MMSE and Cognistat with reference to their respective maximum score and cognitive impairment thresholds are displayed in Table 5.43. All mean scores were above their respective cognitive impairment thresholds, although the lower end of the SD crossed those thresholds for the Cognistat domains of construction (4.67 \pm 0.94) and memory (10.39 \pm 1.89).

Mean (\pm SD) values for HRV frequency and time domain parameters for baseline and active states are provided in Table 5.44 and Table 5.45, respectively.

Table 5.43 Mean cognitive scores from the MMSE and Cognistat for subjects with hypertension (n=39)

		Cognitive assessment	Cognitive domain	Maximum possible score	Cognitive impairment threshold	Mean ± SD
Hypertension n=39	MMSE		Orientation	10	-	9.67 ± 0.48
			Registration	3	-	3.00 ± 0.00
			Attention	5	-	4.49 ± 0.79
			Recall	3	-	2.46 ± 0.76
			Language	9	-	8.46 ± 0.66
		Total MMSE		30	≤23	28.08 ± 1.42
	Cognistat		Orientation	12	<10	11.90 ± 0.31
			Attention	8	<6	7.64 ± 0.74
			Comprehension	6	<5	5.54 ± 0.53
			Repetition	12	<11	11.95 ± 0.22
			Naming	8	<7	7.95 ± 0.22
			Construction	6	<4	4.67 ± 0.94
			Memory	12	<10	10.39 ± 1.89
			Calculation	4	<3	3.73 ± 0.59
		Similarity	8	<5	7.28 ± 0.10	
		Judgment	6	<4	4.89 ± 0.67	
	Total Cognistat		82	<65	75.92 ± 2.94	

Table 5.43 shows mean cognitive scores from the MMSE (Folstein et al., 1975) and the Cognistat (Kiernan et al., 1987) for subjects with hypertension (n=39). The maximum score possible and the cognitive impairment threshold are provided for each cognitive domain. Scores below the cognitive impairment threshold indicate cognitive impairment. The Cognistat domains where the lower end of the SD crossed the cognitive impairment threshold are shown in **bold**.

Key: MMSE = Mini Mental State Examination; n = Sample size; SD = Standard deviation

Table 5.44 Mean frequency domain HRV values for subjects with hypertension (n=39)

HRV State		HRV frequency domain	Mean (\pm SD) ms ²
Hypertension n=39	Baseline	Low frequency (absolute)	1408.05 \pm 2057.06
		High frequency (absolute)	1841.72 \pm 3063.88
		LF/HF (absolute)	1.37 \pm 1.54
		Total power (absolute)	5565.05 \pm 10368.94
		Log low frequency	2.79 \pm 0.73
		Log high frequency	2.83 \pm 0.83
		Log LF/HF	-0.05 \pm 0.57
		Log total power	3.39 \pm 0.69
	Active	Low frequency (absolute)	2310.28 \pm 2508.23
		High frequency (absolute)	2764.39 \pm 3427.61
		LF/HF (absolute)	1.85 \pm 2.18
		Total power (absolute)	6155.26 \pm 6597.98
		Log low frequency	3.12 \pm 0.59
		Log high frequency	3.09 \pm 0.79
		Log LF/HF	0.03 \pm 0.47
		Log total power	3.67 \pm 0.52
	Cardiac reactivity	Low frequency (absolute)	702.04 \pm 2524.63
		High frequency (absolute)	482.80 \pm 2731.62
		LF/HF (absolute)	0.35 \pm 1.81
		Total power (absolute)	2938.27 \pm 8898.84
		Log low frequency	0.33 \pm 0.61
		Log high frequency	0.26 \pm 0.70
		Log LF/HF	0.16 \pm 0.44
		Log total power	0.33 \pm 0.51

Table 5.44 shows mean frequency domain HRV values for subjects with hypertension (n=39) during baseline and active states. Cardiac reactivity refers to the active minus baseline HRV data.

Key: HRV = Heart rate variability; LF/HF = Low frequency divided by high frequency (sympathovagal balance); ms² = Milliseconds squared; n = Sample size; SD = Standard deviation

Table 5.45 Mean time domain HRV values for subjects with hypertension (n=39)

HRV state		HRV time domain (unit)	Mean ± SD
Hypertension n=39	Baseline	Mean RR (ms)	863.89 ± 122.90
		SDNN (ms)	69.86 ± 51.73
		Mean heart rate (bpm)	70.62 ± 10.81
		RMSSD (ms)	83.86 ± 81.12
		pNN50 (%)	10.48 ± 12.81
		Log RMSSD (ms)	1.79 ± 0.41
		Log SDNN (ms)	1.75 ± 0.27
	Active	Mean RR (ms)	822.96 ± 112.61
		SDNN (ms)	77.15 ± 35.05
		Mean heart rate (bpm)	74.52 ± 11.19
		RMSSD (ms)	86.40 ± 52.33
		pNN50 (%)	10.62 ± 10.79
		Log RMSSD (ms)	1.88 ± 0.34
		Log SDNN (ms)	1.87 ± 0.23
	Cardiac reactivity	Mean RR (ms)	-40.93 ± 43.05
		SDNN (ms)	17.25 ± 35.61
		Mean heart rate (bpm)	3.52 ± 3.17
		RMSSD (ms)	18.26 ± 39.99
		pNN50 (%)	1.10 ± 7.23
		Log RMSSD (ms)	0.13 ± 0.29
		Log SDNN (ms)	0.12 ± 0.22

Table 5.45 shows mean time domain HRV values for subjects with hypertension (n=39) during baseline and active states. Cardiac reactivity refers to the active minus baseline HRV data.

Key: bpm = Beats per minute; HRV = Heart rate variability; ms = Milliseconds; n = Sample size; pNN50 = Total number of interval differences (greater than 50 milliseconds) of consecutive NN (beat to beat) intervals divided by the total number of NN intervals; RMSSD = Square root of the mean squared differences of successive NN intervals; RR = Duration in milliseconds from one R peak to the next R peak of the electrocardiogram; SD = Standard deviation; SDNN = SD of all NN intervals (the square root of variance)

Dependent sample t-tests were performed to determine significant differences between baseline and active (cognitive task) HRV states (Table 5.46).

Table 5.46 Dependent sample t-test between baseline and active HRV states in subjects with hypertension (n=39)

	Variable (unit)	t	df	p	Baseline mean ± SD	Active mean ± SD	Mean difference (active – baseline)
Hypertension n=39	Mean RR (ms)	5.86	37	<0.001	863.89 ± 122.90	822.96 ± 112.61	-40.93
	Mean heart rate (bpm)	-6.18	38	<0.001	70.62 ± 10.81	74.52 ± 11.19	3.90
	Log LF (ms ²)	-3.39	38	0.002	2.79 ± 0.73	3.12 ± 0.59	0.33
	Log HF (ms ²)	-0.28	38	0.03	2.83 ± 0.83	3.09 ± 0.79	0.26
	Log total power (ms ²)	-2.78	38	0.01	3.39 ± 0.69	3.67 ± 0.52	0.28
	Log SDNN (ms)	-3.42	37	0.002	1.75 ± 0.27	1.87 ± 0.23	0.12

Table 5.46 displays significant results from a dependent sample t-test between baseline and active HRV states for subjects with hypertension (n=39).

Key: bpm = Beats per minute; df = Degrees of freedom; HF = High frequency; HRV = Heart rate variability; LF = Low frequency; ms = Milliseconds; ms² = Milliseconds squared; n = Sample size; p = Level of statistical significance (p<0.05); RR = Duration in milliseconds from one R peak to the next R peak of the electrocardiogram; SDNN = Standard deviation of all NN intervals (the square root of variance); t = T statistic

Pearson’s bivariate and partial correlations were performed between HRV measures and the cognitive scores to address aims 1 and 5 (Table 5.47 and Table 5.48, respectively). After a Bonferroni correction, a hierarchical multiple regression was performed between the dependent variable (judgment (Cognistat)) and independent variables listed in Table 5.47 and Table 5.48 (Table 5.49).

Table 5.47 Pearson’s correlation coefficients between cognitive scores and HRV in subjects with hypertension (n=39)

	Dependent variable	Independent variable	r	p
Hypertension n=39	Judgment Cognistat	Log baseline SDNN	-0.48	0.002
		Log baseline RMSSD	-0.38	0.02*
		Log cardiac reactivity HF	0.40	0.01
		Log cardiac reactivity total power	0.42	0.01
		Log cardiac reactivity SDNN	0.37	0.02*
		Log cardiac reactivity RMSSD	0.34	0.04*
	Total MMSE	Log cardiac reactivity SDNN	0.40	0.01
		Log cardiac reactivity RMSSD	0.38	0.02
	Language MMSE	Log cardiac reactivity RMSSD	0.45	0.01
	Attention MMSE	Log cardiac reactivity SDNN	0.34	0.04

Table 5.47 displays significant results from a Pearson’s correlation between cognitive scores (MMSE (Folstein et al., 1975) and Cognistat (Kiernan et al., 1987)) and HRV in subjects with hypertension (n=39).

Key: HF = High frequency; HRV = Heart rate variability; MMSE = Mini Mental State Examination; n = Sample size; p = Level of statistical significance ($p < 0.05$); r = Correlation coefficient; RMSSD = Square root of the mean squared differences of successive NN (beat to beat) intervals; SDNN = Standard deviation of all NN intervals (the square root of variance); * = Bonferroni correction excludes this significant correlation

Table 5.48 Partial Pearson’s correlation coefficients between cognitive scores and HRV in subjects with hypertension (n=39)

	Covariate	Dependent variable	Independent variable	r	p
Hypertension (n=39)	LAQ part one (lifestyle risk factors)	Total Cognistat	Cardiac reactivity mean heart rate	0.37	0.02
	Years of education	Judgment Cognistat	Log baseline LF	-0.41	0.01
			Log baseline HF	-0.47	0.003
			Log baseline total power	-0.44	0.01
	Number of illnesses	Total MMSE	Baseline mean heart rate	0.32	0.048
		Orientation MMSE	Baseline mean heart rate	0.40	0.01
	LAQ part two (stress coping)	Similarity Cognistat	Log cardiac reactivity SDNN	0.33	0.04*
			Log cardiac reactivity RMSSD	0.35	0.04*
	Age	Construction Cognistat	Log baseline RMSSD	-0.34	0.04
	Sex	Orientation Cognistat	Log baseline RMSSD	0.34	0.04

Table 5.48 displays significant results from a partial Pearson’s correlation between cognitive scores (MMSE (Folstein et al., 1975) and Cognistat (Kiernan et al., 1987)) and HRV in subjects with hypertension (n=39).

Key: HF = High frequency; HRV = Heart rate variability; LAQ = Lifestyle Appraisal Questionnaire (Craig et al., 1996); LF = Low frequency; MMSE = Mini Mental State Examination; n = Sample size; p = Level of statistical significance ($p < 0.05$); r = Correlation coefficient; RMSSD = Square root of the mean squared differences of successive NN (beat to beat) intervals; SDNN = Standard deviation of all NN intervals (the square root of variance); * = Bonferroni correction excludes this significant correlation

Log baseline LF, log baseline HF, log baseline TP, log baseline SDNN, log CR HF, and log CR TP (controlled for years of education) significantly predicted the judgment domain (Cognistat) in a hierarchical multiple regression model ($F(7,30)=2.54, p=0.04$). Together the independent variables explained 23% of the variability in the total Cognistat score, addressing aim 6. None of the independent variables individually added significantly to the prediction. Table 5.49 displays regression coefficients and standard errors.

Table 5.49 Hierarchical multiple regression between judgment (Cognistat) and HRV variables in subjects with hypertension (n=39)

Hypertension (n=39)	R	R square	Adjusted R square	Std. error of the estimate	p
Judgment Cognistat	0.61	0.37	0.23	0.59	0.04
	B	Std. error	Beta	t	p
(Constant)	7.02	1.12		6.27	<0.001
Log baseline LF	-0.60	0.42	-0.65	-1.42	0.17
Log baseline HF	-0.11	0.28	-0.14	-0.40	0.69
Log baseline total power	1.17	0.68	1.20	1.74	0.09
Log baseline SDNN	-2.13	1.07	-0.87	-1.99	0.06
Log cardiac reactivity HF	0.50	0.31	0.52	1.62	0.12
Log cardiac reactivity total power	-0.16	0.42	-0.12	-0.39	0.71
Years of education	-0.03	0.03	-0.15	-0.89	0.38

Table 5.49 shows a hierarchical multiple regression analysis between judgment (Cognistat (Kiernan et al., 1987)) score with HRV variables: log baseline LF, log baseline HF, log baseline total power, log baseline SDNN, log cardiac reactivity HF and log cardiac reactivity total power, controlled for years of education in subjects with hypertension (n=39).

Key: B = Unstandardised regression coefficient; Beta = Standardised regression coefficient; HF = High frequency; HRV = Heart rate variability; LF = Low frequency; n = Sample size; p = Level of statistical significance ($p < 0.05$ (in bold)); R = Correlation coefficient; R square = Proportion of variance; SDNN = Standard deviation of all NN intervals (the square root of variance); Std. = Standard; t = t statistic

5.1.8 Control group without hypertension (n=31)

Mean (\pm SD) demographics for the control group without hypertension (n=31) are provided in Table 5.50.

Table 5.50 Mean sample demographics for the control group without hypertension (n=31)

Control group without hypertension (n=31)	Demographics	Value
	Years of age (mean \pm SD)	53.52 \pm 11.83
	Male (%)	61
	Years of education (mean \pm SD)	18.74 \pm 4.32
	BMI (mean \pm SD)	26.12 \pm 3.42
	Smoker (%)	16
	LAQ part one (mean \pm SD)	15.90 \pm 7.54
	LAQ part two (mean \pm SD)	20.10 \pm 10.46

Table 5.50 shows mean demographic scores for the control group without hypertension (n=31). BMI normal reference range is 19-25 (Garrouste-Orgeas et al., 2004). The maximum score of LAQ part one (lifestyle risk factors) is 70 and LAQ part two (stress coping) is 75. Higher LAQ scores reflect increased risk for developing chronic illnesses (Craig et al., 1996).

Key: BMI = Body mass index; LAQ = Lifestyle Appraisal Questionnaire (Craig et al., 1996); n = Sample size; SD = Standard deviation

Mean (\pm SD) scores from the MMSE and Cognistat with reference to their respective maximum score and cognitive impairment thresholds are displayed in Table 5.51. All mean scores were above their respective cognitive impairment thresholds, although the lower end of the SD crossed those thresholds for the Cognistat domains of comprehension (5.44 \pm 0.76), repetition (11.42 \pm 1.23), memory (10.77 \pm 2.14) and judgment (4.71 \pm 0.91). Mean (\pm SD) values for HRV frequency and time domain parameters for baseline and active states are provided in Table 5.52 and Table 5.53, respectively.

Table 5.51 Mean cognitive scores from the MMSE and Cognistat for the control group without hypertension (n=31)

		Cognitive assessment	Cognitive domain	Maximum possible score	Cognitive impairment threshold	Mean ± SD
Control group without hypertension n=31	MMSE		Orientation	10	-	9.94 ± 0.25
			Registration	3	-	3.00 ± 0.00
			Attention	5	-	4.23 ± 1.33
			Recall	3	-	2.77 ± 0.43
			Language	9	-	8.29 ± 0.85
		Total MMSE		30	≤23	28.23 ± 1.86
	Cognistat		Orientation	12	<10	11.90 ± 0.30
			Attention	8	<6	7.39 ± 1.23
			Comprehension	6	<5	5.44 ± 0.76
			Repetition	12	<11	11.42 ± 1.23
			Naming	8	<7	7.65 ± 0.61
			Construction	6	<4	5.26 ± 0.82
			Memory	12	<10	10.77 ± 2.14
			Calculation	4	<3	3.77 ± 0.50
		Similarity	8	<5	7.10 ± 1.11	
		Judgment	6	<4	4.71 ± 0.91	
	Total Cognistat		82	<65	75.40 ± 5.25	

Table 5.51 shows mean cognitive scores from the MMSE (Folstein et al., 1975) and the Cognistat (Kiernan et al., 1987) for the control group without hypertension (n=31). The maximum score possible and the cognitive impairment threshold are provided for each cognitive domain. Scores below the cognitive impairment threshold indicate cognitive impairment. The Cognistat domains where the lower end of the SD crossed the cognitive impairment threshold are shown in **bold**.

Key: MMSE = Mini Mental State Examination; n = Sample size; SD = Standard deviation

Table 5.52 Mean frequency domain HRV values for the control group without hypertension (n=31)

HRV State		HRV frequency domain	Mean (\pm SD) ms ²
Control group without hypertension n=31	Baseline	Low frequency (absolute)	1145.02 \pm 1178.17
		High frequency (absolute)	703.31 \pm 806.04
		LF/HF (absolute)	2.29 \pm 2.43
		Total power (absolute)	3220.37 \pm 2647.11
		Log low frequency	2.81 \pm 0.52
		Log high frequency	2.56 \pm 0.55
		Log LF/HF	0.25 \pm 0.38
		Log total power	3.34 \pm 0.42
	Active	Low frequency (absolute)	2276.65 \pm 1922.77
		High frequency (absolute)	1735.82 \pm 3103.94
		LF/HF (absolute)	3.64 \pm 3.34
		Total power (absolute)	6021.97 \pm 6004.58
		Log low frequency	3.25 \pm 0.33
		Log high frequency	2.82 \pm 0.64
		Log LF/HF	0.40 \pm 0.39
		Log total power	3.63 \pm 0.37
	Cardiac reactivity	Low frequency (absolute)	1131.62 \pm 1997.01
		High frequency (absolute)	1032.51 \pm 2790.62
		LF/HF (absolute)	0.89 \pm 3.60
		Total power (absolute)	2801.60 \pm 5799.12
		Log low frequency	0.41 \pm 0.42
		Log high frequency	0.26 \pm 0.51
		Log LF/HF	0.15 \pm 0.43
		Log total power	0.25 \pm 0.31

Table 5.52 shows mean frequency domain HRV values for the control group without hypertension (n=31) during baseline and active states. Cardiac reactivity refers to the active minus baseline HRV data.

Key: HRV = Heart rate variability; LF/HF = Low frequency divided by high frequency (sympathovagal balance); ms² = Milliseconds squared; n = Sample size; SD = Standard deviation

Table 5.53 Mean time domain HRV values for the control group without hypertension (n=31)

HRV state		HRV time domain (unit)	Mean ± SD
Control group without hypertension n=31	Baseline	Mean RR (ms)	856.53 ± 121.58
		SDNN (ms)	56.00 ± 22.11
		Mean heart rate (bpm)	71.58 ± 8.95
		RMSSD (ms)	43.69 ± 28.60
		pNN50 (%)	11.85 ± 16.55
		Log RMSSD (ms)	1.55 ± 0.29
		Log SDNN (ms)	1.71 ± 0.19
	Active	Mean RR (ms)	832.78 ± 114.05
		SDNN (ms)	71.86 ± 27.02
		Mean heart rate (bpm)	73.81 ± 9.25
		RMSSD (ms)	60.84 ± 39.62
		pNN50 (%)	14.33 ± 14.52
		Log RMSSD (ms)	1.71 ± 0.27
		Log SDNN (ms)	1.83 ± 0.16
	Cardiac reactivity	Mean RR (ms)	-23.75 ± 41.95
		SDNN (ms)	15.86 ± 22.51
		Mean heart rate (bpm)	2.23 ± 3.78
		RMSSD (ms)	17.15 ± 29.96
		pNN50 (%)	1.28 ± 8.35
		Log RMSSD (ms)	0.16 ± 0.22
		Log SDNN (ms)	0.12 ± 0.14

Table 5.53 shows mean time domain HRV values for the control group without hypertension (n=31) during baseline and active states. Cardiac reactivity refers to the active minus baseline HRV data.

Key: bpm = Beats per minute; HRV = Heart rate variability; ms = Milliseconds; n = Sample size; pNN50 = Total number of interval differences (greater than 50 milliseconds) of consecutive NN (beat to beat) intervals divided by the total number of NN intervals; RMSSD = Square root of the mean squared differences of successive NN intervals; RR = Duration in milliseconds from one R peak to the next R peak of the electrocardiogram; SD = Standard deviation; SDNN = SD of all NN intervals (the square root of variance)

Dependent sample t-tests were performed to determine significant differences between HRV data in the baseline and active (cognitive task) states (Table 5.54).

Table 5.54 Dependent sample t-test between baseline and active HRV states for the control group without hypertension (n=31)

	Variable (unit)	t	df	p	Baseline mean ± SD	Active mean ± SD	Mean difference (active – baseline)
Control group without hypertension n=31	Mean RR (ms)	3.51	30	0.004	856.53 ± 121.58	832.78 ± 114.05	-23.75
	Mean heart rate (bpm)	-3.28	30	0.003	71.58 ± 8.95	73.81 ± 9.25	2.23
	Log LF (ms ²)	-5.19	29	<0.001	2.81 ± 0.52	3.25 ± 0.33	0.44
	Log HF (ms ²)	-2.84	30	0.01	2.56 ± 0.55	2.85 ± 0.64	0.29
	Log total power (ms ²)	-4.19	30	<0.001	3.34 ± 0.42	3.63 ± 0.37	0.29
	Log SDNN (ms)	-4.52	30	<0.001	1.71 ± 0.19	1.83 ± 0.16	0.12
	Log RMSSD (ms)	-3.90	30	<0.001	1.55 ± 0.29	1.71 ± 0.27	0.16

Table 5.54 displays significant results from a dependent sample t-test between baseline and active HRV states for the control group without hypertension (n=31).

Key: bpm = Beats per minute; df = Degrees of freedom; HF = High frequency; HRV = Heart rate variability; LF = Low frequency; ms = Milliseconds; ms² = Milliseconds squared; n = Sample size; p = Level of statistical significance (p<0.05); RMSSD = Square root of the mean squared differences of successive NN intervals; RR = Duration in milliseconds from one R peak to the next R peak of the electrocardiogram; SD = Standard deviation; SDNN = Standard deviation of all NN intervals (the square root of variance); t = T statistic

Pearson’s bivariate and partial correlations were performed between HRV and cognitive scores to address aims 1 and 5 (Table 5.55 and Table 5.56, respectively).

After a Bonferroni correction, a multiple regression was performed between the dependent variable (orientation MMSE) and independent variables listed in Table 5.55 to address aim 6 (Table 5.57).

Table 5.55 Pearson’s correlation coefficients between cognitive scores and HRV in the control group without hypertension (n=31)

	Dependent variable	Independent variable	r	p
Control group without hypertension n=31	Orientation MMSE	Log cardiac reactivity LF	-0.49	0.01
		Log cardiac reactivity HF	-0.53	0.002
		Log cardiac reactivity SDNN	-0.45	0.01
	Comprehension Cognistat	Log cardiac reactivity RMSSD	0.39	0.03
	Repetition Cognistat	Log cardiac reactivity RMSSD	0.37	0.04
	Memory Cognistat	Log cardiac reactivity LF/HF	-0.37	0.04
	Calculation Cognistat	Cardiac reactivity mean heart rate	-0.37	0.04

Table 5.55 displays significant results from a Pearson’s correlation between cognitive scores (MMSE (Folstein et al., 1975) and Cognistat (Kiernan et al., 1987)) and HRV in the control group without hypertension (n=31).

Key: HF = High frequency; HRV = Heart rate variability; LF = Low frequency; LF/HF = Low frequency divided by high frequency (sympathovagal balance); MMSE = Mini Mental State Examination; n = Sample size; p = Level of statistical significance (p<0.05); r = Correlation coefficient; RMSSD = Square root of the mean squared differences of successive NN (beat to beat) intervals; SDNN = Standard deviation of all NN intervals (the square root of variance)

Table 5.56 Partial Pearson’s correlation coefficients between cognitive scores and HRV in the control group without hypertension (n=31)

	Covariate	Dependent variable	Independent variable	r	p
Control group without hypertension n=31	Smoking status	Attention Cognistat	Log baseline HF	0.47	0.01
	Sex	Orientation MMSE	Log cardiac reactivity total power	-0.42	0.02
		Judgment Cognistat	Baseline pNN50	-0.38	0.04

Table 5.56 displays significant results from a partial Pearson’s correlation between cognitive scores (MMSE (Folstein et al., 1975) and Cognistat (Kiernan et al., 1987)) and HRV in the control group without hypertension (n=31).

Key: HF = High frequency; HRV = Heart rate variability; MMSE = Mini Mental State Examination; n = Sample size; p = Level of statistical significance ($p < 0.05$); pNN50 = Total number of interval differences (greater than 50 milliseconds) of consecutive NN (beat to beat) intervals divided by the total number of NN intervals; r = Correlation coefficient

Log CR LF, log CR HF, and log CR SDNN significantly predicted orientation MMSE score in a multiple regression model ($F(3,27)=4.37, p=0.01$). Together, the independent variables explain 25% of the variability of the orientation MMSE score. None of the independent variables added statistically significantly to the prediction model. Table 5.57 displays regression coefficients and standard errors.

Table 5.57 Multiple regression between orientation (MMSE) and HRV variables in the control group without hypertension (n=31)

Control group without hypertension (n=31)	R	R square	Adjusted R square	Std. error of the estimate	p
Orientation MMSE	0.57	0.33	0.25	0.22	0.01
	B	Std. error	Beta	t	p
(Constant)	10.05	0.05		184.60	<0.001
Log cardiac reactivity LF	-0.12	0.21	-0.21	-0.59	0.56
Log cardiac reactivity HF	-0.18	0.10	-0.36	-1.82	0.08
Log cardiac reactivity SDNN	-0.13	0.57	-0.08	-0.24	0.82

Table 5.57 shows a multiple regression analysis between orientation (MMSE (Folstein et al., 1975)) score with HRV variables: log cardiac reactivity LF, log cardiac reactivity HF, log cardiac reactivity SDNN in the control group without hypertension (n=31).

Key: B = Unstandardised regression coefficient; Beta = Standardised regression coefficient; HF = High frequency; HRV = Heart rate variability; LF = Low frequency; MMSE = Mini Mental State Examination; n = Sample size; p = Level of statistical significance ($p < 0.05$ (in bold)); R = Correlation coefficient; R square = Proportion of variance; SDNN = Standard deviation of all NN intervals (the square root of variance); Std. = Standard; t = t statistic

5.1.8.1 Hypertension (n=39) and the control group (n=31)

Mean cognitive scores (Cognistat and MMSE) for the hypertension and control group without hypertension are displayed in Figure 5.5.

Figure 5.5 Mean cognitive scores (Cognistat and MMSE) for the hypertension (n=39) and control group without hypertension (n=31)

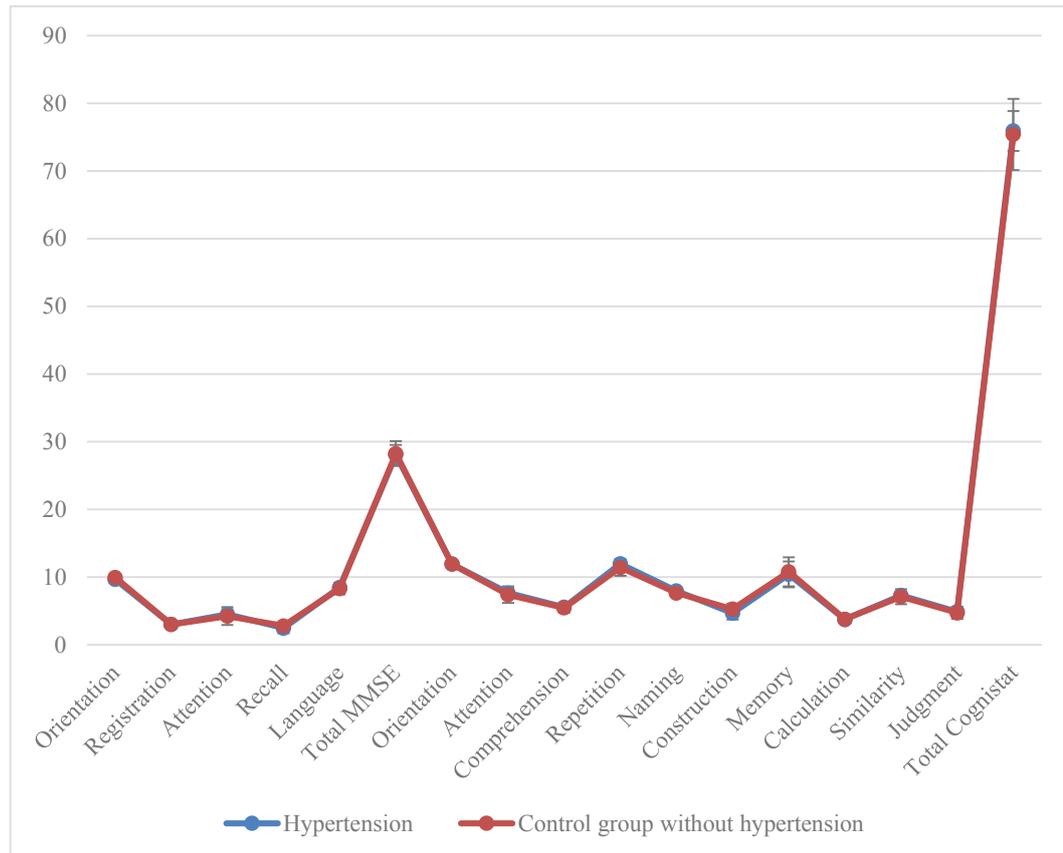


Figure 5.5 displays mean cognitive scores (Cognistat (Kiernan et al., 1987) and MMSE (Folstein et al., 1975)) for the hypertension (n=39) and control group without hypertension (n=31).

MMSE = Mini Mental State Examination

A dependent sample t-test was used to compare HRV data between the baseline and active states in the hypertension and control groups (Table 5.46 and Table 5.54). It was observed that mean RR fell significantly across both groups and, mean HR, log LF, log HF, log TP and, log SDNN all increased significantly. Log RMSSD increased significantly in the control group yet was not found to be statistically significantly different between the baseline and active states in the hypertension group.

An independent sample t-test was used to compare cognitive scores between the hypertension sample and the control group. Repetition (Cognistat) score was significantly higher in the hypertension group (11.95 ± 0.22) than the control group (11.42 ± 1.23) ($t=-2.36$, $df=31.57$, $p=0.03$, Levene's test $p<0.001$ (equal variances not assumed)). Orientation (MMSE) was also significantly different between the hypertension group (11.90 ± 0.31) and the control group (11.90 ± 0.30), although it is not clear which group had higher or lower values as the mean was the same ($t=3.03$, $df=59.69$, $p=0.004$, Levene's test $p<0.001$ (equal variances not assumed)).

An independent sample t-test with covariates was used to compare cognitive scores between the hypertension and the control groups (Table 5.58).

Table 5.58 Independent sample t-test with covariates of cognitive scores between subjects with hypertension (n=39) and the control group (n=31)

	Covariate	Variable	F	df	p	Control mean ± SD	Clinical mean ± SD	Mean difference (clinical – control)
Hypertension and control	Smoking status	Attention MMSE	4.17	1, 67	0.045	4.23 ± 1.33	4.49 ± 0.79	0.26
	Years of education	Naming Cognistat	8.34	2, 59	0.004	7.65 ± 0.61	7.95 ± 0.22	0.30
	LAQ part one (lifestyle risk factors) and age	Construction Cognistat	7.06	2, 67	0.04	5.26 ± 0.82	4.67 ± 0.94	-0.59

Table 5.58 displays significant results from independent sample t-tests with covariates of cognitive scores (from the MMSE (Folstein et al., 1975) and Cognistat (Kiernan et al., 1987)) between the hypertension group (n=39) and the control group (n=31).

Key: df = Degrees of freedom; F = F statistic; LAQ = Lifestyle Appraisal Questionnaire (Craig et al., 1996); MMSE = Mini Mental State Examination; n = Sample size; p = Level of statistical significance (p<0.05); SD = Standard deviation

An independent sample t-test was used to compare HRV values between the hypertension group and the control group. The hypertension group had significantly higher log baseline RMSSD (t=2.70, df=68, p=0.01) (1.79 ± 0.41 ms) and log active RMSSD (t=2.34, df=68, p=0.02) (1.88 ± 0.34 ms) than the control group (1.55 ± 0.29 ms; 1.71 ± 0.27 ms, respectively).

An independent sample t-test with covariates compared HRV values between the hypertension group and the control group. The control group showed higher log baseline LF/HF (F=7.39, df=2, 64, p=0.001) (0.25 ± 0.42 ms²) (controlled for age) and log active LF/HF (F=11.38, df=2, 67, p=0.003) (0.40 ± 0.39 ms²) (controlled for LAQ part one and age) than the hypertension sample (-0.05 ± 0.57 ms², 0.03 ± 0.47 ms², respectively).

There were no matching correlations found between the same variables in the hypertension and control groups to perform a Z score comparison.

5.2 Discussion: HRV and cognition (clinical groups)

This chapter explores the relationships between HRV (including HR) and cognition in participants with depression, DM (type 1 and 2) and hypertension, and compares findings to a sex- and age-matched healthy control group. Each of these clinical groups has been associated with an increased risk of developing autonomic neuropathy (which may be reflected in HRV) and cognitive impairment. Data in the smaller groups (depression (n=10) and type 1 DM (n=9)) was examined using non-parametric statistics.

5.2.1 Depression (n=10)

In line with the literature, in the depressed sample, HR increased after cognitive interaction (baseline versus active neutral conversation), accompanied by a corresponding drop in mean RR intervals (Simpson et al., 2001, Fleiss et al., 1992). Increases in HR promote blood flow and thereby metabolic substrates to the brain in response to cerebral activation and neuronal demand (Kennedy and Scholey, 2000). Several experiments by Thayer's laboratory have previously linked increased anxiety and affective disorders (such as depression) to higher HR and lower HRV (Brosschot et al., 2006, Lyonfields et al., 1995, Thayer et al., 1996). Other research has shown various ANS changes occur in affective disorders, notably: vagal withdrawal and increased tonic (sympathetic) cardiac control (Liang et al., 2015, Vasudev et al., 2015, Nugent et al., 2011a, Agelink et al., 2002). Depression may also affect ANS responsivity, showing sympathetic predominance during baseline states and parasympathetic predominance in response to stressors (as shown in the present study by the significant SDNN increase from baseline to active state), as opposed to healthy controls who exhibit the opposite relationships (Liang et al., 2015). Cortisol levels are higher in depression, which also impact ANS responsivity to stressors (Taylor et al., 2006, Ahrens et al., 2008).

Others report no significant differences in vagal activity (HF) between depressed and non-depressed samples (Udupa et al., 2007, Volkers et al., 2003). The contention in the literature may be attributed to disparities in sample size and methodological considerations such as length of the ECG recording, type of HRV measure, controlling for covariates, etc. Interestingly, these same changes in autonomic activity are also risk factors for cognitive decline, as previously detailed in section 1.2.4.3 and 1.3.3.

The present study identified better comprehension skills (Cognistat) were linked to declines in CR SDNN. CR of SDNN reflects changes in overall HRV activity (Task Force of The European Society of Cardiology and The North American Society of Pacing and Electrophysiology, 1996). Negative values correspond to decreases from baseline to active state. In a study by Nugent et al. (2011a), 10 depressed female participants (as well as the 7 female controls) also experienced decreases in overall HRV when performing an array of cognitive and motor tasks (mean age 32 ± 10 years) however they did not examine the effect of CR HRV on cognitive performance, as provided by the present research.

Levels of HRV have also been shown to decline upon cognitive interaction in other studies assessing healthy participants. For example, Sato and Miyake (2004) noted decreases in overall HRV measures with mental stress, albeit in a non-depressed sample ($n=28$, mean age 21 ± 2 years, 50% male). However, there is difficulty comparing HRV reactivity between experiments, as the degree of CR is dependent upon the cognitive intervention applied (e.g. the Stroop task (Stroop, 1935), public speaking tasks (Wagner et al., 2013), and mental arithmetic (Liang et al., 2015)). Further, studies differ in methodology deriving cardiac change, for example 'active state minus baseline state' or 'active state return to baseline state (recovery)' as well as the disease state and cardiac parameter (HRV, HR, or RSA) being examined.

The present study also identified negative correlations between CR LF/HF and the Cognistat domains of comprehension and construction in the depressed sample. This suggests that increased LF/HF ratio could be worse for cognitive performance. The higher LF/HF ratio was due to increases in LF of a greater magnitude than the increased in HF. In partial support of these findings, Sheffield's team (1998) reported higher depression scores were linked to greater changes in the LF/HF ratio during a public speaking task, yet did not examine cognitive performance ($n=41$, mean age 61 ± 1 years, 83% male). It is interesting to note that strikingly similar autonomic changes have been observed in both depression and poor cognitive performance (decreases in HF and increases in the LF/HF ratio) (Nugent et al., 2011a, Thayer et al., 2012, Marin et al., 2011, Reppermund et al., 2011). Increased HF activity has been linked to better cognitive scores, increased resting cerebral perfusion (as shown in neuroimaging studies) and more successful depression outcomes (particularly when utilised as a biofeedback therapeutic target) (Allen et al., 2015, Hansen et al., 2009, Siepmann et al., 2008).

Calculation performance declined as mean HR (baseline) increased (correspondingly, there was an inverse link between calculation skill and mean RR intervals). In depression, HR may be elevated by increased sympathetic cardiac control. In addition, inappropriate physiological responses to stressors may also alter neuronal environments and lead to cognitive impairment (Phillips et al., 2013, Carroll et al., 2012, Gianaros et al., 2008). Yu and Zhang's research (2012) demonstrated healthy controls exhibited the opposite response, with increases in HR benefitting mental arithmetic, as did earlier experiments (Bernardi et al., 2000, Vuksanović and Gal, 2007). These disparities suggest further research is required to better understand the effects of ANS responsivity on cognitive performance in those with clinical states of depression.

5.2.1.1 Depression (n=10) and the control group (n=10)

Both the depression group and the age and sex-matched control group exhibited increases in mean HR. SDNN increased significantly in the group with depression while LF/HF and LF both increased significantly in the control group. In contrast, Liang's recent study (2015) in a larger cohort did not find any significant differences in HRV responses to mental stress between depressed (n=156) and control groups (n=49) (mean age 24 ± 3 years, 100% male).

Despite a lack of significant differences in cognitive scores between the depressed and control group in the present study, many studies have previously established the negative effects of depression on cognitive scores, particularly cognitive skills involving the prefrontal cortex such as executive function, learning, and episodic memory (Austin, 1992, Beckwé et al., 2014, De Lissnyder et al., 2012, Hinkelmann et al., 2009). Johnco's group (2015) concluded depressed individuals (n=47, 47% male) had lower memory performance, verbal fluency, word association skills, selective attention, task switching, and total score compared to controls (n=53, 26% male) (total mean age 67 ± 5 years). In analyses on stress and cognition, sustained stress (increased cortisol and inflammatory cytokines) has been linked to increased risk of diseases such as depression, autonomic neuropathies (affecting HRV), cardiovascular disease, and cognitive decline (Juster et al., 2010, Lampert et al., 2008). As mentioned in the previous section (5.2.1), the stress hormone cortisol is elevated in depression (Rubinow et al., 1984, Brown et al., 2004) and exerts effects in various areas of the body, of particular relevance, in the prefrontal and

limbic regions of the brain. This justifies the cognitive symptoms observed in depression (O'Brien et al., 2004, Cavanagh and Shackman, 2015).

Upon comparison of HRV values, the present study revealed new findings to the existing literature, that the control group had higher CR LF/HF than the depression group. This has been indirectly supported by other researchers as studies on CR HRV in depression remain scant. Ahrens' laboratory (2008) identified depressed women (n=22) had blunted cortisol reactions to cognitive stressors (speech task and mental arithmetic) compared to matched controls (n=20), although no significant HRV differences were observed (mean age 53 ± 2 years). A meta-analysis of 18 articles involving n=673 depressed and n=407 control individuals highlighted that the LF/HF ratio and HR were higher in persons with depression, attributed to higher sympathetic and lower parasympathetic activity (Kemp et al., 2010). Salomon and others (2009) compared an array of cardiac measures during baseline and a speech and visuo-motor task between depressed participants (n=25, 20% male) and healthy controls (n=25, 32% male) (total mean age 32 ± 10 years). They observed significantly lower SBP, HR, and cardiac output reactivity in depressed participants. Additionally, depressed participants perceived the tasks as more stressful, demanding, and threatening than the controls. The authors cited a theory proposed by McEwen (1998) which suggests that the physiological under-responsiveness may reflect the allostatic load. In reference to depression, the HPA axis is over-active and thus physiological stress responses may be less responsive to compensate. These measures of reactivity suggest depressed persons may have a more blunted response to stressors, however, both papers call for further investigation in the area of CR and affective disorders.

5.2.2 Type 1 DM (n=9)

Mean HR, LF, HF, TP, SDNN, and RMSSD all significantly increased from baseline to active state in the type 1 DM group. Kuehl et al. (2015) also identified significant increases in HR in patients (albeit with type 2 diabetes) during a challenging reaction time task, yet found significant declines in HRV parameters. Most studies agree that HRV indices decline with cognitive challenge (Li et al., 2009, Byrd et al., 2014). The type of intervention used in the present analysis (active neutral conversation) may not have elicited the same response as the mental stressor tasks typically used in others research (e.g. the Stroop task (Stroop, 1935)). Active neutral conversation aims to activate an array of cognitive modalities without eliciting a stress response (such as memory, orientation, verbal reasoning) and has been shown to invoke vagal control (thought to be involved with RSA during speaking) (Potter, 2006, Turkstra, 2008, Sloan et al., 1991).

Type 1 DM involves an immune-mediated degeneration of the pancreatic beta cells, reducing production of endogenous insulin leading to increased circulating glucose levels (Gispén and Biessels, 2000). Poor glycaemic control has been linked to a plethora of immune, cardiovascular, autonomic, and cognitive changes (Koekkoek et al., 2015, Ninomiya, 2014). Many studies have established decreases in HRV indices and cognitive performance in type 1 DM, yet few have correlated the relationship between HRV and cognition in subjects with diabetes. The present study identified many positive relationships between various cognitive domains and higher vagal modulation indicated by HRV parameters: attention (Cognistat) with baseline TP and baseline SDNN; orientation (Cognistat) with baseline pNN50; Cognistat similarity, construction, and comprehension, with baseline HF; comprehension (Cognistat) with baseline RMSSD and baseline LF; judgment (Cognistat) with baseline TP; total Cognistat score with baseline TP and baseline SDNN. There is a lack of supporting literature comparing these relationships in type 1 DM samples, however, these findings are well supported by healthy samples (Thayer et al., 2009). For instance, Hansen and colleagues (2003) identified higher HRV was linked to better cognitive performance in male military personnel, particularly prefrontal skills such as executive function (n=53, age range 18-34 years). This was also supported by Mathewson et al. (2010), who identified better pictorial Stroop test performance in those with higher vagal tone, as measured by RSA activity (n=76, mean age 31 ± 11 years, 43% male) (Ekman and Friesen, 1975, Stroop, 1935).

The present study also identified positive correlations between the Cognistat variables of memory and total score with CR pNN50 in the type 1 DM group. This suggests greater increases in pNN50 (another measure of cardiac vagal tone) from baseline to active state are linked to better cognitive outcomes, which has not previously been examined by other researchers. When comparisons are drawn between healthy samples the present findings are not supported. Duschek's group (2009) examined several markers of autonomic activity (baroreflex sensitivity, r-wave to pulse intervals, RSA, and mid-frequency HRV indices) and found all parameters significantly decreased in an attentional performance test performed by participants without diabetes. They also identified a positive correlation between higher RSA reactivity and the percentage of error during the attention task, suggesting higher vagal reactivity is worse for attention skills (Duschek et al., 2009). It is proposed that the nature of the ECG recorded cognitive task (neutral conversation) used in the present study could account for these differences.

Additionally, orientation (MMSE) was positively correlated to CR mean HR, suggesting greater increases in HR may benefit performance in the orientation domain. Ginty and co-workers (2011) assessed a large community sample without diabetes and found high HR reactivity beneficial to performance in a mental arithmetic phonological memory task (n=1647, age range 24-63 years, 46% male). They also found higher HR reactivity was associated with increased IQ scores later in life. Greater HR reactivity has been linked to adaptability and appropriate responsivity to external stressors (Ginty et al., 2013, Carroll, 2011).

Higher baseline HR was also related to better construction (Cognistat) and total MMSE score. Previous research has identified increased HR in diabetes (Kahn et al., 1986, Valensi et al., 1998, Lindqvist et al., 1986), yet few have drawn links between autonomic and cognitive changes in diabetes. A study exploring HR and cognition observed an inverse relationship, with lower baseline HR linked to better accuracy in memory tasks from the Brief Test of Adult Cognition by Telephone (Tun and Lachman, 2006) (n=817, mean age 57 ± 11 years, 44% male) (Kimhy et al., 2013). The sample included n=79 (10%) type 1 DM subjects although they were controlled for by the regression model. A stratified examination of larger samples would help to clarify differences between HR and cognitive performance in DM and healthy samples.

The current study identified negative correlations between Cognistat domains of repetition and baseline RMSSD and HF, and between calculation (Cognistat) and baseline SDNN. This negative correlation was similarly found between Stroop scores (Stroop, 1935) (a measure of executive function) and RMSSD in an analysis of older women without diabetes ($n=103$, mean age 73 ± 6 years) (Martinez et al., 2014). The authors acknowledged their findings were unlike those of previous investigations and suggest longitudinal analysis to explore this relationship further. Previous research consistently identifies increased parasympathetic activity (as measured by RMSSD) is associated to better cognitive performance (de Vilhena Toledo and Junqueira, 2009, Hansen et al., 2003), while decreases in RMSSD have been correlated with slower reaction times, worse working memory performance, as well as increased white matter lesions, however there remains a lack of clinical groups explored (Galluzzi et al., 2009, Beaumont et al., 2012).

Furthermore, the current analysis identified inverse correlations between comprehension (Cognistat) and CR TP, CR SDNN, and CR RMSSD. In support of these findings, Duschek et al. (2009) noted that declines during on-task mid frequency HRV (between LF and HF) in 60 healthy subjects was linked to better attention performance, and higher RSA (vagal) reactivity was positively correlated to percentage of mistakes (mean age 25 ± 4 years, 47% male). Similarly, Yu and colleagues (2009) noted all frequency domain HRV parameters declined, and HR increased with mental arithmetic (also identified by Tanida et al. (2004)), suggesting the activation of the sympathetic nervous system. Despite a lack of literature on these relationships in diabetes, it has been shown that CR of HRV indices is reduced in type 1 DM compared to healthy controls, attributed to the complex DM complication, autonomic neuropathy (Riihimaa et al., 2002). The findings of the present study provide new data in the field of HRV and cognition in type 1 DM and future research ought to assess the degree of cardiac autonomic neuropathy and the relative effect on cognitive performance.

5.2.2.1 Type 1 DM (n=9) and the control group (n=9)

Both the type 1 DM and control groups exhibited increases in TP from baseline to active states. However, the clinical sample demonstrated significant rises in mean HR, LF, HF, SDNN, and RMSSD. Rises in HR with cognitive intervention in DM is supported by previous research (Kuehl et al., 2015). Stressful interventions (such as time and reward

tasks) have been linked to vagal withdrawal and reduction of HRV parameters whereas neutral conversation evoked a vagal response in both the clinical and control groups (Bernardi et al., 2000, Vuksanović and Gal, 2007, Kimhy et al., 2013).

No significant differences were found in cognitive scores between type 1 DM and the control group. Many studies (including longitudinal experiments and meta-analyses) disagree with these findings, presenting subtle declines in general intelligence, processing speed, mental flexibility, reduced brain volume, and increased risk of MCI and dementia in type 1 DM (Koekkoek et al., 2015, Tonoli et al., 2014, Rexroth et al., 2013, Rawlings et al., 2014a, Brands, 2005, Gaudieri, 2008, Biessels et al., 2008). Type 1 DM commonly develops in childhood, thus adults may exhibit more pronounced cognitive symptoms than type 2 DM which typically has onset later in life. Cognitive decline commences soon after diabetes onset yet the trajectory is usually a gentle deterioration thereafter (Koekkoek et al., 2015).

Complex vascular and immune changes in type 1 DM impact the neuronal environment and increase the risk of cognitive impairment. These changes include reduced capillary blood flow, increased inflammatory mediators and elevated corticosterone levels (previously detailed in section 1.2.4.2.1) (Gispén and Biessels, 2000, Zheng et al., 2014). Neuroimaging studies have identified structural and functional declines in areas such as the hippocampus (involved in memory) and the autonomic ganglia (affecting HRV) (Cameron and Cotter, 2001, Manschot et al., 2003, Sasaki et al., 1997).

Type 1 DM had significantly higher pNN50, CR SDNN and CR RMSSD than the control group. Although HRV reactivity research in type 1 DM is limited, Riihimaa et al. (2002) found the inverse relationship in a younger yet larger sample of 100 type 1 DM patients (mean age 14 ± 2 years, 53% male). They identified CR HRV was lower than controls in response to postural changes. Riihimaa et al. concluded that young type 1 DM patients have attenuated ANS reactivity. These findings were also presented by Lagi et al. (1994), showing reductions in LF, HF, and TP in 27 type 1 diabetes patients (mean age 46 ± 5 years) (compared to 20 controls, mean age 37 ± 6 years), as well as reduced CR during postural changes (sex demographics not provided). Varying links between HRV and cognition may be influenced by the small sample size of this cohort ($n=9$) which ought to be increased in future analyses.

5.2.3 Type 2 DM (n=38)

In the type 2 DM group, in line with the literature, HR rose with cognitive interaction, paired with a corresponding drop in mean RR intervals (Fleiss et al., 1992, Kuehl et al., 2015). Higher HR increases cerebral blood flow to supply metabolic substrates in response to increased neuronal activity (Kennedy and Scholey, 2000). Baseline TP, SDNN, and RMSSD (markers of vagal tone) all significantly increased in the active state. In contrast, Kuehl et al. (2015) found the HF bandwidth (also reflective of vagal tone), significantly decreased during a choice and reaction timed task in a smaller sample of eight type 2 DM subjects (mean age 50 ± 1 years, 88% male). As previously discussed (section 5.2.2), the differences in HRV changes identified may be attributed to the type of cognitive intervention (in the present study, neutral conversation).

Memory (Cognistat) was positively correlated to baseline LF, HF, TP, SDNN, and RMSSD. Orientation (MMSE) was also positively correlated to baseline LF, as was naming (Cognistat) with baseline SDNN. Increases in all of these HRV parameters suggest greater parasympathetic control of the heart at baseline benefits various domains of cognition. This relationship has been consistently demonstrated by others (Capuana et al., 2014, Mathewson et al., 2011), although rarely in participants with diabetes. The present study contributes new knowledge of HRV and cognition in this field. A recent investigation by Lopez et al. (2015) examined HRV and cognitive performance in a large sample of 10623 individuals as part of the Atherosclerosis Risk in Communities study (non-diabetic cohort) (mean age 54 years, 57% female). They found the same relationship, although in the opposite direction, that is, lower HRV (LF and LF/HF) was linked to reduced scores in word recall, digit symbol substitution and word fluency tests and suggested further research is required to explore the mechanism of the relationship.

The present study showed a positive relationship between similarity (Cognistat) and CR TP. This suggests increases in TP supported performance in similarity skills. This finding is not well supported by other studies, as there is a general decreasing shift of HRV activity during cognitive challenge (Byrd et al., 2014, Weippert et al., 2009). Active neutral conversation was used in the present study to elicit various cognitive domains without causing a stress response (Potter, 2006), as opposed to other research where mental stressors are used to evoke a physiological reaction (e.g. Stroop task (Stroop, 1935)). This methodological difference may account for the disparity of results.

Negative correlations were identified between memory (Cognistat) and CR TP, CR SDNN, and CR RMSSD, and between orientation (Cognistat) and CR LF/HF in type 2 DM. These findings are generally supported in the literature, which has shown decreases in HRV during cognitive challenge are linked to better cognitive performance, although there is a lack of research examining this relationship in diabetes. Kuehl et al. (2015) identified a significant decreasing shift of HRV upon mental stress in a smaller sample of eight type 2 diabetes subjects, yet did not explore how well they performed on a reaction time challenge (mean age 50 ± 1 years, 88% male). Mathewson's team (2010), however, did investigate this relationship in 76 healthy participants, and found greater declines in HRV upon cognitive challenge (Stroop test (Stroop, 1935)) were linked to better test performance (measured by RSA) (mean age 31 ± 11 years, 43% male). Studies suggest CR is blunted due to autonomic changes seen in DM and that higher CR (such as HR, RSA, or HRV reactivity) is an indicator of robust and responsive cardiac activity (Phillips, 2011, Mathewson et al., 2010, Lovallo, 2004, Ginty et al., 2011, Gao et al., 2015a).

5.2.3.1 Type 2 DM (n=38) and the control group (n=30)

Both the type 2 DM and control groups in the present study exhibited significant increases in mean HR, TP, SDNN, and RMSSD from baseline to active states. Also, LF, HF, and LF/HF all increased significantly in the matched sample, yet were not significantly different between baseline and active states in the type 2 DM sample. These findings are also supported in the literature with Li et al. (2014) reporting that those with type 2 diabetes (n=63, mean age 57 ± 7 years, 46% male) show reduced HRV activity over a 24 hour period than controls (n=29, mean age 52 ± 9 years, 48% male).

The control group had significantly higher orientation (MMSE), recall (MMSE), total MMSE score, construction (Cognistat), and similarity (Cognistat) compared to the type 2 DM group. Cognitive decline in type 2 DM has been well examined in systematic reviews and meta-analyses, and results support the current findings, showing significant declines in memory, processing speed, executive function and global cognitive scores (Koekkoek et al., 2015, Feinkohl et al., 2015, Strachan and Price, 2014, Ravona-Springer et al., 2014, Rawlings et al., 2014b). A prospective study by Nooyens and researchers (2010) examined 2613 men and women twice over five years, finding cognitive decline in type 2 diabetes was 2.6 times more likely than without the illness. Diabetes-related cognitive

deterioration has been likened to accelerated aging and an increased risk of AD (Yaffe et al., 2012, Twig et al., 2014, Cheng et al., 2012). However, it should be noted that the cognitive differences were subtle in the present study, all being less than one mark difference between means of the two groups. Another small but significant difference was found in language (MMSE) scores, which were significantly higher in the clinical group than the matched sample (<1 mark different). This finding is not well supported by the literature, as it is commonly seen that cognitive decline accompanies DM progression (Bruce, 2015, Moheet et al., 2015). However, not all cognitive domains are affected equally and it may be that language skills are less affected than other cognitive domains. Demonstrating this, Foster et al. (1998) found increased blood glucose levels to be beneficial to verbal memory in 30 young females (mean age 20 years). These differences ought to be further examined, taking into account blood glucose levels in larger cohorts to increase accuracy of results.

The control group presented significantly higher baseline and active LF/HF and active pNN50 than the type 2 DM group. This is well supported by other research, for example, recent work by Abubaker et al. (2014) identified that SDNN was significantly lower in type 2 DM (n=55, mean age 58 ± 11 years, 53% female) than controls (n=43, mean age 42 ± 11 years, 81% female). Singh (2000) also found HRV indices of SDNN, LF, and HF were lower in people with impaired fasting glucose levels (n=56, mean age 55 ± 1 years, 61% male) and DM (n=84, mean age 55 ± 1 years, 62% male) compared to controls (n=1779, mean age 47 ± 0.2 years, 47% male).

The type 2 DM group had significantly higher CR pNN50 and mean HR (baseline and active) than the controls. Higher CR has not been consistently identified in DM, with the majority of research highlighting the ‘blunting’ effect that diabetic autonomic neuropathy has on CR. For example, Lagi et al. (1994) examined 27 subjects with type 2 DM and 20 control subjects, finding the DM sample had lower LF as well as less responsivity when changing postures (lying and standing). Others suggest that the ANS in diabetes reacts inappropriately by physiologically over-responding to stressors, associated with a primed HPA axis, increased circulating cortisol and preponderance of sympathetic activity (Surwit and Feinglos, 1988, Champaneri et al., 2010). However, many studies agree that diabetes patients present with higher HR than healthy controls (Kahn et al., 1986, Ewing et al., 1983). They reason that higher HR is a carry-on effect of vagal withdrawal seen in diabetic autonomic neuropathy.

Increased HR has also been hypothesised to predispose individuals to metabolic syndrome and DM, based on findings from a prospective study in 614 participants over a 20 year span (mean age at commencement 43 years, 36% male) (Shigetoh et al., 2009). Awareness of baseline HR (as well as BP) is important to trigger individuals to seek medical advice, reducing risk of underlying disease progression without intervention.

5.2.4 Hypertension (n=39)

Mean HR, LF, HF, TP, and SDNN all significantly rose in the hypertension group from baseline to active states. As mentioned previously, increases in HR with cognitive intervention are well supported by other researchers (Bernardi et al., 2000, Yu and Zhang, 2012, Turner et al., 1987). The disparities between HRV activity in the present study and findings in other studies may be attributed to the type of cognitive intervention utilised, that is, neutral conversation versus mental stressors (previously explained in section 5.2.2).

Many positive correlations were identified between CR and cognitive domains: language (MMSE) and CR RMSSD; attention (MMSE) with CR SDNN; total MMSE score with CR SDNN and CR RMSSD; judgment (Cognistat) with CR HF, CR TP, CR SDNN, and CR RMSSD; orientation (Cognistat) with baseline RMSSD; and similarity (Cognistat) with CR SDNN and CR RMSSD. These correlations all support that increased HRV from baseline to active states was beneficial to cognitive performance in subjects with hypertension. Increases in all of these HRV parameters indicate dominance of parasympathetic cardiac tone (Goldberger et al., 2001, Task Force of The European Society of Cardiology and The North American Society of Pacing and Electrophysiology, 1996) and higher vagal tone has been linked to better cognitive performance (although there are no studies to date exploring HRV reactivity links with cognitive performance in participants with hypertension - the present study contributes new knowledge of HRV and cognition in this field). A study in a healthy cohort by Duschek's group (2009) is in contrast to the present findings, showing declines in vagal tone upon cognitive stimulation, and inverse correlations between vagal reactivity (measured using RSA) and attention skills (n=60, mean age 25 ± 4 years, 47% male). The lack of comparable literature suggests more research is required in the area.

Interestingly, baseline mean HR was also positively correlated with orientation (MMSE) and total MMSE score. Studies examining this relationship tend to disagree, showing higher HR increases the risk for developing cognitive dysfunction and other chronic illnesses (such as hypertension and metabolic syndrome) (Mancia et al., 2007, Grassi et al., 2009, Palatini, 2013). Additionally, total Cognistat score was inversely correlated with CR mean HR, proposing that higher HR reactivity in hypertension aids cognitive function. Ginty and colleagues (2011) found high HR reactivity beneficial to performance in a mental arithmetic phonological memory task and IQ examined 5 and 12 years later in a non-hypertensive community sample (n=1647, age range 24-63 years, 46% male).

On the other hand, negative correlations were found between judgment (Cognistat) and baseline LF, HF, TP, SDNN, and RMSSD. Construction (Cognistat) was also negatively correlated to baseline RMSSD. As multiple independent variables were correlated to the Cognistat judgment domain, a hierarchical multiple regression was performed (baseline LF, HF, TP, SDNN, CR HF, and CR TP (controlled for years of education)). Together the independent variables explained 23% of the variability in the judgment score. Despite the regression findings, there is overwhelming evidence in the literature supporting the opposite, that higher vagal tone at baseline is positively correlated to cognitive performance (Kim et al., 2006, Kimhy et al., 2013, Mathewson et al., 2011). Shehab and Abdulle (2011) also examined this relationship in white coat and borderline hypertensives, showing lower 24 hour RMSSD values were related to a greater number of errors (poorer cognitive performance) (n=69, mean age 38 ± 11 years, 51% male) (Shehab and Abdulle, 2011). Disparities in the hypertension cohort may be attributed to the small sample size and methodological differences to other research (e.g. cognitive stressor versus neutral conversation).

5.2.4.1 Hypertension (n=39) and the control group (n=31)

Mean HR, LF, HF, TP and, SDNN all significantly rose in the hypertension group and the age and sex matched control group. RMSSD increased significantly in the control group, yet was not significantly different between baseline and active states in the hypertension group. As previously discussed, increases in HR parallel cognitive interaction, yet HRV indices typically decline in cases of mental challenge in both healthy and hypertensive cohorts (Palatini et al., 2006, Byrd et al., 2014). The neutral

conversation task may have evoked different responses than a mental stressor and thus HRV responded in a different way (see earlier discussion in section 5.2.2).

The control group scored significantly higher in construction (Cognistat), while the hypertension group scored significantly higher in attention (MMSE), repetition (Cognistat), and naming (Cognistat). This is not supported by other research, with most identifying that hypertension decreases cognitive performance (Chen et al., 2015, DeCarli, 2015). Gottesman et al. (2014) assessed BP and cognition in a healthy community sample over 20 years (The Atherosclerosis Risk in Communities Neurocognitive Study), and found a significant inverse linear relationship between SBP and attention, short term memory, retrieval and global cognitive performance ($n=13476$, mean age 57 ± 6 years). Interestingly, Maillard and colleagues from the Framingham Heart Study identified increased SBP was linked to subtle vascular changes early in life, affecting white and grey matter integrity ($n=579$, mean age 39 ± 8 years, 40% male). DeCarli (2015) suggests early hypertension predisposes cognitive decline and increasing awareness and effective treatment of hypertension in younger years is crucial. Again, it should be noted that the significant cognitive differences described for the present study were all less than one cognitive score apart. Discrepancies in the data may be attributed to the small sample size and methodological differences between the studies.

The hypertension group had significantly higher baseline and active RMSSD than the controls. Again, this is not well supported by other research, which states that vagal withdrawal has been associated with increased BP and hypertension even after covariate adjustment (Thayer et al., 2010). Several large epidemiological studies also demonstrate this, showing hypertension is significantly linked to lower HF (Liao et al., 1996), LF (Singh et al., 1998), and RMSSD (Schroeder et al., 2003).

In the present study, the matched control sample showed higher baseline and active LF/HF than the hypertension group. As discussed earlier, the nature of the sympathovagal ratio may not truly reflect sympathetic and parasympathetic divisions when the LF band is not a pure reflection of sympathetic activity alone (mediated by sympathetic, parasympathetic, respiratory and baroreflex activity (Quintana and Heathers, 2014)). Thus, the clinical interpretation of the sympathovagal balance has been unclear and is advised to be used with caution (Heathers, 2012). Also, relative increases or decreases in both variables may not affect the LF/HF ratio. These observations may account for the

disparities in the literature regarding the LF/HF ratio in hypertension, some finding it higher in hypertensives (Liao et al., 1996), while others reporting it was lower (Singh et al., 1998), or that no significant difference existed (Hojo et al., 1997).

5.3 Conclusion: HRV and cognition (clinical groups)

Overall, the current study identified various associations between vagal activity and cognitive performance. Hypothesis 1, that there will be a significant direct relationship between HRV and cognitive function in clinical groups, was supported by the results. Higher baseline vagal activity, and in particular LF, was significantly and positively correlated to cognitive performance in all clinical states examined, which has been well supported by other studies in non-clinical cohorts however there is a lack of comparative literature, particularly in depression and diabetes (type 1 and 2) (Kimhy et al., 2013, Mathewson et al., 2010, de Vilhena Toledo and Junqueira, 2009). This highlights the contribution of new knowledge to the field of HRV and cognition in clinical groups. Lower vagal activity was also linked to higher cognitive scores in the type 1 DM and the hypertension groups which suggests that HRV parameters may have a different impact depending on the cognitive domain and disease state. It was also identified that HRV reactivity was mostly inversely correlated to cognitive function except in the hypertension group, partially supporting hypothesis 3 which predicts an inverse relationship would exist. These differences may be related to the different pathophysiological mechanisms of the disease cohort. Further research is therefore required to explore the mechanisms behind these differences and in the field of HRV reactivity, as it has not previously been examined in clinical groups. The present research provides the foundation for the relationships between HRV reactivity and cognitive function in clinical cohorts. Refer to Table 5.59, Table 5.60, Table 5.61, and Table 5.62 for a summary of significant results in each clinical group.

Table 5.59 Summary of significant correlations between HRV and cognitive domains in subjects with depression (n=10)

	Cognitive domain	HRV parameter			
		Baseline	HRV reactivity		
		LF	HR	LF/HF	SDNN
Cognitive test: Cognistat	Comprehension			-	-
	Construction			-	
	Memory	+			
	Calculation		-		

Table 5.59 displays significant correlations between HRV parameters and cognitive domains from the MMSE (Folstein et al., 1975) and Cognistat (Kiernan et al., 1987) in subjects with depression (n=10). HRV reactivity refers to the active minus baseline HRV data.

Key: HR = Heart rate; HRV = Heart rate variability; LF = Low frequency; LF/HF = Low frequency divided by high frequency (sympathovagal balance); MMSE = Mini Mental State Examination; SDNN = SD of all NN intervals (the square root of variance); + = Positive correlation; - = Negative correlation

Table 5.60 Summary of significant correlations between HRV and cognitive domains in subjects with type 1 diabetes (n=9)

Cognitive test	Cognitive domain	HRV parameter						
		Baseline						
		LF	HF	TP	RMSSD	SDNN	pNN50	HR
MMSE	Total score							+
Cognistat	Orientation						+	
	Attention			+		+		
	Comprehension	+	+		+			
	Repetition		-		-			
	Construction		+					+
	Calculation					-		
	Similarity		+					
	Total score			+		+		
		HRV reactivity						
		LF	TP	RMSSD	SDNN	pNN50	HR	
MMSE	Orientation						+	
Cognistat	Comprehension		-	-	-			
	Construction	-	-					
	Memory					+		
	Total score					+		

Table 5.60 displays significant correlations between HRV parameters and cognitive domains from the MMSE (Folstein et al., 1975) and Cognistat (Kiernan et al., 1987) in subjects with type 1 diabetes (n=9). HRV reactivity refers to the active minus baseline HRV data.

Key: HF = High frequency; HR = Heart rate; HRV = Heart rate variability; LF = Low frequency; pNN50 = Total number of interval differences (greater than 50 milliseconds) of consecutive NN (beat to beat) intervals divided by the total number of NN intervals; RMSSD = Square root of the mean squared differences of successive NN intervals; SDNN = SD of all NN intervals (the square root of variance); TP = Total power; + = Positive correlation; - = Negative correlation

Table 5.61 Summary of significant correlations between HRV and cognitive domains in subjects with type 2 diabetes (n=38)

Cognitive test	Cognitive domain	HRV parameter				
		Baseline				
		LF	HF	TP	RMSSD	SDNN
MMSE	Orientation	+				
Cognistat	Naming					+
	Memory	+	+	+	+	+
		HRV reactivity				
		LF/HF	TP	RMSSD	SDNN	
Cognistat	Orientation	-				
	Memory		-	-	-	
	Similarity		+			

Table 5.61 displays significant correlations between HRV parameters and cognitive domains from the MMSE (Folstein et al., 1975) and Cognistat (Kiernan et al., 1987) in subjects with type 2 diabetes (n=38). HRV reactivity refers to the active minus baseline HRV data.

Key: HF = High frequency; HRV = Heart rate variability; LF = Low frequency; LF/HF = Low frequency divided by high frequency (sympathovagal balance); MMSE = Mini Mental State Examination; RMSSD = Square root of the mean squared differences of successive NN intervals; SDNN = SD of all NN intervals (the square root of variance); TP = Total power; + = Positive correlation; - = Negative correlation

Table 5.62 Summary of significant correlations between HRV and cognitive domains in subjects with hypertension (n=39)

Cognitive test	Cognitive domain	HRV parameter					
		Baseline					
		LF	HF	TP	RMSSD	SDNN	HR
MMSE	Orientation						+
	Total score						+
Cognistat	Orientation				+		
	Construction				-		
	Judgment	-	-	-	-	-	
		HRV reactivity					
		HF	TP	RMSSD	SDNN	HR	
MMSE	Attention				+		
	Language			+			
	Total score			+	+		
Cognistat	Similarity			+	+		
	Judgment	+	+	+	+		
	Total score					+	

Table 5.62 displays significant correlations between HRV parameters and cognitive domains from the MMSE (Folstein et al., 1975) and Cognistat (Kiernan et al., 1987) in subjects with hypertension (n=39). HRV reactivity refers to the active minus baseline HRV data.

Key: HF = High frequency; HR = Heart rate; HRV = Heart rate variability; LF = Low frequency; MMSE = Mini Mental State Examination; pNN50 = Total number of interval differences (greater than 50 milliseconds) of consecutive NN (beat to beat) intervals divided by the total number of NN intervals; RMSSD = Square root of the mean squared differences of successive NN intervals; SDNN = SD of all NN intervals (the square root of variance); TP = Total power; + = Positive correlation; - = Negative correlation

6. BP and cognition (non-clinical groups)

Despite a large amount of literature in the field of BP and cognition, there remains some disparity in the conclusions drawn. Most studies show BP and cognition are limited to older age ranges and male populations (typically targeting at-risk cardiovascular disease cohorts). Assessing BP and cognition earlier in life may elucidate BP patterns which may precede cognitive impairment. Further, some contention in findings exist, with most studies suggesting hypertension as a risk factor for cognitive impairment (Feinkohl et al., 2015, Exalto et al., 2014, Crichton et al., 2014), while others have found that lower blood pressure is linked to cognitive dysfunction (Pandav et al., 2003), that both high and low BP is correlated to cognitive impairment (Waldstein et al., 2005) or that no associations were found (Di Carlo et al., 2000). There is also a lack of literature examining the relationships between BP reactivity and cognition, addressed in the present study.

Therefore the following results and discussion chapters 6.1 and 6.2 explore specific aims 1, 2, 3, 5 and 6 (as shown in section 2.1.2.1), to identify the relationship between BP and cognitive function; to examine if age group differences show variable links between BP and cognitive function; to examine if sex differences will show variable links between BP and cognitive function; to identify the relationships between BP reactivity and cognition; and to identify significant relationships between BP and different cognitive domains as a potential predictive marker for identifying those at higher risk of cognitive impairment.

6.1 Results: BP and cognition (non-clinical groups)

A total of 123 volunteers with no chronic illnesses, aged 18-71 years, were recruited for the present study and added to an existing data base of 100 participants obtained using similar experimental protocols and laboratory conditions in the Neuroscience Research Unit at UTS (De Leon, 2009, Smith, 2010).

This chapter reports the descriptive statistics for the total non-clinical sample (n=223), followed by the results for cognitive function and BP in females and males in three age

groups (18-35, 36-50, 51-65 years (n=1 male aged 71 not included)) and also provides descriptive statistics and comparisons for the total male and female groups using the same volunteers as reported in chapter 4.

6.1.1 Total non-clinical group demographics (females and males) (n=223)

Mean (\pm SD) demographics and cognitive scores from the MMSE and Cognistat for the total non-clinical group (n=223) are provided in the previous section 4.1.1 (Table 4.1 and Table 4.2, respectively). Mean BP values are provided in Table 6.1.

Table 6.1 Mean BP values for the total non-clinical group (n=223)

	Variable	SBP mean \pm SD (mmHg)	DBP mean \pm SD (mmHg)
Total non-clinical females and males n=223	Pre study (baseline)	123.34 \pm 12.50	78.11 \pm 9.17
	Post study	124.03 \pm 13.49	78.78 \pm 8.82
	BP reactivity (post - pre)	0.69 \pm 7.63	0.68 \pm 5.83

Table 6.1 shows mean BP values for the total non-clinical group aged 18-71 years (n=223). Key: BP = Blood pressure; DBP = Diastolic blood pressure; mmHg = Millimetres of mercury; n = Sample size; SBP = Systolic blood pressure; SD = Standard deviation

6.1.2 18-35 years

6.1.2.1 Females (n=41)

Mean (\pm SD) demographics and cognitive scores from the MMSE and Cognistat for females aged 18-35 years (n=41) are provided in the previous section 4.1.2.1 (Table 4.5 and Table 4.6, respectively). Mean BP values for this group are provided in Table 6.2.

Table 6.2 Mean BP values for females 18-35 years (n=41)

	Variable	SBP mean \pm SD (mmHg)	DBP mean \pm SD (mmHg)
Females 18-35 years n=41	Pre study (baseline)	113.80 \pm 9.32	74.98 \pm 7.33
	Post study	113.51 \pm 10.94	74.34 \pm 8.02
	BP reactivity (post - pre)	-0.29 \pm 7.95	-0.63 \pm 6.55

Table 6.2 shows mean BP values for females 18-35 years (n=41).

Key: BP = Blood pressure; DBP = Diastolic blood pressure; mmHg = Millimetres of mercury; n = Sample size; SBP = Systolic blood pressure; SD = Standard deviation

Dependent sample t-tests were performed to determine differences between pre and post study BP values. No significant differences were identified.

Pearson’s bivariate and partial correlations were performed separately between BP and cognitive scores to address aims 1 and 5 (Table 6.3). Partial correlations were not significant.

Table 6.3 Significant Pearson’s correlation coefficients between cognitive scores and blood pressure values in females 18-35 years (n=41)

	Dependent variable	Independent variable	r	p
Females 18-35 years n=41	Language MMSE	DBP reactivity	0.32	0.04
	Naming Cognistat	DBP reactivity	0.43	0.01
	Attention MMSE	SBP reactivity	0.32	0.04
	Total MMSE	SBP reactivity	0.40	0.01
	Orientation Cognistat	SBP reactivity	0.35	0.03
	Comprehension Cognistat	Baseline DBP	0.40	0.01
	Construction Cognistat	Baseline DBP	0.33	0.04

Table 6.3 displays significant results from a Pearson’s correlation between cognitive scores (MMSE (Folstein et al., 1975) and Cognistat (Kiernan et al., 1987)), blood pressure values in females 18-35 years (n=41).

Key: DBP = Diastolic blood pressure; MMSE = Mini Mental State Examination; n = Sample size; p = Level of statistical significance (p<0.05); r = Correlation coefficient; SBP = Systolic blood pressure

6.1.2.2 Males (n=42)

Mean (\pm SD) demographics and cognitive scores from the MMSE and Cognistat standard deviation for males aged 18-35 years (n=42) are provided in the previous section 4.1.2.2 (Table 4.12 and Table 4.13, respectively). Mean BP values are provided in Table 6.4.

Table 6.4 Mean BP values for males 18-35 years (n=42)

	Variable	SBP mean \pm SD (mmHg)	DBP mean \pm SD (mmHg)
Males 18-35 years n=42	Pre study (baseline)	129.81 \pm 9.40	77.84 \pm 9.09
	Post study	130.69 \pm 12.35	78.36 \pm 8.50
	BP reactivity (post - pre)	0.88 \pm 8.89	0.52 \pm 5.43

Table 6.4 shows mean BP values for males 18-35 years (n=42).

Key: BP = Blood pressure; DBP = Diastolic blood pressure; mmHg = Millimetres of mercury; n = Sample size; SBP = Systolic blood pressure; SD = Standard deviation

Dependent sample t-tests were performed to determine significant differences between pre and post study BP values. No significant differences were identified.

Pearson’s bivariate and partial correlations were performed separately between BP and cognitive scores to address aims 1 and 5. Negative correlations were identified between attention (MMSE) and total MMSE score with SBP reactivity ($r=-0.56$, $p<0.001$; $r=-0.40$, $p=0.01$, respectively).

Partial Pearson’s correlations showed negative correlations between orientation (MMSE) and judgment (Cognistat) with baseline DBP ($r=-0.42$, $p=0.01$; $r=-0.39$, $p=0.01$, respectively).

6.1.2.3 Comparison between females (n=41) and males (n=42) (18-35 years)

Mean BP values for the females and males aged 18-35 years are displayed in Figure 6.1.

Figure 6.1 Mean BP values for the females (n=41) and males (n=42) aged 18-35

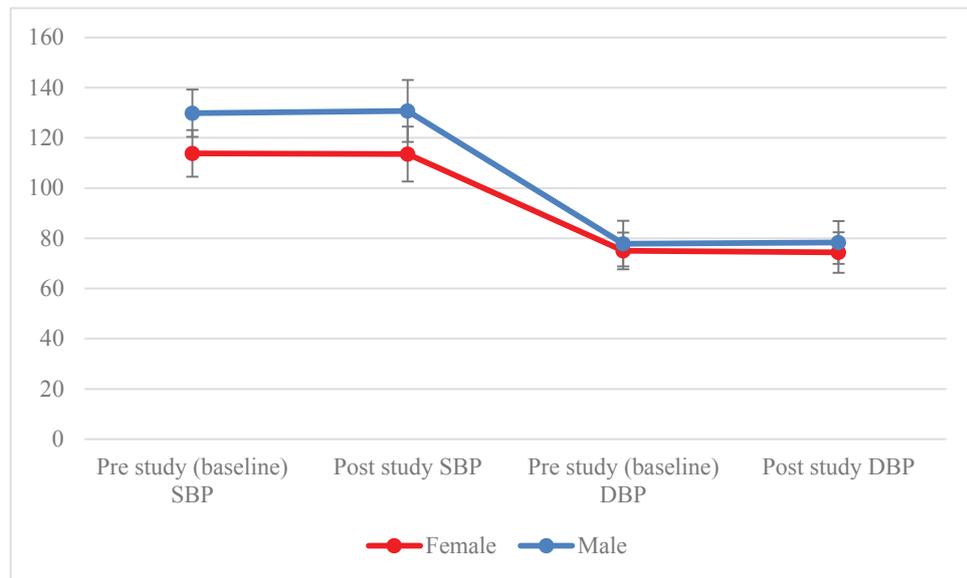


Figure 6.1 displays mean BP values for the females (n=41) and males (n=42) aged 18-35.

Key: BP = Blood pressure; DBP = Diastolic blood pressure; SBP = Systolic blood pressure

An independent sample t-test was used to compare BP values between females and males aged 18-35 years. Post study SBP was found to be significantly higher in males than females ($t=-6.70$, $df=81$, $p<0.001$) (130.69 ± 12.35 mmHg, 113.51 ± 10.94 mmHg, respectively). Refer to previous section 4.1.2.3 for independent sample t-tests (with and/or without covariates) comparing cognitive scores between the groups.

An independent sample t-test with covariates was used to compare BP values between females and males aged 18-35 years (Table 6.5).

Table 6.5 Independent sample t-test with covariance of blood pressure values between females (n=41) and males (n=42) aged 18-35 years

	Covariate	Variable	F	df	p	Females mean ± SD (mmHg)	Males mean ± SD (mmHg)	Mean difference (males – females) (mmHg)
Females and males 18-35 years	BMI	Baseline SBP	32.79	2, 78	<0.001	113.80 ± 9.32	129.81 ± 9.40	16.01
	LAQ part one (lifestyle risk factors)	Baseline DBP	5.06	2, 80	0.01	74.98 ± 7.33	77.84 ± 9.09	2.86
		Post DBP	6.64	2, 80	0.002	74.34 ± 8.02	78.36 ± 8.50	4.02

Table 6.5 displays significant results from an independent sample t-test with covariance (performed by ANCOVA and MANCOVA) of blood pressure values between females (n=41) and males (n=42) aged 18-35 years.

Key: ANCOVA = Analysis of covariance; BMI = Body mass index; DBP = Diastolic blood pressure; df = Degrees of freedom; F = F statistic; LAQ = Lifestyle Appraisal Questionnaire (Craig et al., 1996); MANCOVA = Multiple analysis of covariance; mmHg = Millimetres of mercury; n = Sample size; p = Level of statistical significance (p<0.05); SBP = Systolic blood pressure; SD = Standard deviation

Significant correlations in 18-35 year old males and females were compared using Z scores to address aim 3. Correlations between attention (MMSE) (Z=-4.23, p<0.001) (males r=-0.56, p<0.001; females r=0.32, p=0.04) and total MMSE score (Z=-3.67, p<0.001) (males r=-0.40, p=0.01; females r=0.40, p=0.01) with SBP reactivity were significantly different.

6.1.3 36-50 years

6.1.3.1 Females (n=37)

Mean (\pm SD) demographics and cognitive scores from the MMSE and Cognistat for females aged 36-50 years (n=37) are provided in the previous section 4.1.3.1 (Table 4.22 and Table 4.23, respectively). Mean BP values are provided in Table 6.6.

Table 6.6 Mean BP values for females 36-50 years (n=37)

	Variable	SBP mean \pm SD (mmHg)	DBP mean \pm SD (mmHg)
Females 36-50 years n=37	Pre study (baseline)	117.57 \pm 11.61	76.46 \pm 8.45
	Post study	118.24 \pm 11.12	79.24 \pm 8.56
	BP reactivity (post - pre)	0.68 \pm 7.62	2.78 \pm 5.37

Table 6.6 shows mean BP values for females 36-50 years (n=37).

Key: BP = Blood pressure; DBP = Diastolic blood pressure; mmHg = Millimetres of mercury; n = Sample size; SBP = Systolic blood pressure; SD = Standard deviation

Dependent sample t-tests were performed to determine significant differences between pre and post study BP values. DBP significantly rose from pre to post study ($t=-3.15$, $df=36$, $p=0.003$) (pre study (baseline) 76.46 \pm 8.45 mmHg, post study 79.24 \pm 8.56 mmHg).

Pearson’s bivariate and partial correlations were performed separately between BP and cognitive scores to address aims 1 and 5 (Table 6.7). No bivariate correlations were significant.

Table 6.7 Partial Pearson’s correlation coefficients between cognitive scores and blood pressure values in females 36-50 years (n=37)

	Covariate	Dependent variable	Independent variable	r	p
Females 36-50 years n=37	BMI	Attention MMSE	Baseline SBP	0.45	0.01
		Total MMSE		0.37	0.03
		Attention Cognistat		0.33	0.048
		Repetition Cognistat		0.42	0.01
		Naming Cognistat		0.34	0.04
	Smoking status	Attention MMSE	SBP reactivity	-0.38	0.02

Table 6.7 displays significant results from a Pearson’s correlation between cognitive scores (MMSE (Folstein et al., 1975) and Cognistat (Kiernan et al., 1987)) and blood pressure values in females 36-50 years (n=37).

Key: BMI = Body mass index; mmHg = Millimetres of mercury; MMSE = Mini Mental State Examination; n = Sample size; p = Level of statistical significance (p<0.05); r = Correlation coefficient; SBP = Systolic blood pressure

6.1.3.2 Males (n=37)

Mean (\pm SD) demographics and cognitive scores from the MMSE and Cognistat for males aged 36-50 years (n=37) are provided in the previous section 4.1.3.2 (Table 4.31 and Table 4.32, respectively). Mean BP values are provided in Table 6.8.

Table 6.8 Mean BP values for males 36-50 years (n=37)

	Variable	SBP mean \pm SD (mmHg)	DBP mean \pm SD (mmHg)
Males 36-50 years n=37	Pre study (baseline)	129.30 \pm 10.76	81.68 \pm 8.56
	Post study	128.78 \pm 11.93	81.60 \pm 8.18
	BP reactivity (post - pre)	-0.51 \pm 7.48	-0.08 \pm 5.62

Table 6.8 shows mean BP values for males 36-50 years (n=37).

Key: BP = Blood pressure; DBP = Diastolic blood pressure; mmHg = Millimetres of mercury; n = Sample size; SBP = Systolic blood pressure; SD = Standard deviation

Dependent sample t-tests were performed to determine significant differences between pre and post study BP values. No significant differences were identified.

Pearson’s bivariate and partial correlations were performed separately between BP and cognitive scores to address aims 1 and 5. No significant results were found.

6.1.3.3 Comparison between females (n=37) and males (n=37) (36-50 years)

Mean BP values for the females and males aged 36-50 years are displayed in Figure 6.2.

Figure 6.2 Mean BP values for the females (n=37) and males (n=37) aged 36-50 years

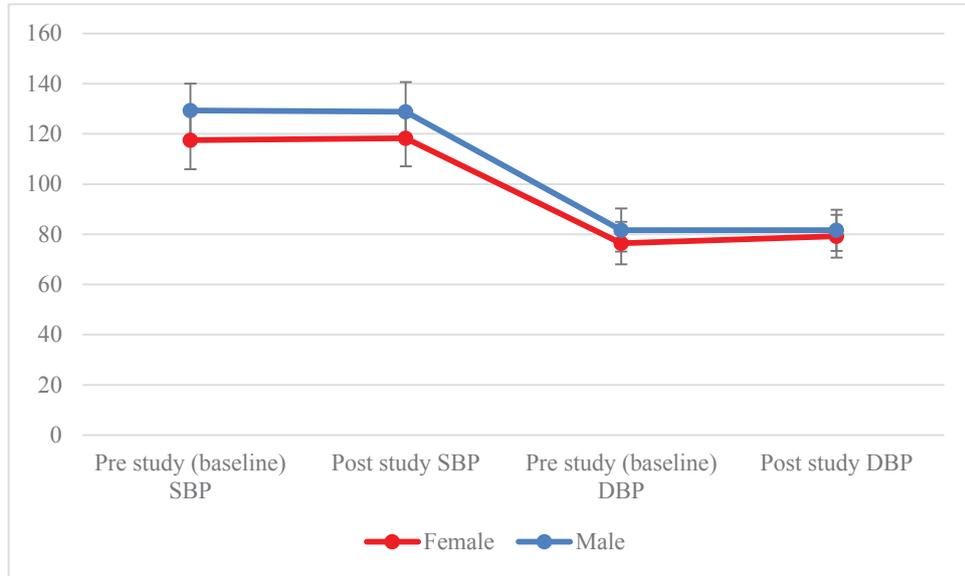


Figure 6.2 displays mean BP values for the females (n=37) and males (n=37) aged 36-50 years.

Key: BP = Blood pressure; DBP = Diastolic blood pressure; SBP = Systolic blood pressure

An independent sample t-test with covariates was used to compare BP values between females and males aged 36-50 years (Table 6.9). All the t-tests in this cohort required covariate adjustment, as each variable was significantly correlated to a covariate.

Refer to previous section 4.1.4.3 for independent sample t-tests (with and/or without covariates) comparing cognitive scores between the groups.

Table 6.9 Independent sample t-test with covariance of blood pressure values between females and males aged 36-50 years

	Covariate	Variable	p	F	df	Females mean \pm SD (mmHg)	Males mean \pm SD (mmHg)	Mean difference (males – females)
Females and males 36-50 years	BMI, LAQ part one (lifestyle risk factors) and LAQ part two (stress coping)	Baseline SBP	0.01	4.54	2, 71	117.57 \pm 11.61	129.30 \pm 10.76	11.73
	BMI and LAQ part one (lifestyle risk factors)	Baseline DBP	<0.001	15.61	2, 71	76.46 \pm 8.45	81.68 \pm 8.56	5.22
		Post DBP	0.01	5.55	2, 71	79.24 \pm 8.56	81.60 \pm 8.18	2.36
	BMI and LAQ part two (stress coping)	Post SBP	0.01	5.58	2, 71	118.24 \pm 11.12	128.78 \pm 11.93	10.54
	LAQ part one (lifestyle risk factors) and smoking status	SBP reactivity	0.002	6.80	2, 71	0.68 \pm 7.62	-0.51 \pm 7.48	-0.119
	LAQ part one (lifestyle risk factors)	DBP reactivity	0.03	3.69	2, 68	2.78 \pm 5.37	-0.08 \pm 5.62	-2.86

Table 6.9 displays significant results from an independent sample t-test with covariance (performed by ANCOVA and MANCOVA) of blood pressure values between females (n=37) and males (n=37) aged 36-50 years.

Key: ANCOVA = Analysis of covariance; BMI = Body mass index; DBP = Diastolic blood pressure; df = Degrees of freedom; F = F statistic; LAQ = Lifestyle Appraisal Questionnaire (Craig et al., 1996); MANCOVA = Multiple analysis of covariance; mmHg = Millimetres of mercury; n = Sample size; p = Level of statistical significance (p<0.05); SBP = Systolic blood pressure; SD = Standard deviation

6.1.4 51-65 years

6.1.4.1 Females (n=42)

Mean (\pm SD) demographics and cognitive scores from the MMSE and Cognistat for females aged 51-65 years (n=42) are provided in the previous section 4.1.4.1 (Table 4.40 and Table 4.41, respectively). Mean BP values are provided in Table 6.10.

Table 6.10 Mean BP values for females 51-65 years (n=42)

	Variable	SBP mean \pm SD (mmHg)	DBP mean \pm SD (mmHg)
Females 51-65 years n=42	Pre study (baseline)	122.38 \pm 13.14	77.36 \pm 11.33
	Post study	124.21 \pm 13.46	78.71 \pm 10.16
	BP reactivity (post - pre)	1.83 \pm 5.78	1.36 \pm 6.14

Table 6.10 shows mean BP values for females 51-65 years (n=42).

Key: BP = Blood pressure; DBP = Diastolic blood pressure; mmHg = Millimetres of mercury; n = Sample size; SBP = Systolic blood pressure; SD = Standard deviation

Dependent sample t-tests were performed to determine significant differences between pre and post study BP values. SBP rose significantly from pre to post study ($t=-2.06$, $df=41$, $p=0.046$) (122.38 \pm 13.14 mmHg, 124.21 \pm 13.46 mmHg, respectively).

Pearson’s bivariate and partial correlations were performed separately between BP and cognitive scores to address aims 1 and 5. Significant bivariate correlations are displayed in Table 6.11.

Table 6.11 Pearson’s correlation coefficients between cognitive scores and BP in females 51-65 years (n=42)

	Dependent variable	Independent variable	r	p
Females 51-65 years n=42	Repetition Cognistat	DBP reactivity	0.36	0.02
	Naming Cognistat		0.32	0.04
	Similarity Cognistat		0.40	0.01

Table 6.11 displays significant results from a Pearson’s correlation between cognitive scores (MMSE (Folstein et al., 1975) and Cognistat (Kiernan et al., 1987)) and BP in females 51-65 years (n=42).

Key: BP = Blood pressure; DBP = Diastolic blood pressure; MMSE = Mini Mental State Examination; n = Sample size; p = Level of statistical significance ($p < 0.05$); r = Correlation coefficient

Partial Pearson’s correlations showed negative relationships between similarity (Cognistat) and total Cognistat score with baseline SBP ($r = -0.32$, $p = 0.045$; $r = -0.32$, $p = 0.04$, respectively) (controlled for LAQ part one).

6.1.4.2 Males (n=23)

Mean (\pm SD) demographics and cognitive scores from the MMSE and Cognistat are provided in the previous section 4.1.4.2 for males aged 51-65 years (n=23) (Table 4.48 and Table 4.49, respectively). Mean BP values are provided in Table 6.12.

Table 6.12 Mean BP values for males 51-65 years (n=23)

	Variable	SBP mean \pm SD (mmHg)	DBP mean \pm SD (mmHg)
Males 51-65 years n=23	Pre study (baseline)	129.61 \pm 10.62	82.22 \pm 7.53
	Post study	131.26 \pm 10.56	81.87 \pm 6.82
	BP reactivity (post - pre)	1.65 \pm 8.11	-0.35 \pm 5.16

Table 6.12 shows mean BP values for males 51-65 years (n=23).

Key: BP = Blood pressure; DBP = Diastolic blood pressure; mmHg = Millimetres of mercury; n = Sample size; SBP = Systolic blood pressure; SD = Standard deviation

Wilcoxon signed rank tests were performed to determine significant differences between pre and post study BP. No significant results were identified.

Spearman’s bivariate and partial correlations were performed separately between BP and cognitive scores to address aims 1 and 5. No significant correlations were identified for bivariate correlations. Significant partial Spearman’s correlations are displayed in Table 6.13.

Table 6.13 Spearman’s correlation coefficients between cognitive scores and BP in males 51-65 years (n=23)

	Covariate	Dependent variable	Independent variable	r	p
Males 51-65 years n=23	LAQ part one (lifestyle risk factors)	Recall MMSE	Baseline SBP	-0.43	0.02
		Naming Cognistat	Baseline SBP	-0.39	0.04
		Judgment Cognistat	Baseline DBP	0.39	0.04
	Age	Attention Cognistat	DBP reactivity	0.41	0.03
		Calculation Cognistat	DBP reactivity	-0.42	0.03

Table 6.13 displays significant results from a Spearman’s correlation between cognitive scores (MMSE (Folstein et al., 1975) and Cognistat (Kiernan et al., 1987)) and BP in males 51-65 years (n=23).

Key: BP = Blood pressure; DBP = Diastolic blood pressure; LAQ = Lifestyle Appraisal Questionnaire (Craig et al., 1996); MMSE = Mini Mental State Examination; n = Sample size; p = Level of statistical significance (p<0.05); r = Correlation coefficient; SBP = Systolic blood pressure

6.1.4.3 Comparison between females (n=42) and males (n=23) (51-65 years)

Mean BP values for the females and males aged 51-65 years are displayed in Figure 6.3.

Figure 6.3 Mean BP values for the females (n=42) and males (n=23) aged 51-65 years

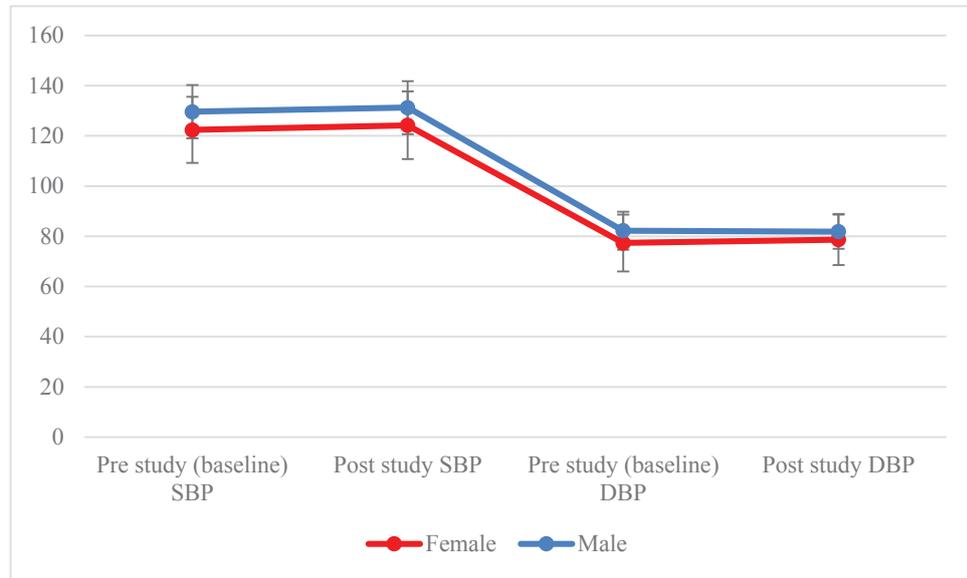


Figure 6.3 displays mean BP values for the females (n=42) and males (n=23) aged 51-65 years.

Key: BP = Blood pressure; DBP = Diastolic blood pressure; SBP = Systolic blood pressure

Mann-Whitney U test was used to compare BP values between females and males aged 51-65 years. Males had significantly higher pre study (baseline) SBP than females (p=0.03, Z=2.14, U=638.50) (male median (IQR) 131 (18), female 122 (19.25); mean rank male 39.76, female 29.30).

Refer to previous section 4.1.5.3 (Table 4.68) for independent sample t-tests (with and/or without covariates) comparing cognitive scores between the groups.

6.1.5 Females and males total sample (18-65 years)

6.1.5.1 Females 18-65 years (n=120)

Mean (\pm SD) demographics and cognitive scores from the MMSE and Cognistat for females aged 18-65 years (n=120) are provided in the previous section 4.1.5.1 (Table 4.57 and Table 4.58, respectively). Mean BP values are provided in Table 6.14.

Table 6.14 Mean BP values for females 18-65 years (n=120)

	Variable	SBP mean \pm SD (mmHg)	DBP mean \pm SD (mmHg)
Females 18-65 years n=120	Pre study (baseline)	117.97 \pm 11.93	76.27 \pm 9.21
	Post study	118.72 \pm 12.65	77.38 \pm 9.18
	BP reactivity (post - pre)	0.75 \pm 7.15	1.12 \pm 6.17

Table 6.14 shows mean BP values for females 18-65 years (n=120).

Key: BP = Blood pressure; DBP = Diastolic blood pressure; mmHg = Millimetres of mercury; n = Sample size; SBP = Systolic blood pressure; SD = Standard deviation

6.1.5.1.1 Female age group comparison (18-35, 36-50, 51-35 years)

Mean BP values for females aged 18-35 (n=41), 31-50 (n=37), and 51-65 (n=42) years are displayed in Figure 6.4.

Figure 6.4 Mean BP values for females aged 18-35 (n=41), 31-50 (n=37), and 51-65 (n=42) years

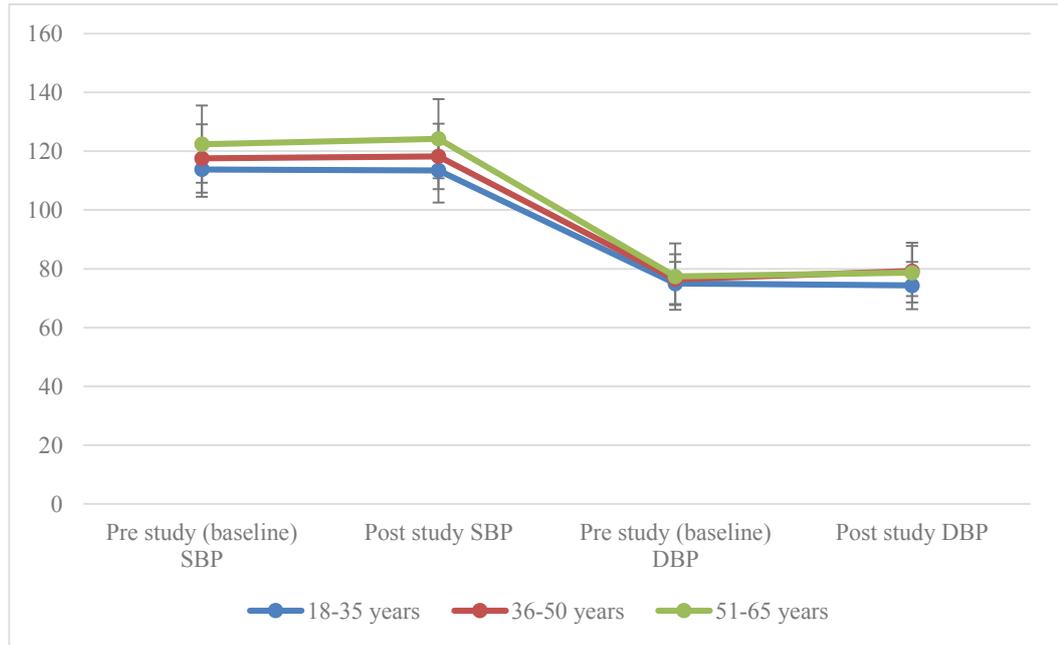


Figure 6.4 displays mean BP values for females aged 18-35 (n=41), 31-50 (n=37), and 51-65 (n=42) years.

Key: BP = Blood pressure; DBP = Diastolic blood pressure; SBP = Systolic blood pressure

Observations were made to compare the previously conducted dependent sample t-tests between pre and post study BP values across the three female age groups. In the 36-50 year age group, it was observed that DBP rose significantly and in the 51-65 year age group, SBP rose significantly from pre to post study.

Correlations with covariates were initially performed to determine whether to apply ANOVA or ANCOVA in order to compare cognitive scores and BP values in the three female age groups (18-35, 36-50, and 51-65 years). If ANOVA statistical significance was achieved ($p < 0.05$), Bonferroni post hoc tests were performed to determine which groups were significantly different. DBP reactivity values were significantly higher in the middle age group than the youngest age group ($F=3.14$, $df=2, 117$, $p=0.047$ (Bonferroni $p=0.04$)) (2.78 ± 5.37 mmHg, -0.63 ± 6.55 mmHg, respectively).

Refer to previous section 4.1.5.1 (Table 4.61 and Table 4.62) for significant differences in cognitive scores between female age groups.

6.1.5.2 Males 18-65 years (n=102)

Mean (\pm SD) demographics and cognitive scores from the MMSE and Cognistat for males aged 18-65 years (n=102) are provided in the previous section 4.1.5.2 (Table 4.64 and Table 4.65, respectively). Mean BP values are provided in Table 6.15.

Table 6.15 Mean BP values for males 18-65 years (n=102)

	Variable	SBP mean \pm SD (mmHg)	DBP mean \pm SD (mmHg)
Males 18-65 years n=102	Pre study (baseline)	129.59 \pm 10.04	80.25 \pm 8.68
	Post study	130.22 \pm 11.73	80.41 \pm 8.14
	BP reactivity (post - pre)	0.63 \pm 8.19	0.17 \pm 5.40

Table 6.15 shows mean BP values for males 18-65 years (n=102).

Key: BP = Blood pressure; DBP = Diastolic blood pressure; mmHg = Millimetres of mercury; n = Sample size; SBP = Systolic blood pressure; SD = Standard deviation

6.1.5.2.1 Male age group comparison (18-35, 36-50, 51-35 years)

Mean BP values for males aged 18-35, 31-50, and 51-65 years are displayed in Figure 6.5.

Figure 6.5 Mean BP values for males aged 18-35 (n=42), 31-50 (n=37), and 51-65 (n=23) years

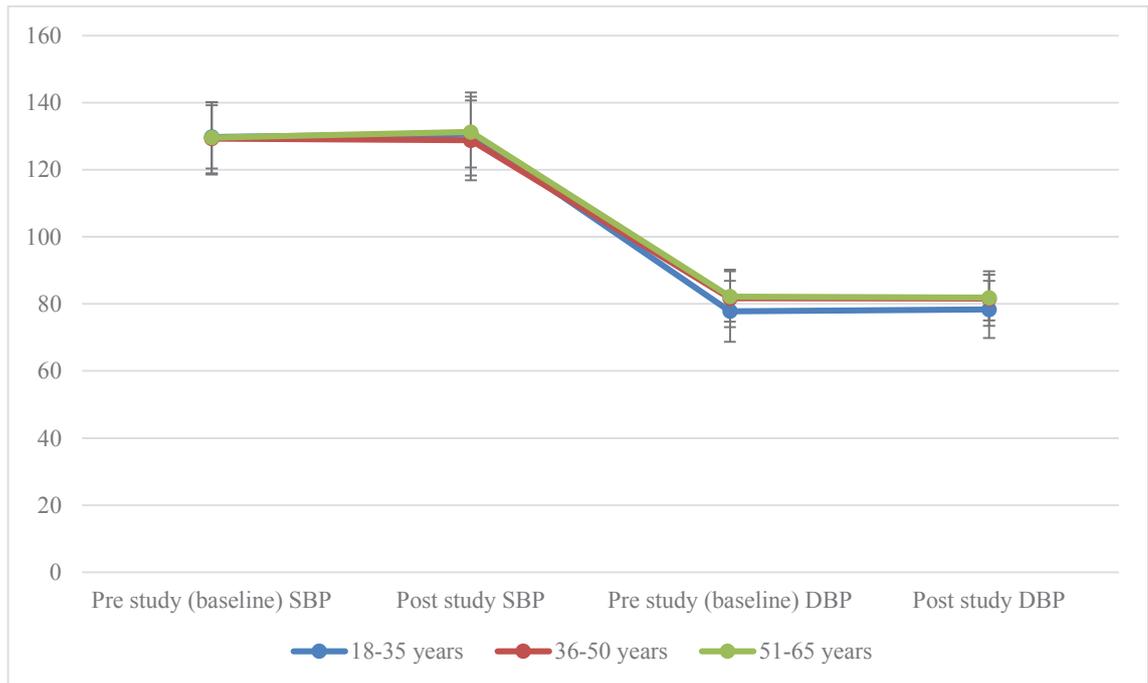


Figure 6.5 displays mean BP values for males aged 18-35 (n=42), 31-50 (n=37), and 51-65 (n=23) years.

Key: BP = Blood pressure; DBP = Diastolic blood pressure; SBP = Systolic blood pressure

Observations were made to compare the previously conducted dependent sample t-tests between pre and post study BP values across the three male age groups. No significant differences were identified in any of the age groups from pre to post study.

A Kruskal Wallis test was performed to determine significant differences in BP variables between the three male age groups. No significant differences were identified.

Refer to previous section 4.1.5.2 for significant differences in cognitive scores between the male age groups.

6.1.5.3 Comparison between total females (n=120) and males (n=102)

Mean BP values for the total females (n=120) and males (n=102) are displayed in Figure 6.6

Figure 6.6 Mean BP values for the total females (n=120) and males (n=102) (non-clinical groups)

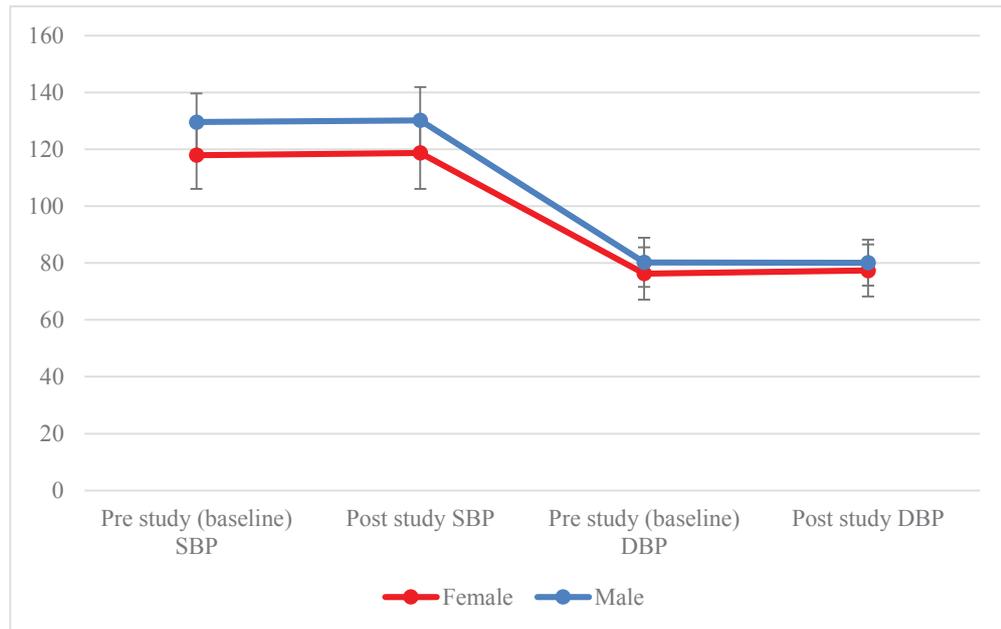


Figure 6.6 displays mean BP values for the total females (n=120) and males (n=102) (non-clinical groups).

Key: BP = Blood pressure; DBP = Diastolic blood pressure; SBP = Systolic blood pressure

Although independent sample t-tests did not provide significant results, independent sample t-tests with covariance identified significant differences shown in Table 6.16.

Table 6.16 Independent sample t-test with covariance of BP values between total females (n=120) and males (n=102) aged 18-65 years

	Covariate	Variable	F	df	p	Females mean ± SD (mmHg)	Males mean ± SD (mmHg)	Mean difference (males – females)
Females and males 18-65 years	BMI and LAQ part one (lifestyle risk factors)	Baseline SBP	30.99	1	<0.001	117.97 ± 11.93	129.59 ± 10.04	11.62
	Age, BMI, and LAQ part one (lifestyle risk factors)	Post SBP	15.86	1	<0.001	118.72 ± 12.65	130.22 ± 11.73	11.50
		Baseline DBP	4.07	1	0.045	76.27 ± 9.21	80.25 ± 8.68	3.98

Table 6.16 displays significant results from an independent sample t-test with covariance (performed by ANCOVA and MANCOVA) of BP values between females (n=120) and males (n=102) aged 18-65 years.

Key: ANCOVA = Analysis of covariance; BMI = Body mass index; DBP = Diastolic blood pressure; df = Degrees of freedom; F = F statistic; LAQ = Lifestyle Appraisal Questionnaire (Craig et al., 1996); MANCOVA = Multiple analysis of covariance; mmHg = Millimetres of mercury; n = Sample size; p = Level of statistical significance (p<0.05); SBP = Systolic blood pressure; SD = Standard deviation

6.2 Discussion: BP and cognition (non-clinical groups)

This chapter discusses the relationships between BP and cognition in participants without chronic illnesses, aged 18-65 years. This discussion section is presented by age (in groups of 18-35, 36-50, and 51-65 years) and sub-grouped by sex.

Cardiovascular reactivity refers to the degree of change in cardiovascular variables (e.g. BP) in response to a stressor or physiological intervention. In the present study, BP reactivity was determined by subtracting the pre study BP reading (baseline) from the post study BP reading (after the cognitive tests). Both exaggerated and blunted BP reactivity have been linked to negative health outcomes (Phillips et al., 2013, Ginty et al., 2013, Carroll et al., 2012). Exaggerated BP reactivity has been linked to cardiovascular pathology such as atherosclerosis, thickened carotid intima (vascular remodelling), hypertension, and an overall increased risk of a cardiovascular event (Lovallo and Gerin, 2003, Schwartz et al., 2003, Treiber et al., 2003, Carroll et al., 2003). Diminished BP reactivity has similarly been associated with conditions such as anxiety, obesity, alcoholism and overall decreased immune responsivity (Phillips et al., 2009, Panknin et al., 2002, York et al., 2007, Lovallo, 2011). These associations highlight the presence of an optimal homeostatic range of responsivity considered healthy, while deviations above and below the range have adverse health consequences (Figure 6.7).

Figure 6.7 Normal BP reactivity

Table/Figure removed due to copyright restrictions for digital thesis submission

Figure 6.7 illustrates the concept of a homeostatic range for optimal BP reactivity, where deviations above and below the range have been linked to negative health outcomes. Adapted and modified from Lovallo (2011).

Key: BP = Blood pressure; CVD = Cardiovascular disease

6.2.1 18-35 years

6.2.1.1 Females (n=41)

In younger females, BP did not significantly change from before to after the experiment, however, significant correlations were identified between baseline (pre study) BP and BP reactivity with particular cognitive domains. Baseline DBP was positively linked to comprehension and construction scores (Cognistat). In contrast, other studies have shown increased baseline BP is associated with cognitive impairment (Allen et al., 2011, Chen et al., 2015, Yaffe et al., 2014).

Studies assessing BP and cognitive performance in younger age groups (as in the present study) are less common than for older age groups. The first longitudinal study examining BP and cognition in younger ages (18-46 year olds) showed higher baseline SBP and DBP was predictive of cognitive decline in visual functioning and fluid intelligence scores in all ages (Elias et al., 2004). However, crystallised intelligence and verbal abilities were spared (n=285, mean age 46 ± 8 years, 52% female). Some authors also suggest changes in BP occurring earlier in life negatively influence cognitive performance and vascular health later in life (DeCarli, 2015).

In the present study, positive correlations were identified between language (MMSE) and naming domains (Cognistat) with DBP reactivity, and between attention (MMSE), total score (MMSE), and orientation (Cognistat) with SBP reactivity. Allen and co-workers (2011) found young females with lower SBP performed better in mental arithmetic tasks and that lower SBP, DBP, and HR reactivity were linked to better overall health. They

also noted that less CR was associated with higher perceived stress scores, suggesting anxiety has a blunting effect on cardiovascular reactivity (n=149, mean age 20 ± 3 years, 56% female). As previously discussed, diminished BP reactivity has also been linked to negative health outcomes (Lovallo, 2011). Disparities between findings are particularly pertinent in this field due to the lack of studies exploring BP reactivity and cognition in young cohorts. The findings from the present study therefore contribute new knowledge to the field of BP reactivity and cognition.

6.2.1.2 Males (n=42)

Although no significant differences were identified between BP values before and after the experiment, negative correlations were found between orientation (MMSE) and judgment (Cognistat) with baseline DBP in young males. In agreement with a majority of the literature, higher BP had a negative effect on cognitive performance, yet this is not always apparent in younger-aged samples, such as the present cohort. Yaffe et al. (2014) prospectively examined a large cohort with a 25 year follow-up, finding higher SBP and DBP were consistently linked to worse cognitive performance in memory, response inhibition, and learning processes (n=3381, mean age 50 ± 4 years at follow-up, 44% male). They concluded that cardiovascular changes occurring earlier in life had a more damaging effect on cognition in later life, attributed to cumulative microvascular damage impairing neuronal health.

Negative relationships were also found between attention (MMSE) and total score (MMSE) with SBP reactivity. This suggests lower BP reactivity could be better for cognitive performance. Higher BP reactivity shows more volatile BP changes to stressors which has been associated to decreased cognitive performance. This is supported by Allen et al. (2011), who also found young males with lower SBP reactivity performed better in mental arithmetic tasks (n=149, mean age 20 ± 3 years, 44% male). That study also observed that these participants had a better general health status. Similarly, a large study of young males and females showed higher BP reactivity to a video game stressor was linked to increases in SBP five years later in men (n=3364, aged 20-32 years, 47% male) (Markovitz et al., 1998).

6.2.1.3 Comparison between females (n=41) and males (n=42) (18-35 years)

Males had significantly higher baseline and post study SBP and DBP than females. In a study examining BP between males and premenopausal females, Tersman et al. (1991) also found young males had higher SBP than age-matched females (n=30, mean age 29 ± 6 years, 50% male). Dimkpa et al. (2008) also noted baseline DBP was significantly higher in young males than females (n=325, mean age 22 ± 3 years, 49% male). Although the reasons underlying these baseline differences have not yet been fully elucidated in the literature, experiments in rat models indicate that androgens increase BP via the renin-angiotensin-aldosterone system, potentially also leading to oxidative stress causing release of vasoconstrictive molecules and reduced nitric oxide (vasodilator) (Reckelhoff, 2001).

In the present study, no significant difference in BP reactivity was identified between the sexes. However, other researchers have shown males of similar age present with higher SBP reactivity than females (Allen et al., 2011, Allen et al., 1993, Tersman et al., 1991, Carroll et al., 2003). A meta-analysis by Davis et al. (1999) on sex differences in stress assessed 119 research papers and found females exhibit increased stress perception and anxiety which has been linked to blunted CR, and may form the basis for the differences in CR between sexes (Salomon et al., 2009, Phillips et al., 2013, Phillips, 2011).

Allen et al. (2011) further suggests males exhibit more ‘vascular’ reactions to stressors, exemplified by increased BP changes, whereas females demonstrate more ‘cardiac’ reactions, shown by higher HR reactivity than males. These sex differences may justify the opposing relationships between correlations of BP and cognition noted in males and females above. Females showed positive links between SBP reactivity and attention and total score (MMSE) whereas males showed the inverse relationships.

Lash et al. (1995) proposes differences in CR between sexes may be involved with societal gender roles, with males exhibiting increased CR than females out of competitiveness when their intelligence or physicality is being challenged. Others suggest these differences are becoming less pronounced as sex equality progresses and gender roles become more ambiguous (Miller and Halpern, 2014, Feingold, 1988).

6.2.2 36-50 years

6.2.2.1 Females (n=37)

As expected, DBP rose significantly from baseline to post study in the middle aged female group. It is well known that BP rises accompany cognitive interventions and mental stressors, such as those in the Cognistat and MMSE (Gyekis and Gerin, 2015).

Attention (in both the MMSE and Cognistat), total score (MMSE), repetition (Cognistat), and naming (Cognistat) were all positively correlated to baseline SBP. This disagrees with most other research, which typically found an association between higher baseline BP and worse cognitive performance. Gustat et al. (2011), for example, examined 351 healthy middle age participants in the Bogalusa Heart Study and found those with higher SBP had worse performance on 6 of 19 neuropsychological tests (mean age 43 ± 5 years, 57% female). Similarly, an earlier study by Singh-Manoux and Marmot (2005) assessed a larger cohort using data from the Whitehall II study (Marmot and Brunner, 2005), and concluded an inverse relationship existed between cognitive performance (semantic fluency, comprehension, and mathematical reasoning) and both SBP and DBP, which was more pronounced in middle-aged females than males ($n=5838$, mean age 44 ± 6 years, 29% female).

The correlations identified in the present study also suggest the opposite relationship is true, that is, lower BP is linked to poor cognitive function. The inverted U-shaped hypothesis of BP addresses both of these scenarios, where a middle optimal homeostatic BP range is desirable, and above or below this range has a negative impact on cognition (as well as organ and vasculature health) (refer to Figure 6.7 for a diagrammatic representation of this theory) (Waldstein et al., 2005).

Attention (MMSE) was inversely correlated to SBP reactivity. This suggests the higher the reactivity of BP to cognitive stressors, the worse participants performed. Waldstein's team (2005) also found SBP reactivity (and DBP reactivity) inversely related to verbal memory and executive function tasks in a slightly older sample ($n=94$, aged 54-79 years, 38% female). A longitudinal study using data from the Coronary Artery Risk Development in Young Adults study assessed BP reactivity in young adulthood and identified higher BP reactivity was significantly linked to poor performance in psychomotor speed and verbal memory 25 years later (mean age 50 ± 4 years at follow up) ($n=2326$, 57% female) (Yano et al., 2014). As previously discussed, higher BP reactivity has been linked to cardiovascular disease, which is also a risk factor for cognitive decline, and, in particular, vascular dementia (Qiu and Fratiglioni, 2015).

6.2.2.2 Males (n=37)

No significant differences were identified between BP values before and after the experiment, and no significant correlations were found between BP and cognitive scores in the middle aged male group. Despite these findings, other researchers have shown higher SBP to be linked to diminished cognition (also tested with the MMSE), increased white matter hyperintensities, and reduced brain parenchyma over a 10 year period (n=392, aged 43-53 years, 100% male) (Swan et al., 1998). More recent and larger sample longitudinal studies by Kivipelto (2006) and Exalto (2014) found higher SBP midlife significantly increased risk of cognitive decline and dementia 20 and 36 years later, respectively (n=1348, mean age 50 ± 6 years, 38% male (Kivipelto et al., 2006)), (n=8469, mean age 46 ± 4 years, 45% male (Exalto et al., 2014)).

High DBP midlife has also been linked to cognitive impairment 20 years later in males (Kilander et al., 1998), particularly in those without antihypertensive treatment (n=999, mean age 50 ± 6 years). In males, the reduction of BP by antihypertensive treatment such as beta-blockers has been shown to reduce the rate of cognitive decline, yet does not stop its progression (Gelber et al., 2013). A review by DeCarli (2015) promotes the neuroprotective benefits of antihypertensive use for hypertension earlier life (<50 years) to curb health risks in later life.

6.2.2.3 Comparison between females (n=37) and males (n=37) (36-50 years)

As expected, males had higher baseline and post study SBP and DBP than females. These findings agree with the consensus of previous research; that males exhibit higher BP (and sympathetic nerve activity) than premenopausal females, despite large inter-individual variability (Hart and Charkoudian, 2014). A large retrospective study by Exalto et al. (2012), assessed midlife participants and also found males had significantly higher DBP (n=5226, age range 40-55 years at baseline, 45% male). They stated that vascular risk factors for dementia had a more significant impact on men than women in follow-up experiments 36 years later. It was also found that females had significantly greater SBP and DBP reactivity than males, however, other studies in similar age groups and sample sizes have shown males demonstrated increased BP reactivity to mental stressors, highlighting disagreement in the literature (Steptoe, 1996, Traustadottir, 2003, Matthews, 2001).

Providing a potential physiological basis for these differences, a rat model experiment showed males possessed more reactive catecholamine (vasoconstrictive) receptors than females (Stallone et al., 1991). Despite this, males in the present study showed no significant relationships between BP reactivity and cognitive performance. Other researchers suggest further investigation is warranted regarding sex differences of BP reactivity to mental stressors since other research has found females with higher BP reactivity than males (Rausch et al., 2008), or no significant differences in BP reactivity between the sexes (Larson, 2001, Owens, 1993, Ginty et al., 2012).

6.2.3 51-65 years

6.2.3.1 Females (n=42)

SBP rose significantly from pre to post study in the older females. Sympathetic reactions such as increased BP are expected upon encountering cognitive stressors such as performing psychometric tests (MMSE and Cognistat) (Rausch et al., 2008).

Similarity (Cognistat) and total score (Cognistat) were inversely linked to baseline SBP; a relationship that is well supported in the literature (Yano et al., 2014, Singh-Manoux and Marmot, 2005, Suhr et al., 2004). Recently, Chen et al. (2015) examined a cohort of 247 women from the Women's Healthy Ageing Project and found participants exhibiting pre-hypertensive BP values (120–139/80–89 mmHg) at age 50 significantly predicted diminished processing speed and verbal episodic memory ten years later. Similarly, in a larger all-female study by Joas et al. (2012), higher SBP midlife predicted dementia and AD over a 37 year span (n=1462, mean age 45 years).

Repetition, naming, and similarity (Cognistat) were all positively correlated with DBP reactivity. This suggests a greater increase of BP from pre to post study was linked to better cognitive performance. A meta-analysis of 39 studies, however, showed increased BP reactivity is worse for cognitive performance, increasing the risk of future hypertension and cardiovascular disease (Chida and Steptoe, 2010). As previously discussed, a prominent theory regarding the curvilinear relationship of BP reactivity to cognitive performance also suggests that low BP reactivity has negative effects on cognitive function (supported by the current finding) (Lovallo, 2011).

Appraisal and response to the particular stressor increases neuronal demand for blood flow. Inadequate supporting mechanisms (BP reactivity) impacts cognitive performance over time (de Rooij, 2013). Ginty et al. (2012) found low SBP and DBP reactivity were linked to poorer general intelligence and memory performance ($n=724$, mean age 58 ± 1 years, 53% female). Interestingly, they discussed the theory of central motivational dysregulation, which associates suboptimal brain functioning in areas such as the striatum and prefrontal cortex (involved in motivational control) to both decreased CR and diminished cognition, and, as such, provides a physiological basis for lower CR being linked to cognitive decline (Carroll, 2009, Carroll, 2011, Lovallo, 2011, Busato, 2000).

6.2.3.2 Males ($n=23$)

No significant BP differences were identified before and after the experiment in older males, however, a positive correlation was identified between judgment (Cognistat) and baseline DBP and inverse correlations were identified between both recall (MMSE) and naming (Cognistat) with baseline SBP. Many large studies support the latter finding, associating higher BP to cognitive decline, typically involving endothelial dysfunction, oxidative stress and neuronal damage (Yano et al., 2014, Crichton et al., 2014, Gottesman et al., 2014, Dinh et al., 2014). Studies examining smaller sample sizes have also found increased BP is detrimental to cognitive performance (Mahmoud et al., 2015, Brown et al., 2009, Herd et al., 2003). Mahmoud et al. (2015) recently assessed 24 hour ambulatory BP in 77 subjects and found SBP and DBP were inversely linked to MMSE scores (SBP was a stronger predictor of MMSE score) (mean age 69 ± 3 years, 53% male).

The present study also identified a positive correlation between attention (Cognistat) and DBP reactivity and an inverse correlation between calculation (Cognistat) and DBP reactivity. As previously detailed in section 6.2.3.1, Lovallo et al. (2011) proposes a curvilinear relationship exists between CR and cognition, that is, deviations above and below a normal range increase the risk of reduced cognitive performance. Low BP reactivity has been linked to cerebral hypoperfusion (de Rooij, 2013) yet, more commonly, researchers have found increased BP reactivity is worse for cognitive performance (Chida and Steptoe, 2010, Brown et al., 2009, Ginty et al., 2012). Brown's team (2009) explored BP reactivity in healthy participants from the Baltimore

Longitudinal Study of Aging and found greater SBP and DBP reactivity was correlated to worse attention, working memory, and naming skills ($n=73$, mean age 70 ± 13 years, 53% male). Increased BP reactivity has been linked to an increased risk of cerebrovascular disease by mechanisms such as microvascular damage (vessel shearing, vasospasms, hypoperfusion etc.), silent brain infarcts and white matter disease (Waldstein et al., 2004, Elias et al., 1993, Harrington et al., 2000, Kario et al., 1996). These cerebral pathologies located in the prefrontal and temporal cortices contribute to cognitive symptoms; particularly attention and working memory deficits (Lezak et al., 2012). Others also suggest cortisol reactivity should be examined, as a potential concomitant factor for cognitive decline, leading to decreased hippocampal volume and affecting memory, attention, and executive function (Lupien et al., 2005a, Li et al., 2006, Wright et al., 2005, Brown et al., 2009).

6.2.3.3 Comparison between females ($n=42$) and males ($n=23$) (51-65 years)

Males in the 51-65 year old cohort had significantly higher baseline SBP than females, which has been well supported by the literature. The American Heart Association has shown males have higher BP than females up until menopausal ages of approximately 45-65 years, where the differences in BP are minimal between sexes. After 65 years of age, females can show higher BP than males (Go, 2013). BP changes post-menopause have been linked to the changes in the renin-angiotensin-aldosterone system, decreased nitric oxide (vasodilator), increased oxidative stress, and changes in androgen levels such as the cardio-protective hormone oestrogen (Reckelhoff, 2001). Unfortunately, menopausal data was not collected in this analysis and which may have proved useful.

Ginty et al. (2012) compared BP between sexes in a larger cohort with a similar age range to the present study, finding no significant differences of BP between males and females and that BP reactivity was positively linked to cognitive performance for both sexes ($n=724$, mean age 58 ± 1 years, 47% male). In contrast, in the present study, females showed BP reactivity links to cognitive performance, yet males showed no such significant relationships. Recent work by Cherbuin et al. (2015) also found sex disparities in BP and cognitive relationships, showing higher mean arterial BP was linked to better cognitive performance in males, yet the opposite relationship was identified in females ($n=266$, age range 68-73 years). They suggested that the involvement of exposure to

different risks over a lifetime, cardiovascular differences, and other physiological disparities may contribute to the cardiovascular differences identified between the sexes (Cherbuin et al., 2015, Mercurio et al., 2010).

6.2.4 Age group comparisons (18-35, 36-50, 51-65 years) in females and males

6.2.4.1 Females (18-35, 36-50, 51-65 years)

In females, in the 36-50 year age group, DBP rose significantly, and in the 51-65 year age group, SBP rose significantly from pre to post study. Further, DBP reactivity values were significantly higher in the middle age group (36-50 years) than the youngest age group (18-35 years). This agrees with the literature, as increasing age is linked to rises in BP and BP reactivity (Carrington et al., 2010, Uchino et al., 2010). A meta-analysis of 31 experiments showed significant links between aging and higher SBP reactivity (Uchino et al., 2010). The meta-analysis also revealed that results were consistent with the dynamic integration theory, which details that increasing difficulty of a task and increased motivation to perform the task (e.g. monetary reward) increases the physiological response. The theory suggests that as age increases, the greater the impact on the homeostatic resources, the greater the physiological reaction (Labouvie-Vief, 2008).

In response to these findings, it was proposed that natural cognitive decline with aging may affect the ability to physiologically regulate and to respond appropriately to mental stressors (Uchino et al., 2005, Labouvie-Vief, 1999). Recovery time after the cognitive tests to the final BP readings may also affect the degree of BP reactivity measured and ought to be recorded, particularly as physiological recovery takes longer in older age (Salomon et al., 2009).

In the present study there were different relationships between baseline BP and cognitive performance in the three female age groups. The baseline BP readings in the 18-35 and 36-50 year groups both showed positive correlations to cognitive domains whereas the 51-65 year group showed an inverse correlation. Most researchers agree there is an inverse relationship between BP and cognitive performance, in all three age groups (Allen et al., 2011, Chen et al., 2015, Yaffe et al., 2014, Gustat et al., 2011, Singh-Manoux and Marmot, 2005, Yano et al., 2014). It has also been reported, however, that in the 'old-old' (>85 years), increased BP can be beneficial to support cerebral perfusion, cognitive

processes, and overall longevity in a system with reduced cardiac output and weakened vasculature (Hospers et al., 2014). Studies have reported better survival rates in ‘old-old’ cohorts with higher rather than lower baseline BP ($>140/90\text{mmHg}$) (Oates et al., 2007, Satish et al., 2001).

Both the 18-35 and 51-65 year female groups had positive correlations between BP reactivity and cognitive domains, however, the middle age group, 36-50 years, showed an inverse correlation. Literature supports both the inverse and positive relationships between BP reactivity and cognition (Ginty et al., 2012, Lovallo, 2011, Carroll et al., 2012), where over- or under-responsive BP changes may be detrimental to cognitive performance.

6.2.4.2 Males (18-35, 36-50, 51-65 years)

No significant differences were observed between baseline and post study BP recordings in any of the three male age groups, nor were there any significant differences between these age groups. Literature with larger sample sizes strongly supports the notion that rising BP is linked to aging in both males and females (DeCarli, 2015, Nilsson et al., 2013, Hart and Charkoudian, 2014, Carrington et al., 2010). A large cross-sectional study by Carrington et al. (2010) examined 13825 participants and found older aged subjects had significantly higher BP than the younger, in both males and females (mean age 48 ± 16 years, 45% male). Uchino et al. (2005) also identified BP reactivity increases with aging in a longitudinal analysis over 10 months ($n=108$, mean age 48 ± 11 years, 48% male), which was also supported by cross sectional research (Carroll et al., 2003). In addition, increases in sympathetic nervous activity have been shown to accompany aging during baseline and stressor states, also increasing the risk of high BP ($n=21$, age range 20-30 years, $n=12$, age range 60-75 years, 100% male) (Esler et al., 1995).

In the younger male age group, aged 18-35 years, negative correlations were identified between cognitive domains and both baseline BP and BP reactivity (e.g. baseline DBP and orientation and judgment (Cognistat)), yet the 30-50 year old group did not show any significant correlations. The oldest group, aged 51-65 years, exhibited a range of contrasting relationships, both inverse and direct links between cognitive domains and baseline BP and BP reactivity (e.g. inverse correlation: baseline SBP and recall (MMSE), DBP reactivity and calculation (Cognistat); direct correlation: baseline DBP and

judgment (Cognistat), DBP reactivity and attention (Cognistat)). These differences may potentially be attributed to the lower sample size in the older group (n=23) compared to the middle (n=37) and younger groups (n=42) and further analysis is recommended to confirm results. Other studies have also reported both negative and positive associations between BP reactivity and cognition (Ginty et al., 2012, Lovallo, 2011, Carroll et al., 2012), where exaggerated or diminished BP responses may have negative cognitive outcomes.

6.2.4.3 Comparison of BP and cognition between total females (n=120) and males (n=102)

Comparisons of BP between total male and female groups identified males had significantly higher baseline DBP, SBP, and post study SBP. The American Heart Association (2005) acknowledges that males have higher BP than females until the menopausal ages of approximately 45-65 years, after which BP levels become similar. The sample distribution congregating towards the younger groups may have inflated this difference in the present sample.

6.3 Conclusion: BP and cognition (non-clinical groups)

Overall, the current study identified various associations between BP and cognitive performance partially supporting hypothesis 2 (predicting a significant inverse relationship between BP and cognitive function). Higher baseline BP was significantly correlated to better cognitive performance in females aged 18-65 years and in males aged 51-65 years, which (in both cases) has not been well supported by other studies (Yaffe et al., 2014, Singh-Manoux and Marmot, 2005, Allen et al., 2011). In contrast, inverse correlations were identified between baseline BP and cognitive performance in males (18-35 and 51-65 years), which is strongly supported by other research (Crichton et al., 2014, Gottesman et al., 2014, Dinh et al., 2014). The majority of BP studies tend to focus on older age samples, however, the current study identified that BP was positively correlated to cognitive performance (comprehension and construction (Cognistat)) in the young female cohort yet inversely correlated to orientation and judgment in young males. This new contribution to the literature suggests that sex may impact the link between baseline BP and cognition in early life. It was also interesting to observe the changes in the direction of the correlation between baseline BP and cognition over the three female age groups; lower baseline BP was linked to poorer cognitive performance in the 18-50 year group, yet higher BP was linked to poorer cognitive performance in the 51-65 year group. The mechanisms behind this shift may involve hormonal changes or menopause and the effects on the cardiovascular system, however, more research is required.

Hypothesis 3 was not well supported by the findings of the current study showing BP reactivity was mostly positively correlated to cognitive performance, indicating increased reactivity is beneficial to cognition and that declines in reactivity may be a marker for cognitive dysfunction. These relationships also exhibited a sex dimorphism, with females showing more positive correlations between BP parameters and cognitive performance than males, potentially linked to differences in stress responsivity between sexes (Allen et al., 2011). Refer to Table 6.17, Table 6.18 and Table 6.19 for a summary of significant results in each age group.

Table 6.17 Summary of significant correlations between BP values and cognitive domains in females (n=41) and males (n=42) aged 18-35 years

Cognitive test	Cognitive domain	BP parameter		
		Baseline	BP reactivity	
		DBP	SBP	DBP
MMSE	Orientation	-		
	Attention		- +	
	Language			+
	Total score		- +	
Cognistat	Orientation		+	
	Comprehension	+		
	Naming			+
	Construction	+		
	Judgment	-		

Table 6.17 displays significant correlations between BP values and cognitive domains from the MMSE (Folstein et al., 1975) and Cognistat (Kiernan et al., 1987) in females (shown in red) (n=41) and males (shown in black) (n=42) aged 18-35 years. BP reactivity refers to the post minus pre study (baseline) BP data.

Key: BP = Blood pressure; DBP = Diastolic blood pressure; MMSE = Mini Mental State Examination; SBP = Systolic blood pressure; + = Positive correlation; - = Negative correlation

Table 6.18 Summary of significant correlations between BP values and cognitive domains in females (n=37) and males (n=37) aged 36-50 years

Cognitive test	Cognitive domain	BP parameter	
		Baseline	BP reactivity
		SBP	SBP
MMSE	Attention	+	-
	Total score	+	
Cognistat	Attention	+	
	Repetition	+	
	Naming	+	

Table 6.18 displays significant correlations between BP values and cognitive domains from the MMSE (Folstein et al., 1975) and Cognistat (Kiernan et al., 1987) in females (shown in red) (n=37) and males (shown in black) (n=37) aged 36-50 years. BP reactivity refers to the post minus pre study (baseline) BP data.

Key: BP = Blood pressure; MMSE = Mini Mental State Examination; SBP = Systolic blood pressure; + = Positive correlation; - = Negative correlation

Table 6.19 Summary of significant correlations between BP values and cognitive domains in females (n=42) and males (n=23) aged 51-65 years

Cognitive test	Cognitive domain	BP parameter		
		Baseline	BP reactivity	
		SBP	DBP	DBP
MMSE	Recall	-		
Cognistat	Attention			+
	Repetition			+
	Naming	-		+
	Calculation			-
	Similarity	-		+
	Judgment		+	
	Total score	-		

Table 6.19 displays significant correlations between BP values and cognitive domains from the MMSE (Folstein et al., 1975) and Cognistat (Kiernan et al., 1987) in females (shown in red) (n=42) and males (shown in black) (n=23) aged 51-65 years. BP reactivity refers to the post minus pre study (baseline) BP data.

Key: BP = Blood pressure; DBP = Diastolic blood pressure; MMSE = Mini Mental State Examination; SBP = Systolic blood pressure; + = Positive correlation; - = Negative correlation

7. BP and cognition (clinical groups)

Although existing literature in the area of BP and cognitive function is vast there remains some contention in the field, particularly regarding this relationship in the clinical groups (depression, DM (type 1 and 2), and hypertension). There is a particular focus on BP change or cognitive change in a disease rather than the link between them within a clinical group. Higher BP in each of the clinical groups have previously been linked to poorer cognitive scores (Gustat et al., 2011, Jacobson et al., 2010, Feinkohl et al., 2015, Exalto et al., 2014) however researchers call for further analysis of these links as others have found that hypotension is linked to cognitive dysfunction (Pandav et al., 2003), or that both high and low BP is correlated to cognitive impairment (Waldstein et al., 2005). In addition BP reactivity and cognitive performance in the aforementioned clinical cohorts has not been well examined in the literature.

Therefore the following results and discussion chapters 7.1 and 7.2 explore specific aims 1, 4, 5, and 6 (as shown in section 2.1.2.1), to identify the relationship between BP and cognitive function; to examine if clinical conditions, depression, type 1 DM, type 2 DM, hypertension, will affect the relationship between BP, to identify the relationships between cardiac autonomic reactivity and cognition in clinical and control groups and cognition; and to identify significant relationships between BP and different cognitive domains as a potential predictive marker for identifying those at higher risk of cognitive impairment.

7.1 Results: BP and cognition (clinical groups)

A total of 74 volunteers with chronic illnesses, aged 18-80 years, were recruited for the present study in the Neuroscience Research Unit at UTS. Subjects with the following illnesses were included: depression (n=10), type 1 diabetes (n=9), type 2 diabetes (n=38), and hypertension (n=39). There was some overlap with participants exhibiting > 1 chronic illness. This was adjusted for as a covariate in the analysis as ‘number of chronic illnesses’. There were also individual volunteers with ‘other’ chronic illnesses (silicosis, gout, osteoporosis, and idiopathic peripheral neuropathy) which were not included in the data analysis due to small sample numbers (n=4). Refer to Figure 5.1 for a sample size

breakdown for the clinical groups and Table 5.1 for the number of chronic illnesses in each group.

This chapter reports the results for cognitive function and BP in the chronic illness groups and compares them to a sex and age matched control group selected from previously collected non-clinical cohort (see chapter 3 section 3.9 for matching criteria).

7.1.1 Depression (n=10)

Mean (\pm SD) demographics and cognitive scores from the MMSE for participants with depression (n=10) are provided in the previous section 5.1.1 (Table 5.2 and Table 5.3, respectively). Mean BP values for these participants are provided in Table 7.1.

Table 7.1 Mean BP values for participants with depression (n=10)

Variable		SBP mean \pm SD (mmHg)	DBP mean \pm SD (mmHg)
Depression n=10	Pre study (baseline)	130.10 \pm 13.73	77.20 \pm 11.88
	Post study	127.20 \pm 12.84	78.50 \pm 9.86
	BP reactivity (post - pre)	-2.90 \pm 11.29	1.30 \pm 8.90

Table 7.1 displays the mean BP values for the sample with depression (n=10).

Key: BP = Blood pressure; DBP = Diastolic blood pressure; mmHg = Millimetres of mercury; n = Sample size; SBP = Systolic blood pressure; SD = Standard deviation

Wilcoxon signed rank tests did not identify any significant differences between pre and post study BP values in the depression sample.

Spearman’s bivariate and partial correlations were performed separately between BP and cognitive scores to address aims 1 and 5 (Table 7.2 and Table 7.3, respectively).

Table 7.2 Bivariate Spearman’s correlation coefficients between cognitive scores and blood pressure values in subjects with depression (n=10)

	Dependent variable	Independent variable	r	p
Depression n=10	Orientation MMSE	Baseline DBP	-0.72	0.02
	Language MMSE	Baseline DBP	-0.67	0.03
	Total MMSE	Baseline SBP	-0.67	0.04*
		Baseline DBP	-0.95	<0.001
	Similarity Cognistat	Baseline DBP	-0.65	0.04
	Recall MMSE	SBP reactivity	0.70	0.03

Table 7.2 displays significant results from a bivariate Spearman’s correlation between cognitive scores (MMSE (Folstein et al., 1975) and Cognistat (Kiernan et al., 1987)) and blood pressure values in the sample with depression (n=10).

Key: DBP = Diastolic blood pressure; MMSE = Mini Mental State Examination; n = Sample size; p = Level of statistical significance (p<0.05); r = Correlation coefficient; SBP = Systolic blood pressure; * = Bonferroni correction excludes this significant correlation

Table 7.3 Partial Spearman’s correlation coefficients between cognitive scores and blood pressure values in subjects with depression (n=10)

	Covariate	Dependent variable	Independent variable	r	p
Depression n=10	Sex	Attention MMSE	DBP reactivity	0.58	0.049
		Repetition Cognistat		0.58	0.049
		Naming Cognistat		0.58	0.049
	Years of education	Language MMSE	DBP reactivity	0.62	0.04

Table 7.3 displays significant results from a partial Spearman’s correlation between cognitive scores (MMSE (Folstein et al., 1975) and Cognistat (Kiernan et al., 1987)) and blood pressure values in the sample with depression (n=10).

Key: DBP = Diastolic blood pressure; MMSE = Mini Mental State Examination; n = Sample size; p = Level of statistical significance ($p < 0.05$); r = Correlation coefficient

7.1.2 Control group without depression (n=10)

Mean (\pm SD) demographics and cognitive scores from the MMSE and Cognistat for the control group without depression (n=10) are provided in the previous section 5.1.2 (Table 5.8 and Table 5.9, respectively). Mean BP values are provided in Table 7.4.

Table 7.4 Mean BP values for the control group without depression (n=10)

	Variable	SBP mean \pm SD (mmHg)	DBP mean \pm SD (mmHg)
Control group without depression (n=10)	Pre study (baseline)	126.60 \pm 13.09	81.30 \pm 9.72
	Post study	125.00 \pm 11.02	81.50 \pm 5.76
	BP reactivity (post - pre)	-1.60 \pm 5.56	0.20 \pm 5.39

Table 7.4 displays the mean BP values for the control group without depression (n=10).

Key: BP = Blood pressure; DBP = Diastolic blood pressure; mmHg = Millimetres of mercury; n = Sample size; SBP = Systolic blood pressure; SD = Standard deviation

Wilcoxon signed rank tests did not identify significant differences between pre and post study BP values in the control group without depression.

Spearman’s bivariate and partial correlations were performed separately between BP and cognitive scores to address aims 1 and 5 (Table 7.5).

Table 7.5 Bivariate Spearman’s correlation coefficients between cognitive scores and blood pressure values in the control group without depression (n=10)

	Dependent variable	Independent variable	r	p
Control group without depression (n=10)	Comprehension Cognistat	SBP reactivity	0.64	0.04
	Construction Cognistat		0.66	0.04
	Total Cognistat		0.65	0.04

Table 7.5 displays significant results from a Spearman correlation between cognitive scores (MMSE (Folstein et al., 1975) and Cognistat (Kiernan et al., 1987)) and blood pressure values in the control group without depression (n=10).

Key: MMSE = Mini Mental State Examination; n = Sample size; p = Level of statistical significance (p<0.05); r = Correlation coefficient; SBP = Systolic blood pressure

Partial Spearman’s correlations showed a negative relationship between language (MMSE) and DBP reactivity (r=-0.68, p=0.047) (controlled for LAQ part one and sex).

7.1.2.1 Depression (n=10) and the control group (n=10)

Mean BP values for subjects with depression (n=10) and the control group without depression (n=10) are displayed in Figure 7.1.

Figure 7.1 Mean BP values for subjects with depression (n=10) and the control group without depression (n=10)

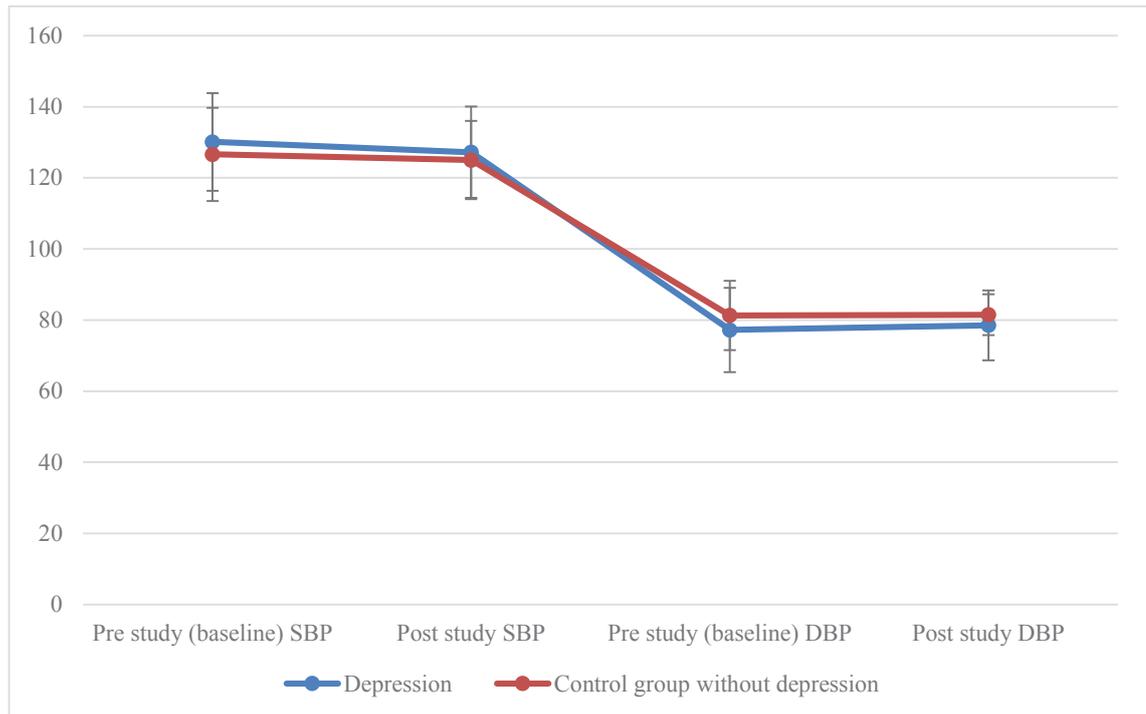


Figure 7.1 displays mean BP values for subjects with depression (n=10) and the control group without depression (n=10).

Key: BP = Blood pressure; DBP = Diastolic blood pressure; SBP = Systolic blood pressure

Neither the depression group nor the matched control group showed significant differences between pre and post study BP values using Wilcoxon signed rank tests.

Refer to previous section 5.1.2.1 for significant cognitive differences between the depression and control group. There were no significant differences identified for BP values between the two groups.

Significant correlations in the depression and control group were compared using Z scores to address aim 4. The language (MMSE) domain correlation with DBP reactivity was

significantly different between the clinical and control group ($Z=2.91$, $p=0.002$) ($r=0.62$, $p=0.04$; $r=-0.68$, $p=0.047$, respectively).

7.1.3 Type 1 DM (n=9)

Mean (\pm SD) demographics and cognitive scores from the MMSE and Cognistat for participants with type 1 diabetes (n=9) are provided in the previous section 5.1.3 (Table 5.14 and Table 5.15, respectively). Mean BP values are provided in Table 7.6.

Table 7.6 Mean BP values for subjects with type 1 diabetes (n=9)

Variable		SBP mean \pm SD (mmHg)	DBP mean \pm SD (mmHg)
Type 1 diabetes n=9	Pre study (baseline)	133.33 \pm 14.76	79.67 \pm 6.86
	Post study	132.11 \pm 18.70	77.78 \pm 8.47
	BP reactivity (post - pre)	-1.22 \pm 9.07	-1.89 \pm 5.09

Table 7.6 displays the mean BP values for subjects with type 1 diabetes (n=9).

Key: BP = Blood pressure; DBP = Diastolic blood pressure; mmHg = Millimetres of mercury; n = Sample size; SBP = Systolic blood pressure; SD = Standard deviation

Wilcoxon signed rank tests did not identify significant differences between pre and post study BP values in the type 1 DM cohort.

Spearman’s bivariate and partial correlations were performed separately between BP and cognitive scores to address aims 1 and 5 (Table 7.7 and Table 7.8).

Table 7.7 Bivariate Spearman’s correlation coefficients between cognitive scores and blood pressure values in subjects with type 1 diabetes (n=9)

	Dependent variable	Independent variable	r	p
Type 1 diabetes n=9	Recall MMSE	Baseline DBP	-0.73	0.03
	Attention Cognistat	Baseline DBP	0.73	0.03
	Total MMSE	SBP reactivity	0.67	0.048

Table 7.7 displays significant results from a bivariate Spearman’s correlation between cognitive scores (MMSE (Folstein et al., 1975) and Cognistat (Kiernan et al., 1987)) and blood pressure values in subjects with type 1 diabetes (n=9).

Key: DBP = Diastolic blood pressure; MMSE = Mini Mental State Examination; n = Sample size; p = Level of statistical significance (p<0.05); r = Correlation coefficient; SBP = Systolic blood pressure

Table 7.8 Partial Spearman’s correlation coefficients between cognitive scores and blood pressure values in subjects with type 1 diabetes (n=9)

	Covariate	Dependent variable	Independent variable	r	p
Type 1 diabetes n=9	Smoking status	Memory Cognistat	SBP reactivity	-0.71	0.02
		Total Cognistat	DBP reactivity	-0.63	0.047
	Age	Orientation MMSE	SBP reactivity	0.71	0.02
			DBP reactivity	0.80	0.01
	Years of education, smoking status, disease duration (years) and LAQ part two (stress coping)	Memory Cognistat	DBP reactivity	-0.90	0.02

Table 7.8 displays significant results from a partial Spearman’s correlation between cognitive scores (MMSE (Folstein et al., 1975) and Cognistat (Kiernan et al., 1987)) and blood pressure values in subjects with type 1 diabetes (n=9).

Key: DBP = Diastolic blood pressure; LAQ = Lifestyle Appraisal Questionnaire (Craig et al., 1996); MMSE = Mini Mental State Examination; n = Sample size; p = Level of statistical significance (p<0.05); r = Correlation coefficient; SBP = Systolic blood pressure

7.1.4 Control group without type 1 DM (n=9)

Mean (\pm SD) demographics and cognitive scores from the MMSE and Cognistat for control group without type 1 diabetes (n=9) are provided in the previous section 5.1.4 (Table 5.21 and Table 5.22, respectively). Mean BP values are provided in Table 7.8.

Table 7.9 Mean BP values for the control group without type 1 diabetes (n=9)

	Variable	SBP mean \pm SD (mmHg)	DBP mean \pm SD (mmHg)
Control group without type 1 diabetes (n=9)	Pre study (baseline)	127.33 \pm 6.86	81.11 \pm 5.73
	Post study	126.22 \pm 9.68	78.33 \pm 6.54
	BP reactivity (post - pre)	-1.11 \pm 4.34	-2.78 \pm 4.21

Table 7.9 displays the mean BP values for the control group without type 1 diabetes (n=9).

Key: BP = Blood pressure; DBP = Diastolic blood pressure; mmHg = Millimetres of mercury; n = Sample size; SBP = Systolic blood pressure; SD = Standard deviation

Wilcoxon signed rank tests did not identify significant differences between pre and post study BP values in the control group without type 1 DM.

Spearman’s bivariate correlations were performed between BP and cognitive scores to address aims 1 and 5, and were not significant. Significant partial Spearman’s correlations are shown in Table 7.10.

Table 7.10 Partial Spearman’s correlation coefficients between cognitive scores and blood pressure values in the control group without type 1 diabetes (n=9)

	Covariate	Dependent variable	Independent variable	r	p
Control group without type 1 diabetes (n=9)	LAQ part one (lifestyle risk factors)	Attention Cognistat	Baseline SBP	0.71	0.02
		Judgment Cognistat		0.66	0.04
		Construction Cognistat		0.70	0.03
		Memory Cognistat	Baseline DBP	0.85	0.004
		Total Cognistat		0.80	0.01
	BMI	Naming Cognistat	DBP reactivity	0.71	0.03
	Age	Language MMSE	SBP reactivity	0.63	0.048
		Total MMSE		0.67	0.04
		Attention Cognistat		0.71	0.02
		Construction Cognistat		0.75	0.02
Total Cognistat		0.70		0.03	

Table 7.10 displays significant results from a partial Spearman’s correlation between cognitive scores (MMSE (Folstein et al., 1975) and Cognistat (Kiernan et al., 1987)) and blood pressure values in control group without type 1 diabetes (n=9).

Key: BMI = Body mass index; DBP = Diastolic blood pressure; LAQ = Lifestyle Appraisal Questionnaire (Craig et al., 1996); MMSE = Mini Mental State Examination; n = Sample size; p = Level of statistical significance (p<0.05); r = Correlation coefficient; SBP = Systolic blood pressure

7.1.4.1 Type 1 DM (n=9) and the control group (n=9)

Mean BP values for subjects with type 1 diabetes (n=9) and the control group without type 1 diabetes (n=9) are displayed in Figure 7.2.

Figure 7.2 Mean BP values for subjects with type 1 diabetes (n=9) and the control group without type 1 diabetes (n=9)

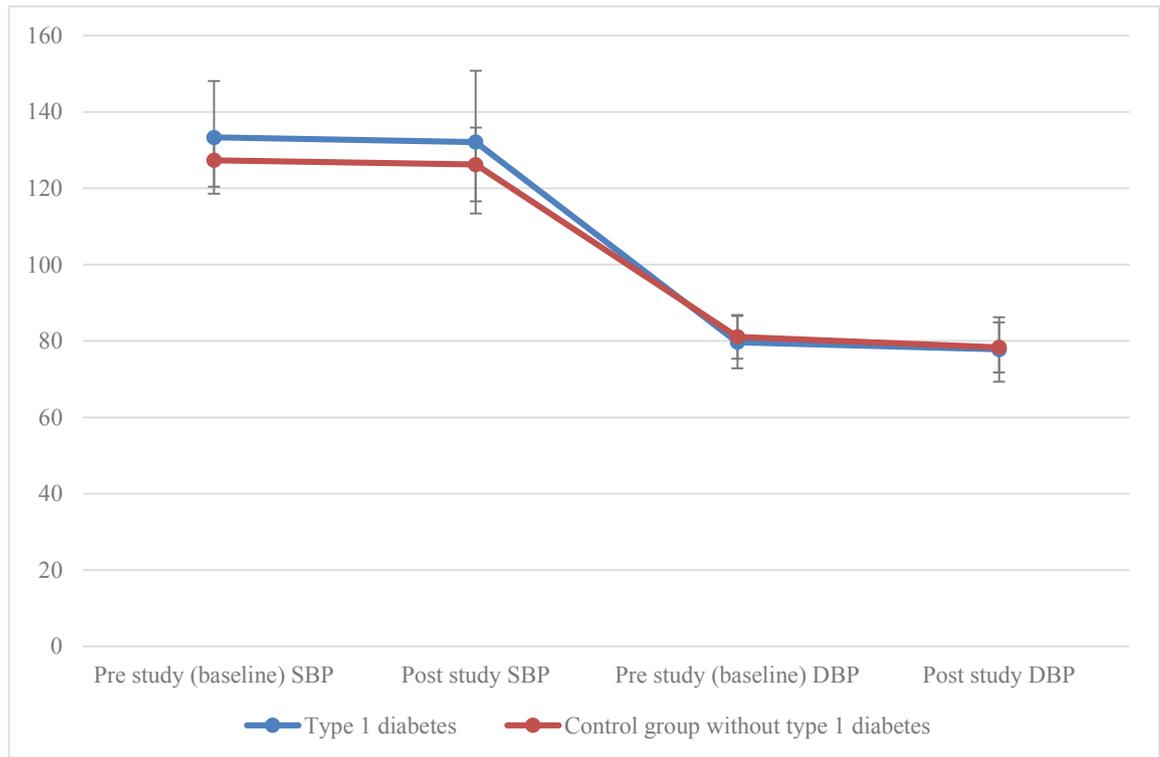


Figure 7.2 displays mean BP values for subjects with type 1 diabetes (n=9) and the control group without type 1 diabetes (n=9).

Key: BP = Blood pressure; DBP = Diastolic blood pressure; SBP = Systolic blood pressure

Neither participants with type 1 diabetes nor control group participants had significantly different BP pre to post study, as determined by Wilcoxon signed rank tests.

Refer to previous section 5.1.4.1 for significant cognitive differences between type 1 diabetes and the control group. There were no significant differences identified for BP values between the two groups.

There were no matching correlations to compare using Z scores between the type 1 diabetes group and the control group.

7.1.5 Type 2 DM (n=38)

Mean (\pm SD) demographics and cognitive scores from the MMSE and Cognistat for participants with type 2 diabetes (n=38) are provided in the previous section 5.1.5 (Table 5.28 and Table 5.29, respectively). Mean BP values are provided in Table 7.11.

Table 7.11 Mean BP values for subjects with type 2 diabetes (n=38)

	Variable	Mean (\pm SD) SBP (mmHg)	Mean (\pm SD) DBP (mmHg)
Type 2 diabetes n=38	Pre study (baseline)	141.24 \pm 14.50	78.24 \pm 9.87
	Post study	142.61 \pm 16.92	81.26 \pm 9.74
	BP reactivity (post - pre)	1.37 \pm 12.01	3.03 \pm 6.34

Table 7.11 displays the mean BP values for subjects with type 2 diabetes (n=38).

Key: BP = Blood pressure; DBP = Diastolic blood pressure; mmHg = Millimetres of mercury; n = Sample size; SBP = Systolic blood pressure; SD = Standard deviation

Dependent sample t-tests showed that DBP significantly rose from pre to post study ($t=2.94$, $df=37$, $p=0.01$) (78.24 ± 9.87 , 81.26 ± 9.74 , respectively).

Pearson’s bivariate and partial correlations were performed separately between BP and cognitive scores to address aims 1 and 5. No correlations without covariates were significant. Significant partial Pearson’s correlations are shown in Table 7.12.

Table 7.12 Partial Pearson’s correlation coefficients between cognitive scores and blood pressure values in subjects with type 2 diabetes (n=38)

Covariate		Dependent variable	Independent variable	r	p
Type 2 diabetes n=38	Years of education and LAQ part one (lifestyle risk factors)	Repetition Cognistat	Baseline SBP	-0.37	0.03
		Comprehension Cognistat		-0.35	0.04
		Memory Cognistat		-0.50	0.002
		Total Cognistat		-0.51	0.001
	Sex, number of illnesses and disease duration (years)	Repetition Cognistat	Baseline DBP	-0.36	0.04*
		Construction Cognistat		0.34	0.049
	LAQ part 1 (lifestyle risk factors)	Total MMSE	DBP reactivity	0.38	0.02
	Number of illnesses, years of education and smoking status	Total MMSE	SBP reactivity	0.36	0.04*
	Smoking status, disease duration (years) and LAQ part 1 (lifestyle risk factors)	Language MMSE	DBP reactivity	0.47	0.01
	Smoking status and disease duration (years)	Language MMSE	SBP reactivity	0.39	0.02

Table 7.12 displays significant results from a partial Pearson’s correlation between cognitive scores (MMSE (Folstein et al., 1975) and Cognistat (Kiernan et al., 1987)) and blood pressure values in subjects with type 2 diabetes (n=38).

Key: DBP = Diastolic blood pressure; LAQ = Lifestyle Appraisal Questionnaire (Craig et al., 1996); MMSE = Mini Mental State Examination; n = Sample size; p = Level of statistical significance ($p < 0.05$); r = Correlation coefficient; SBP = Systolic blood pressure; * = Bonferroni correction excludes this significant correlation

7.1.6 Control group without type 2 DM (n=30)

Mean (\pm SD) demographics and cognitive scores from the MMSE and Cognistat for the control group without type 2 diabetes (n=30) are provided in the previous section 5.1.6 (Table 5.34 and Table 5.35, respectively). Mean BP values are provided in Table 7.13.

Table 7.13 Mean BP values for the control group without type 2 diabetes (n=30)

	Variable	SBP mean \pm SD (mmHg)	DBP mean \pm SD (mmHg)
Control group without type 2 diabetes (n=30)	Pre study (baseline)	127.57 \pm 11.66	80.77 \pm 8.83
	Post study	128.63 \pm 9.02	80.47 \pm 7.11
	BP reactivity (post - pre)	1.07 \pm 6.96	-0.30 \pm 4.40

Table 7.13 displays the mean BP values for the control group without type 2 diabetes (n=30).

Key: BP = Blood pressure; DBP = Diastolic blood pressure; mmHg = Millimetres of mercury; n = Sample size; SBP = Systolic blood pressure; SD = Standard deviation

The dependent sample t-tests did not identify significant differences between pre and post BP values in the control group without type 2 diabetes.

Pearson’s bivariate and partial correlations were performed separately between BP and cognitive scores to address aims 1 and 5. A positive correlation was identified between calculation (Cognistat) and baseline SBP ($r=0.45$, $p=0.01$).

7.1.6.1 Type 2 DM (n=38) and the control group (n=30)

Mean BP values for subjects with type 2 diabetes (n=38) and the control group without type 2 diabetes (n=30) are displayed in Figure 7.3.

Figure 7.3 Mean BP values for subjects with type 2 diabetes (n=38) and the control group without type 2 diabetes (n=30)

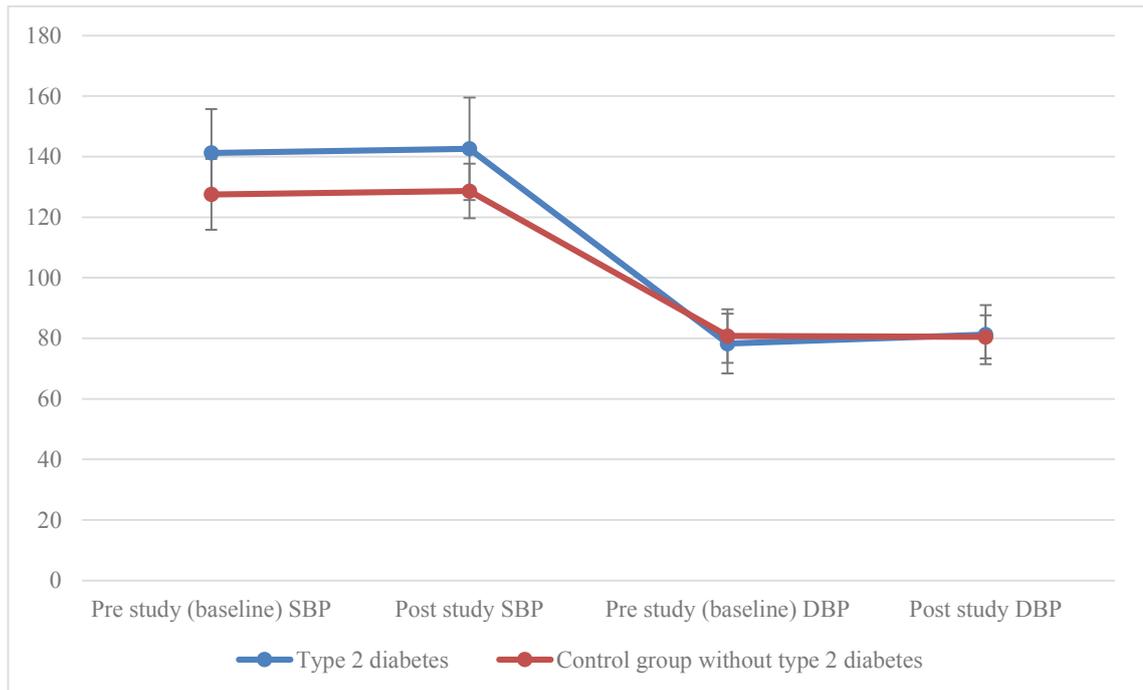


Figure 7.3 displays mean BP values for subjects with type 2 diabetes (n=38) and the control group without type 2 diabetes (n=30).

Key: BP = Blood pressure; DBP = Diastolic blood pressure; SBP = Systolic blood pressure

It was observed that DBP increased significantly in participants with type 2 DM from pre to post study, yet was not significantly different in the control group.

Refer to previous section 5.1.6.1 for significant cognitive differences between type 2 diabetes and the control group. Independent sample t-test showed DBP reactivity was significantly higher in the type 2 diabetes group (3.03 ± 6.34 mmHg) than the control group (-0.30 ± 4.40 mmHg) ($t=-2.55$, $df=65.02$, $p=0.01$, Levene's test $p=0.04$ (equal variances not assumed)).

Independent sample t-tests with covariance were performed between type 2 diabetes and the control group (Table 7.14).

Table 7.14 Independent sample t-test with covariance of blood pressure values between subjects with type 2 diabetes and the control group

Control group without type 2 diabetes (n=30)	Covariate	Variable	F	df	p	Control mean ± SD (mmHg)	Clinical mean ± SD (mmHg)	Mean difference (clinical – control)
	Years of education, age and LAQ part one (lifestyle risk factors)		Pre SBP (baseline)	5.89	2, 56	0.01	127.57 ± 11.66	141.24 ± 14.50
		Post SBP	7.67	2, 56	0.002	128.63 ± 9.02	142.61 ± 16.92	13.98

Table 7.14 displays significant results from an independent sample t-test with covariance (performed by MANCOVA) of blood pressure values between type 2 diabetes group (n=38) and the control group (n=30).

Key: df= Degrees of freedom; F = F statistic; LAQ = Lifestyle Appraisal Questionnaire (Craig et al., 1996); MANCOVA = Multiple analysis of covariance; n = Sample size; p = Level of statistical significance (p<=0.05); SBP = Systolic blood pressure

There were no matching correlations identified between the type 2 diabetes group and control group to compare.

7.1.7 Hypertension (n=39)

Mean (\pm SD) demographics and cognitive scores from the MMSE and Cognistat for subjects with hypertension (n=39) are provided in section 5.1.7 (Table 5.42 and Table 5.43, respectively). Mean BP values are provided in Table 7.15.

Table 7.15 Mean BP values for subjects with hypertension (n=39)

	Variable	SBP mean \pm SD (mmHg)	DBP mean \pm SD (mmHg)
Hypertension n=39	Pre study (baseline)	137.54 \pm 14.43	76.87 \pm 10.89
	Post study	140.05 \pm 15.12	79.72 \pm 10.14
	BP reactivity (post - pre)	2.51 \pm 9.54	2.85 \pm 6.90

Table 7.15 displays the mean BP values for subjects with hypertension (n=39).

Key: BP = Blood pressure; DBP = Diastolic blood pressure; mmHg = Millimetres of mercury; n = Sample size; SBP = Systolic blood pressure; SD = Standard deviation

Dependent sample t-tests were performed, showing DBP rose significantly from pre to post study ($t=-2.58$, $df=38$, $p=0.01$) (pre study (baseline) 76.87 \pm 10.89, post study 79.72 \pm 10.14).

Pearson’s bivariate and partial correlations were performed separately between BP and cognitive scores to address aims 1 and 5. Negative bivariate correlations were identified between the Cognistat domains of attention and baseline DBP ($r=-0.43$, $p=0.01$). Significant partial correlations are shown in Table 7.16.

Table 7.16 Partial Pearson’s correlation coefficients between cognitive scores and blood pressure values in subjects with hypertension (n=39)

	Covariate	Dependent variable	Independent variable	r	p
Hypertension n=39	Years of education and LAQ part one (lifestyle risk factors)	Attention MMSE	Baseline SBP	-0.41	0.01
		Repetition Cognistat		-0.56	<0.001
		Memory Cognistat		-0.46	0.004
		Total Cognistat		-0.46	0.004

Table 7.16 displays significant results from a partial Pearson’s correlation between cognitive scores (MMSE (Folstein et al., 1975) and Cognistat (Kiernan et al., 1987)) and blood pressure values in subjects with hypertension (n=39).

Key: LAQ = Lifestyle Appraisal Questionnaire (Craig et al., 1996); MMSE = Mini Mental State Examination; n = Sample size; p = Level of statistical significance (p<0.05); r = Correlation coefficient; SBP = Systolic blood pressure

7.1.8 Control group without hypertension (n=31)

Mean (\pm SD) demographics and cognitive scores from the MMSE and Cognistat for the control group without hypertension (n=31) are provided in section 5.1.8 (Table 5.50 and Table 5.51, respectively). Mean BP values are provided in Table 7.17.

Table 7.17 Mean BP values for the control group without hypertension (n=31)

	Variable	SBP mean \pm SD (mmHg)	DBP mean \pm SD (mmHg)
Control group without hypertension (n=31)	Pre study (baseline)	128.35 \pm 11.10	81.90 \pm 7.46
	Post study	129.35 \pm 10.69	81.87 \pm 5.75
	BP reactivity (post - pre)	1.00 \pm 7.66	-0.03 \pm 5.36

Table 7.17 displays the mean BP values for the control group without hypertension (n=31).

Key: BP = Blood pressure; DBP = Diastolic blood pressure; mmHg = Millimetres of mercury; n = Sample size; SBP = Systolic blood pressure; SD = Standard deviation

Dependent sample t-tests did not identify significant differences between pre and post study BP values in the control group without hypertension.

Pearson’s bivariate and partial correlations were performed separately between BP and cognitive scores. No significant results were found.

7.1.8.1 Hypertension (n=39) and the control group (n=31)

Mean BP values for subjects with hypertension (n=39) and the control group without hypertension (n=31) are displayed in Figure 7.4.

Figure 7.4 Mean BP values for subjects with hypertension (n=39) and the control group without hypertension (n=31)

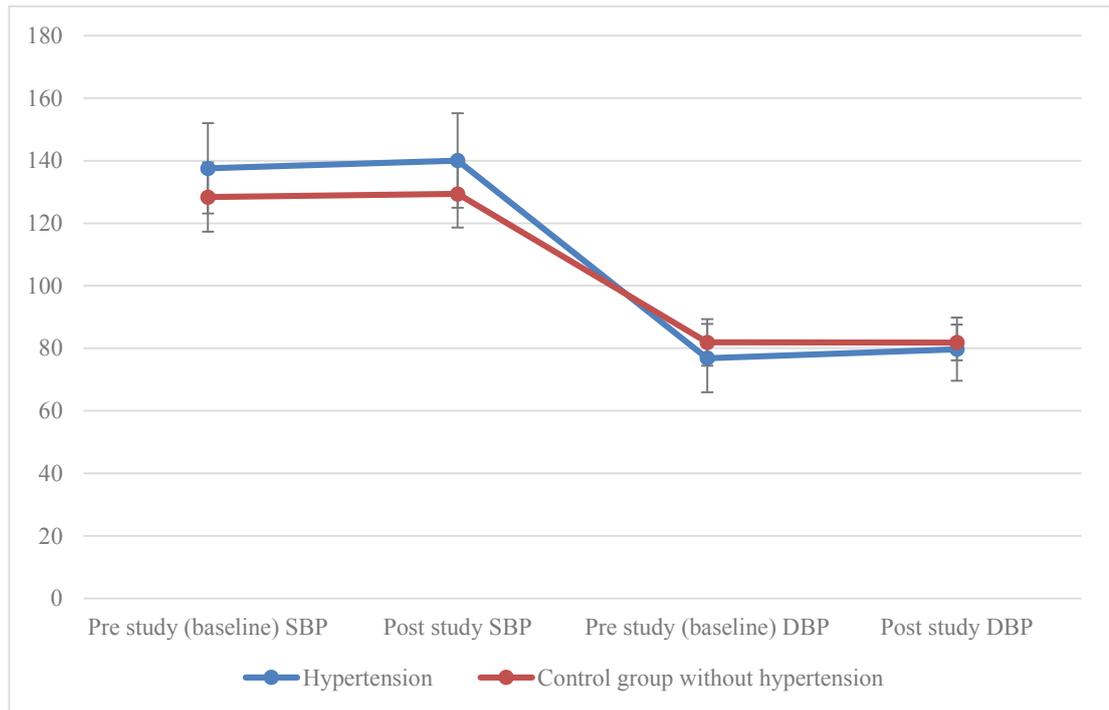


Figure 7.4 displays the mean BP values for subjects with hypertension (n=39) and the control group without hypertension (n=31).

Key: BP = Blood pressure; DBP = Diastolic blood pressure; SBP = Systolic blood pressure

It was observed that DBP increased significantly in the hypertension group from pre to post study, yet BP was not significantly different in the control group.

Refer to previous section 5.1.8.1 for significant cognitive differences between hypertension and the control group. Independent sample t-tests showed pre (baseline) DBP was significantly higher in the control group (81.90 ± 7.46 mmHg) than the hypertension group (76.87 ± 10.89 mmHg) ($t=2.29$, $df=66.68$, $p=0.03$, Levene’s test $p=0.02$ (equal variances not assumed)).

Independent sample t-tests with covariance were performed between the hypertension group and the control group. Pre and post study SBP were significantly higher in the group with hypertension ($F=4.04$, $df=1, 59$, $p=0.049$, 137.54 ± 14.43 mmHg; $F=5.83$, $df=1, 59$, $p=0.02$, 140.05 ± 15.12 mmHg, respectively) compared to the control group (128.35 ± 11.10 mmHg, 129.35 ± 10.69 mmHg, respectively) (controlled for years of education, age and LAQ part one).

There were no matching correlations to compare between the hypertension and control groups.

7.2 Discussion: BP and cognition (clinical groups)

Depression, DM (type 1 and 2), and hypertension have each been associated with an increased risk of developing autonomic neuropathy, which may affect BP control (see chapter 1, sections 1.2.4.1 to 1.2.4.3). This chapter explores the relationships between cognition and BP in participants with depression, DM (type 1 and 2), and hypertension, and compares findings to a sex and age matched healthy control group. Data in the smaller clinical groups (depression (n=10) and type 1 DM (n=9)) were examined using non-parametric statistics. Correlations that survived the Bonferroni corrections (performed to reduce the risk of type 1 errors (false positives)) in the depression (n=10) and type 1 DM (n=9) groups are also discussed.

7.2.1 Depression (n=10)

Comparisons of baseline and post study BP results in the sample with depression produced no significantly different results. However, correlations between BP and particular cognitive domains identified that baseline DBP was inversely linked to orientation (MMSE), language (MMSE), similarity (Cognistat), and total MMSE score.

Higher baseline BP has been consistently associated with cognitive decline in healthy cohorts and, more recently, in depression (Gustat et al., 2011, Doraiswamy et al., 2003). The Bogalusa Heart study identified those with higher BP and depression had inverse correlations to the Wechsler Adult Intelligence Scale (Wechsler, 1981) and the Wechsler Memory Scale scores (Wechsler, 1997) (n=351, mean age 43 ± 5 years, 57% female) (Gustat et al., 2011). Similarly, Doraiswamy et al. (2003) identified that both higher BP and depression severity compounded cognitive impairment in areas of memory, visual tracking, and coding (regardless of the antidepressant used: sertraline, fluoxetine, and nortryptiline) (n=440, mean age 68 ± 6 years, 42% male). It has been proposed that excess cortisol release in depressive states increases the risk of both hypertension and hippocampal atrophy, both of which may lead to cognitive impairment (Brown et al., 2004). Doraiswamy et al. (2003) also found that improvement in depressive symptoms (using antidepressant therapy) also improved cognitive performance in subjects with depression.

The present study identified positive correlations between DBP reactivity and cognitive measures of attention (MMSE), repetition (Cognistat), naming (Cognistat), and language (MMSE). SBP reactivity was also positively linked to recall (MMSE). These relationships suggest that higher BP reactivity (whether DBP or SBP) is better for cognitive function.

BP reactivity and cognitive performance in depression has not been well examined in the literature, hence the present findings contribute new knowledge to this field. Subjects with depression have been found to have attenuated BP reactivity during a speech stressor task, yet the aptitude of performing the task was not evaluated (n=120, mean age 30 ± 11 years, 15% male) (Salomon et al., 2013). This was also demonstrated in a population cohort by Carroll et al. (2007) (n=1608, mean age 42 ± 15 years, 46% males). Findings of the present study are consistent with the available literature, which has linked both lower BP reactivity and cognitive impairment (separately) to depression (de Rooij, 2013, Vasudev et al., 2012, Salomon et al., 2013).

7.2.1.1 Depression (n=10) and the control group (n=10)

Neither the depression group nor the control group showed significant differences between baseline and post study BP values. Also, BP values were not significantly different between the two groups.

Higher baseline BP is typical in depression, and is influenced by medication use, sleep quality and frequency of depressive episodes (Matthews et al., 2004a, Kabir et al., 2006, Licht et al., 2009, Gangwisch et al., 2010, Nabi et al., 2011). Nabi et al. (2011) analysed a large cohort of 10302 subjects (mean age 45 ± 6 years, 67% male, follow up 24 years) using longitudinal data from the Whitehall II study and found that frequent depressive episodes were linked to increased BP over time. The group discussed how ANS dysfunction caused by cortical changes associated with depression can lead to hypertension, and, as these effects develop slowly over time, so too does the development of hypertension. Interestingly, Nabi and team also mentioned the potential reverse causation effect developed by Hamer et al. (2010); that awareness of hypertension may cause psychological distress potentially leading to depression.

Other large sample studies (n=1389-60799), however, have found higher depression severity was linked to lower BP (Licht et al., 2009, Hildrum et al., 2008, Hildrum et al., 2007, Lenoir et al., 2008, Pilgrim et al., 1992, Paterniti et al., 2000), or that no significant relationship existed between the two variables (Yan et al., 2003, Shinn et al., 2001, Nugent et al., 2011a).

Many studies have shown BP reactivity is reduced in depression (York et al., 2007, Phillips, 2011, Carroll et al., 2007). The present study identified a positive correlation between language (MMSE) and DBP reactivity in the depressed cohort yet an inverse relationship for the control group. Both positive and negative correlations between BP reactivity and cognitive function are plausible, as BP reactivity pathology could lead to over- or under- responsive BP reactions (Salomon et al., 2013, Carroll et al., 2007).

The curvilinear relationship between BP reactivity and cognitive performance was previously introduced by Waldstein (2005). Allen et al. (2011) propose that chronic exposure to stress, which is also a risk factor for depression, can lead to both scenarios; that is, heightened physiological responses because of reduced coping mechanisms, or desensitisation as a result of long periods of higher baseline stress levels. It has also been shown that an early blunting of BP reactivity to acute stressors is predictive of depression development five years later, which suggests that it may occur pre-symptomatically as a potential marker or risk factor for depression (n=1608, age range 24-63 years at baseline, 54% female) (Phillips et al., 2011).

Depression has also been extensively linked to cognitive decline, with or without hypertension, as previously detailed in discussion chapter 5.2, section 5.2.1.1.

7.2.2 Type 1 DM (n=9)

No significant differences were identified between BP before and after the cognitive testing in the type 1 DM cohort. This is in contrast to Wiesli's findings (2005), which showed BP increased in response to mental stimulation in a type 1 diabetes cohort (Trier Social Stress Test (Kirschbaum et al., 1993)) (n=40, mean age 38 ± 12 years, 52% female).

The present research identified baseline DBP was positively correlated to attention (Cognistat), yet negatively correlated to recall (MMSE). There appears to be a

contradiction in these results, as recall and attention are closely intertwined modalities (Unsworth et al., 2014). The content of both skills are required to retain information in an available way (recall, a subdomain of working memory) while selectively concentrating on task-relevant stimuli (attention) (Fougnie, 2008). Using data from the Framingham study, Elias et al., (1995) found non-medicated, stroke-free participants with higher SBP and DBP levels had significantly poorer delayed and immediate recall, visual memory, and digit span performance (n=1695, age range 55-88 years, 59% female). Although Elias' study did not examine the relationship in a type 1 diabetes sample, others suggest type 1 DM is associated with an increased risk of cognitive decline (Biessels, 1999), potentially due to recurrent periods of hypoglycaemia (Deary et al., 1993, Perros and Deary, 1999).

As previously discussed in section 5.2.2.1, cognitive dysfunction is a common consequence of type 1 diabetes, particularly compounded by the duration of the disease (Ryan et al., 1992, Sachon et al., 1992, Ryan et al., 1984). The degree of cerebrovascular change experienced in DM, such as hippocampal atrophy, reduced capillary blood flow, and microvascular damage, is accelerated by increased BP, a common comorbidity in DM and an individual predictor of cognitive decline (Ferguson et al., 2003, Allan et al., 2014, Urban et al., 2007). Ryan et al. (2003) examined 103 participants with type 1 DM and concluded that higher SBP, autonomic neuropathy, and macro-vascular complications were independently linked to worse psychomotor speed (mean age 34 ± 7 years, 58% female). High BP also worsened psychomotor performance in a larger cohort of type 1 DM subjects (n=1144, mean age 27 ± 7 years, 53% male) (Jacobson et al., 2010).

The present study identified inverse correlations between SBP reactivity and memory (Cognistat) and between DBP reactivity and total Cognistat score. This suggests lower BP reactivity could be better for cognitive performance (and vice versa). These findings, however, are not well supported by the literature, which shows that as cognitive effort requires increased cerebral circulation, low reactivity may reduce mental performance (Ryan et al., 2003). This positive correlation was also found in the present research, between SBP reactivity and total MMSE score and between both SBP and DBP reactivity and orientation (MMSE).

Anomalously, the total score for the MMSE was positively correlated to SBP reactivity, yet the total score for the Cognistat was inversely correlated to DBP reactivity. Despite

being different cognitive tests, their overall cognitive scores correlate positively, suggesting better cognitive scores on one test will also be shown on the other, particularly as some of the questions are testing similar skills (Dujardin and Dubois, 2010). It is unlikely that the differences in correlation direction between SBP and DBP reactivity affected cognitive domains in such an opposite manner, thus the low sample size ought to be taken into consideration when interpreting these results. There is little research examining BP reactivity and cognitive performance in type 1 diabetes hence the present study contributes new knowledge in this field, however, BP reactivity changes and cognitive impairment have previously, and separately, been linked to type 1 DM (Moheet et al., 2015, Yano et al., 2014).

7.2.2.1 Type 1 DM (n=9) and the control group (n=9)

Differences in cognitive performance between controls and participants with type 1 diabetes were previously discussed in chapter 5.2, section 5.2.2.1. Neither the type 1 DM group nor the control group had significantly different BP pre to post study. Further, there were no significant differences in BP values between the two groups. However, it has been shown that type 1 DM is linked to an increased risk of hypertension and nocturnal hypertension, potentially attributed to diabetic autonomic neuropathy and arterial stiffness as a result of vascular scarring from chronic glucose overexposure (van Ittersum et al., 2004, Machnica et al., 2014, Lurbe et al., 2002).

Examining BP reactivity in type 1 DM against controls has produced conflicting results. On one hand, Newkumet (1994) showed those with type 1 diabetes had exaggerated SBP and DBP reactivity during a handgrip exercise in a small adolescent sample (type 1 DM n=14, mean age 15 ± 1 years, 71% male; control group n=45, mean age 16 ± 0.1 years, 51% male). They suggested that early subclinical vascular changes occurring in diabetes contribute to cardiovascular comorbidities associated with the disease later in life. On the other hand, Philips et al. (2012) showed that BP reactivity, in response to postural change and exercise, was diminished in type 1 DM compared to controls (type 1 DM n=40, mean age 46 ± 10 years, 50% male; control group n=40, mean age 46 ± 10 years, 50% male). This may be attributed to a multitude of diabetic co-morbidities, including central autonomic neuropathy, microvascular damage, and baroreflex receptor insensitivity (Fleischer et al., 2015, Kilvert and Fox, 2015). Orthostatic hypotension, commonly

affecting those with DM, is also explained by BP reactivity dysfunction (Hirai et al., 2009, Purewal and Watkins, 1995). However, Riihimaa et al. (2002), found no significant difference in BP reactivity in subjects with type 1 DM compared to controls in response to postural changes and suggested that future studies should apply 24-hour ambulatory BP monitors to examine BP differences more accurately (type 1 DM n=100, mean age 14 ± 2 years, 51% female; control group n=100, mean age 14 ± 2 years, 51% female).

Total MMSE scores were significantly and positively correlated to SBP reactivity in both the type 1 DM and control groups. Another positive correlation was identified between attention (Cognistat) and baseline DBP in the type 1 diabetes group and to baseline SBP in the control group. These similarities show low baseline BP and low BP reactivity are both detrimental to cognitive performance in those with and without type 1 diabetes, which may be attributed to reduced neuronal circulation impairing cerebral function over time (Phillips et al., 2013).

7.2.3 Type 2 DM (n=38)

As expected, DBP rose significantly from baseline to post study in the type 2 DM group. This has also been shown in other studies, where a mathematic task, similar to sections of the Cognistat and MMSE, elicited a rise in BP in a type 2 DM cohort (Sung et al., 1999, Faulenbach et al., 2012).

The present study identified inverse correlations between baseline DBP and SBP with repetition (Cognistat) and between baseline SBP and Cognistat domains of comprehension, memory, and total score. These findings suggest that higher BP is worse for cognitive performance in type 2 DM, which is well supported by the literature. Feinkohl et al. (2015) identified that higher BP in subjects with type 2 DM significantly predicted cognitive decline four years later, measured by a battery of seven cognitive tests (n=831, mean age 68 ± 4 years, 52% male). This suggests that higher BP has a long term effect on cognition; potentiated by disease duration and severity of hypertension. Lee et al. (2014) also found higher SBP (>135 mmHg) in a type 2 DM cohort increased the risk of MCI by more than threefold (n=226, mean age 75 ± 7 years, 54% male).

Baseline DBP was also positively correlated to construction (Cognistat) in the present research. Talfournier et al. (2013), also examined BP and cognition in type 2 DM, finding

lower DBP was linked to worse scores in a range of cognitive assessments such as trail making and verbal fluency (n=32, mean age 74 ± 6 years, 78% male). This is supported by Qiu et al. (2005), who found the basis for reduced mental performance in low BP states was linked to hypoperfusion and cerebral hypoxia. Low DBP has also been linked to accelerated atherosclerosis, increasing the risk for cerebrovascular disease and consequential cognitive conditions such as VaD and AD (Bots et al., 1996). Further neuropathological damage (such as increased beta-amyloid typically seen in AD (Lanuti et al., 2012)) has been linked to insulin resistance, a hallmark characteristic of type 2 DM (Cholerton et al., 2011). Talfournier et al. (2013) hypothesise that the combination of negative effects from insulin resistance and low BP cumulatively accelerates cognitive dysfunction. Qiu et al. (2003) also reinforced the importance of systematic cognitive evaluation in DM cohorts and suggested larger studies are required to confirm their preliminary findings.

Positive correlations were also identified between DBP reactivity and SBP reactivity with both total MMSE score and language (MMSE), contributing new data to the field of BP reactivity and cognition research. It has been previously shown that lower BP reactivity deprives neurons of adequate blood supply causing cognitive symptoms to develop (Phillips et al., 2013), although normal ranges of BP change in response to mental stimulation have not been well elucidated and require standardisation (Phillips et al., 2013). Although these findings have not been thoroughly researched in type 2 DM cohorts, some studies have shown diminished BP reactivity is associated with abdominal obesity and chronic stress, both of which are also risk factors for developing type 2 DM, and contribute to the vascular changes evident in DM (Singh and Shen, 2013).

7.2.3.1 Type 2 DM (n=38) and the control group (n=30)

DBP increased significantly from baseline to post study in participants with type 2 diabetes, however, this was not significantly different in the matched control group. Subjects with type 2 diabetes exhibited significantly higher DBP reactivity than the control group. These findings may be attributed to an over-reactivity of BP to the cognitive stimulus, and/or impaired cardiovascular recovery from the cognitive tasks. This was also exemplified in an earlier study by Sung et al. (1999), who found patients with type 2 diabetes had exaggerated SBP responses to mental arithmetic than controls,

however, mathematical performance was not included in their analysis (type 2 DM n=22, mean age 52 ± 12 years, 68% male; control n=12, mean age 52 ± 10 years, 67% male). In comparison, a smaller study analysed blood-oxygenation-level dependent magnetic resonance imaging in subjects with hypertension with or without type 2 DM and showed reduced cerebrovascular reactivity and cortical thickness in those with both comorbidities (type 2 DM with hypertension), particularly in the occipitoparietal and temporal regions (Tchistiakova et al., 2014). Cortical thinning was significantly related to reduced executive function, providing a neuroanatomical foundation for changes in cognitive performance in these conditions (hypertension n=22, mean age 73 ± 6 years, 55% female; type 2 DM with hypertension n=18, mean age 72 ± 6 years, 61% male).

Metabolic dysregulation of glucose and insulin in type 2 DM detrimentally impacts cerebral and vascular structures leading to cognitive symptoms (Tchistiakova et al., 2014). Participants with type 2 DM can experience cognitive decline 1.2-2.5 times faster than individuals without the condition (Jacobson et al., 2010, Nooyens et al., 2010). This decline is commonly perpetuated by comorbidities, commonly hypertension (Hassing et al., 2004). A similar study of females by Petrova et al. (2010) found those with type 2 DM and higher BP experienced significantly greater cognitive decline than those with normal BP (normotensive) (normotensive n=27, mean age 53 ± 7 years; type 2 DM with hypertension n=113 (note larger sample size), mean age 56 ± 7 years).

The present study identified baseline SBP was significantly higher in type 2 DM participants than the control group, a result strongly supported by other research (Hazari et al., 2015, Gao et al., 2015b). An estimated 60% of patients with type 2 diabetes also have hypertension, caused by the stimulatory effects of chronic hyperglycaemia and hyperinsulinaemia on sympathetic activity (Ferrannini and Cushman, 2012).

Co-morbid conditions such as hypertension have a cumulatively detrimental effect on cognitive performance (Kalmijn et al., 2000, Kivipelto et al., 2001, Whitmer et al., 2005). Researchers have identified several pathophysiological processes in type 2 DM that increase the likelihood of developing hypertension; notably changes to vasculature due to ischemic injury, inflammation, and autonomic neuropathy (Moțățăianu et al., 2013, Chung et al., 2015). The Memory in Diabetes sub-study of the Action to Control Cardiovascular Risk in Diabetes trialled intensive anti-hypertensive therapy in a large sample of patients with type 2 diabetes, yet found that the intervention did not

significantly reduce rates of cognitive decline 40 months later, suggesting type 2 DM pathogenesis individually impairs cognition (n=2977, mean age 62 years, 53% male) (Williamson et al., 2014). Other hypertension trials, without type 2 DM, have shown significant improvement in cognitive performance at follow-up after the addition of anti-hypertensive treatment (The Progress Collaborative Group, 2003, Starr et al., 1996, Forette, 2002).

7.2.4 Hypertension (n=39)

As expected, DBP rose significantly from baseline to post study following cognitive intervention for the participants with hypertension. Interestingly, longitudinal studies have found prolonged BP recovery from cognitive stressors in normotensives is predictive of developing hypertension later in life (Steptoe and Marmot, 2005, Stewart and France, 2001). Steptoe and Marmot (2005) demonstrated this in a sample of 209 participants undergoing the Stroop task (Stroop, 1935) and a mirror tracing task. It was found that poor BP recovery after the cognitive intervention predicted hypertension onset three years later (mean age 53 ± 3 years, 53% male).

Baseline DBP was negatively correlated with attention (Cognistat), as was baseline SBP with attention (MMSE), repetition (Cognistat), memory (Cognistat), and total Cognistat score. These findings are in line with a majority of the literature, reporting high BP is detrimental to cognitive performance, particularly over long periods of time (Kilander et al., 1998, Exalto et al., 2014).

Harrington et al. (2000) conducted a similar cross-sectional study examining BP and cognitive performance in non-medicated hypertensives and normotensives. Subjects with hypertension had lower scores in spatial and scanning memory, naming, and slower reaction speeds compared to normotensives (normotensives n=107, mean age 76 ± 4 years, 51% female; hypertensives n=116, mean age 76 ± 4 years, 44% female). In a larger longitudinal experiment (Whitehall II study), Singh-Manoux and Marmot (2005) identified inverse correlations between BP and cognitive performance in middle aged men and women with hypertension. They also found these associations were more pronounced in tests measuring executive function and in females (n=5838, mean age 44 ± 6 years, 71% male).

A retrospective analysis of data from the longitudinal Cardiovascular Risk Factors, Aging and Dementia study (2014) identified that midlife SBP greater than 140mmHg significantly increased the risk of developing dementia 36 years later (n=8469, mean age 46 ± 4 years, 55% female). Kilander et al. (2000) showed the opposite relationship, that lower DBP midlife predicts better cognitive performance 20 years later (n=502, mean age 72 ± 1 years, 100% male).

The Systolic Hypertension in Europe trial found antihypertensive treatment of systolic hypertension reduced dementia incidence by 55% compared to an untreated cohort (n=2902, median age 68 years, 66% female) (Forette, 2002). This is well-supported by other longitudinal studies examining cognition and antihypertensive treatments in hypertensive cohorts (The Progress Collaborative Group, 2003, Starr et al., 1996). Some other large studies, however, have not identified significant cognitive benefits with antihypertensive use in hypertensives, although these studies were limited to elderly samples (aged over 55 years) (Lithell et al., 2003, Peters et al., 2008, Prince et al., 1996, Anderson et al., 2011).

7.2.4.1 Hypertension (n=39) and the control group (n=31)

DBP increased significantly between baseline and post study in the hypertension group yet not in the control group. As discussed in the previous section 7.2.4, hypertension is associated with prolonged BP recovery from cognitive stressors (Steptoe and Marmot, 2005, Stewart and France, 2001).

It was surprising to identify that the control group had significantly higher baseline DBP than the subjects with hypertension. In the present study, 92% of the subjects with hypertension managed their condition with antihypertensive medication, which may have affected the baseline DBP. Antihypertensive treatment aims to reduce BP (e.g. diuretics) and some also affect the ability to increase BP (e.g. angiotensin-converting enzyme inhibitors). If untreated, one would expect that the hypertension sample would have significantly higher BP. However, the present study also identified that the hypertension group had significantly higher baseline and post study SBP, agreeing with the majority of literature (and indeed, the definition of the hypertensive state), that BP is significantly higher in subjects with hypertension (Zanchetti et al., 2015, Head et al., 2012). Cognitive

differences between subjects with hypertension and normotensives were discussed in chapter 5.2, section 5.2.4.1.

7.3 Conclusion: BP and cognition (clinical groups)

Each of the clinical groups exhibited inverse correlations between baseline BP and cognitive performance, a finding that is well supported by the literature and was predicted in hypothesis 2 (Exalto et al., 2014, Singh-Manoux and Marmot, 2005, Yaffe et al., 2014). The clinical groups maintained an inverse relationship between BP and cognition, as seen in the healthy cohort (see chapter 4), which was interesting considering the increased risk of autonomic neuropathy and vascular changes in these conditions. BP reactivity, however, has not been well examined in clinical cohorts and the results from the current study contributed new knowledge to this field. The present research identified that low BP reactivity is linked to worse cognitive function in all clinical states (except hypertension (not significant)), signifying lower BP reactivity in response to neutral conversation as a potential marker for cognitive dysfunction. This finding did not support hypothesis 3, that there would be an inverse correlation between BP reactivity and cognition. Lower BP reactivity may increase the risk of reduced cerebral blood flow and buildup of metabolic waste products which may affect cognitive performance (Phillips et al., 2013, de Rooij, 2013). Further research in a larger sample is required to examine the mechanisms behind these relationships. Refer to Table 7.18, Table 7.19, Table 7.20 and Table 7.21 for a summary of significant results in each age group.

Table 7.18 Summary of significant correlations between BP values and cognitive domains in subjects with depression (n=10)

Cognitive test	Cognitive domain	BP parameter			
		Baseline	BP reactivity		
		SBP	DBP	SBP	DBP
MMSE	Orientation		-		
	Attention				+
	Recall			+	
	Language		-		+
	Total score	-	-		
Cognistat	Repetition				+
	Naming				+
	Similarity		-		

Table 7.18 displays significant correlations between BP values and cognitive domains from the MMSE (Folstein et al., 1975) and Cognistat (Kiernan et al., 1987) in subjects with depression (n=10). BP reactivity refers to the post minus pre study (baseline) BP data.

Key: BP = Blood pressure; DBP = Diastolic blood pressure; MMSE = Mini Mental State Examination; SBP = Systolic blood pressure; + = Positive correlation; - = Negative correlation

Table 7.19 Summary of significant correlations between BP values and cognitive domains in subjects with type 1 diabetes (n=9)

Cognitive test	Cognitive domain	BP parameter		
		Baseline	BP reactivity	
		DBP	SBP	DBP
MMSE	Orientation		+	+
	Recall	-		
	Total score		+	
Cognistat	Attention	+		
	Memory		-	-
	Total score			-

Table 7.19 displays significant correlations between BP values and cognitive domains from the MMSE (Folstein et al., 1975) and Cognistat (Kiernan et al., 1987) in subjects with type 1 diabetes (n=9). BP reactivity refers to the post minus pre study (baseline) BP data.

Key: BP = Blood pressure; DBP = Diastolic blood pressure; MMSE = Mini Mental State Examination; SBP = Systolic blood pressure; + = Positive correlation; - = Negative correlation

Table 7.20 Summary of significant correlations between BP values and cognitive domains in subjects with type 2 diabetes (n=38)

Cognitive test	Cognitive domain	BP parameter			
		Baseline	BP reactivity		
		SBP	DBP	SBP	DBP
MMSE	Language			+	+
	Total score			+	+
Cognistat	Comprehension	-			
	Repetition	-	-		
	Construction		+		
	Memory	-			
	Total score	-			

Table 7.20 displays significant correlations between BP values and cognitive domains from the MMSE (Folstein et al., 1975) and Cognistat (Kiernan et al., 1987) in subjects with type 2 diabetes (n=38). BP reactivity refers to the post minus pre study (baseline) BP data.

Key: BP = Blood pressure; DBP = Diastolic blood pressure; MMSE = Mini Mental State Examination; SBP = Systolic blood pressure; + = Positive correlation; - = Negative correlation

Table 7.21 Summary of significant correlations between BP values and cognitive domains in subjects with hypertension (n=39)

Cognitive test	Cognitive domain	BP parameter	
		Baseline	
		SBP	DBP
MMSE	Attention	-	
Cognistat	Attention		-
	Repetition	-	
	Memory	-	
	Total score	-	

Table 7.21 displays significant correlations between BP values and cognitive domains from the MMSE (Folstein et al., 1975) and Cognistat (Kiernan et al., 1987) in subjects with hypertension (n=39). BP reactivity refers to the post minus pre study (baseline) BP data.

Key: BP = Blood pressure; DBP = Diastolic blood pressure; MMSE = Mini Mental State Examination; SBP = Systolic blood pressure; - = Negative correlation

8. Conclusions, limitations and future directions

8.1 Conclusions

By 2050, Australia is expected to have a population with four times the current number of aged persons and approximately one million dementia cases (Alzheimer's Australia, 2012). This forecast has led to a heightened demand for early detection and prevention methods for dementia and there is a particular focus on AD, as it is more common, progressively worsens over time and is incurable. Studies show that autonomic dysfunction precedes cognitive impairment symptoms evident in AD (Collins et al., 2012). Insights into links between HRV, BP and cognitive status could help identify the autonomic factors which may increase the risk for decline in specific cognitive domains, producing potential early predictors for cognitive impairment.

The present study found similar relationships between HRV and cognitive performance in non-clinical and clinical samples. Higher baseline vagal activity was significantly correlated to better cognitive performance in females aged 18-50 years and in males 51-65 years, and in all the clinical groups (depression, DM (type 1 and 2) and hypertension), supporting hypothesis 1. This finding in non-clinical groups has been well supported by other studies (Lopez et al., 2015, Murtazina, 2015, Solernó et al., 2012). The present study contributed new knowledge to the relationships between HRV and cognition in specific disease groups, where literature is scant. Interestingly, higher vagal activity was also linked to poorer cognitive scores in the older age group (females 36-65 years and males 36-50 years), those with type 1 DM, and those with hypertension. Some studies show that higher vagal tone supports attention and verbal reasoning whereas lower vagal tone supports spatial tasks (Solernó et al., 2012, Porges, 2009), which suggests different cognitive domains may exhibit better performance depending on the autonomic environment. The present research partially supports the polyvagal theory (Porges, 1992), with higher HRV being beneficial for attention skill in older males aged 51-65 years and the type 1 DM group, however, the opposite relationship was identified in middle-aged males (36-50 years). It was also identified that HRV reactivity was mostly positively correlated to cognitive function in the hypertension cohort and in non-clinical females

aged 18-35 and 51-65 years, yet displayed an inverse relationship in non-clinical females (36-50 years) and males (51-65 years), and in clinical groups (DM type 1 and 2) and in those with depression. Further research is required to explore the mechanisms behind these differences and to address the lack of literature in the field of HRV reactivity, and in particular, examining clinical groups. The present research provides a strong foundation for the relationships between HRV reactivity and cognitive function in healthy and selected clinical samples.

Non-clinical groups had both positive (females 18-65 years and males 51-65 years) and inverse correlations (males 18-35 and 51-65 years) between baseline BP and cognitive performance whereas the clinical groups showed inverse correlations only, a finding that supports hypothesis 2 and is also seen in others research (Exalto et al., 2014, Singh-Manoux and Marmot, 2005, Yaffe et al., 2014). Hypothesis 3 was not supported by the current findings with both clinical and non-clinical groups (except hypertension which was not significant) had positive correlations between BP reactivity and cognitive performance, suggesting low BP reactivity may be a predictor for cognitive decline. Diminished BP reactivity may be linked to reduced responsivity to external stressors, reduced cerebral blood flow, and buildup of metabolic waste products which may impair cognitive function (Phillips et al., 2013).

These initial findings provide a novel insight into the relationships between the less-studied HRV reactivity and BP reactivity in clinical and non-clinical groups. Cardiac reactivity has been proposed as a potential marker for negative health and behaviour outcomes (Phillips et al., 2013). By gaining a more detailed knowledge of early predictors for cognitive impairment, preventative countermeasures may be applied to slow or cease dementia onset. Prolonging or halting development of dementia has the potential to reduce expected rises in government expenditure, lower the burden on carers and nursing homes, lengthen lifespans, and ultimately improve the quality of life in elderly populations by preserving cognitive function.

8.2 Limitations and future directions

The present research explored the novel relationships between cardiac variables and cognition in clinical and non-clinical groups, however, a number of limitations could be addressed by future research in the field.

The risk for developing cardiac autonomic neuropathy is increased in the health conditions of the clinical groups (depression, diabetes (type 1 and 2) and hypertension) (Vasudev et al., 2015, Cameron and Cotter, 2001, Abubaker et al., 2014, Liao et al., 1996)); however, the degree of this risk was not measured. It would have been useful to test for cardiac autonomic neuropathy (Valsalva manoeuvre, postural systolic blood pressure changes, deep breathing HRV (Udupa et al., 2007)) and use that information either as a covariate or in a separate subgroup to specifically examine the effect of autonomic neuropathy on the relationship between HRV, BP and cognition. A comparison could then be made between HRV, BP and cognition in those without autonomic neuropathy.

Further, respiration has been shown to inflate LF HRV values (Bernardi et al., 2000, Sloan et al., 1991). Respiration ought to have been taken into account, particularly for the active phase, which required the participant to engage in conversation (causing irregular inspiration) (Quintana and Heathers, 2014). This may account for the increase in HRV observed during the neutral conversation task when other studies have identified HRV decreases with cognitive activation (Shi, 2013). This may also explain the shortage of HRV studies using neutral conversation as a cognitive task, limiting comparisons to the present research. Non-verbal cognitive tasks, metronome-paced breathing, and respiratory artefact removal may help improve accuracy and reduce inter-individual variability in future HRV data.

It is also acknowledged that the older age group (51-65 years) may be biased, representing a healthier physiology. For inclusion in this group, participants must not have been diagnosed with any co-morbid conditions nor take any daily medications. In Australia, 78% of people aged over 65 years report having at least one common chronic illness (such as asthma, hypertension, type 2 diabetes, and coronary artery disease) (Australian Institute of Health and Welfare, 2012a). However, the opposite may also occur; that undiagnosed illnesses may be included in the non-clinical groups.

It also would have been interesting to collect information on family history of cognitive impairment to use as a genetic link to cognitive decline. Braskie (2010) discussed that volunteers with relatives with dementia are more likely to volunteer to participate in dementia research than those with no known family history of the disease, which may inflate results to represent those with an increased risk of dementia.

In addition, the poster advertisement recruitment technique may have induced bias. A casual sample is reliant on the subject's willingness to volunteer and accept active participation which may be motivated by a genetic link to cognitive impairment (as mentioned in the previous paragraph) affecting the true representation of the local population. Blinding was considered to reduce the impact of bias, however, the required UTS ethics-approved consent forms detail the study protocol to the participant. Recruitment may also be influenced by the ease of access to the testing environment (UTS location), and the amount of monetary compensation to the participants in the clinical group. It is understood in human recruitment-based research that the greater the sacrifice required by volunteers, the fewer will participate; hence actions were taken to mediate this effect (such as local advertising). Unfortunately, the characteristics of non-volunteers cannot be elucidated.

Measuring blood glucose levels during the study could also be taken into account in future research, particularly as participants were not restricted for food intake (besides caffeine, alcohol, and tobacco). Blood glucose levels may affect cognitive performance and HRV, particularly during periods of high cognitive demand which require increased glucose mobilisation (Kennedy and Scholey, 2000, Singh et al., 2000, Malterer et al., 2015). Interestingly, insulin and mean glycated haemoglobin have an inverse relationship with HRV and could also be considered in future analyses, particularly in subjects with diabetes (Mamta Jaiswal, 2013, Charles et al., 2013). It would also have been interesting to record and take into account female menstrual and menopausal stages, as differing levels of oestrogen have been shown to affect the ANS, as reflected in HRV data (Sato and Miyake, 2004, Saleh and Connell, 2007).

There is no standardised test to assess cognitive ability, but rather, a variety of different psychometric evaluation tools are described in the literature (Mathias and Burke, 2009). Hence, the two cognitive tests utilised in the present study (MMSE (Folstein et al., 1975) and the Cognistat (Kiernan et al., 1987)), although validated and reliable, may not be

accurately comparable to other cognitive studies and do not provide a complete assessment of all cognitive domains (long term memory and emotion perception), however, their use may be justified by their extensive utilisation in current research. Other psychometric analysis tools are designed specifically for MCI detection (e.g. the Demtect (Kalbe et al., 2004)) and will be considered for future cognitive studies in the Neuroscience Research Unit, UTS.

In addition, physiological data is highly variable and cross-sectional analysis provides a snapshot of the patient's physiological status. Despite efforts to reduce variability in the physiological data (e.g. repetition to collect mean values, 10 minute ECG sessions, and two psychometric assessment tools (MMSE and Cognistat)), future research may benefit from using 24-hour ambulatory ECG and BP coupled with a longitudinal study design.

Global standardisation of HRV methodology and normative values (per age, sex, and disease state) is required to develop the efficacy of HRV as a routine clinical detection tool. The present study explored a novel area of HRV and BP reactivity, however, additional research is required to determine the ranges of normal reactivity and the risks of over- or under-responsiveness on cognition and other health outcomes.

Researchers have explored the effect of HRV manipulation on cognition (e.g. by deep breathing biofeedback and exercise), finding higher vagal tone benefits PFC-mediated cognitive processes such as executive function (Kimhy et al., 2013, Hansen et al., 2003). Future studies could build on the foundational links between cardiac variables (baseline and reactivity) and cognition found in the present study to develop biofeedback techniques to reduce the risk of cognitive impairment in healthy and clinical samples, particularly those at higher risk of cardiac autonomic impairment (Nolan et al., 2005, Albinet et al., 2010, Hansen et al., 2004). Delaying or ceasing cognitive impairment in an aging population has the potential to reduce government expenditure, lower the burden on carers and nursing homes, lengthen lifespans, and most importantly, protect quality of life throughout aging.

9. Appendices

9.1 Consent form – No chronic illness (non-clinical group)

CONSENT FORM UNIVERSITY OF TECHNOLOGY SYDNEY

I _____ agree to participate in the research project '*Investigating physiological association to brain (cognitive) function*' (Ethics approval no: UTS HREC REF NO. 2014000110)) being conducted at the Neuroscience Research Unit by Louisa Giblin of the University of Technology Sydney (UTS). Funding for this research has been provided by the School of Medical and Molecular Biosciences (UTS).

I understand that the purpose of this study is to find out if there are any associations of brain physiology to cognitive function. This has implications for development of any algorithms or cognitive management programs in the future.

I understand that my participation in this research will involve baseline measures (quiet sitting and/or math, word or neutral conversation type intervention). I also understand that I will be asked to complete questionnaires on lifestyle and behaviour. I also understand that non-invasive measurements such as blood pressure and electrocardiogram (using non-invasive methods) will be collected. I understand there will be minimal risk and/or inconvenience.

I also understand the study will involve screening for blood pressure and there is the possibility that I may be found to have high blood pressure. If my blood pressure is greater than 140/90 mmHg, I will be advised to consult a doctor. If my blood pressure is greater than 160/100 mmHg prior to commencing the study I will not be included in the study. If my blood pressure is greater than 160/100 mmHg at any time during the study, the study will be stopped. In both latter cases, I will be offered to be escorted to a doctor and/or advised to consult a doctor.

I am aware that I can contact Louisa Giblin on _____ or the supervisor Associate Professor Sara Lal ((02) 9514 1592 or Sara.Lal@uts.edu.au) if I have any concerns about the research. I also understand that I am free to withdraw my participation from this research project at any time I wish, without consequences, and without giving a reason.

I agree that Louisa Giblin has answered all my questions fully and clearly.

I agree that the research data gathered from this project may be published in a form that does not identify me in any way.

_____/_____/_____
Signature (participant)

_____/_____/_____
Signature (researcher or delegate)

NOTE:

This study has been approved by the University of Technology Sydney Human Research Ethics Committee. If you have any complaints or reservations about any aspect of your participation in this research which you cannot resolve with the researcher, you may contact the Ethics Committee through the Research Ethics Officer (ph.: 02 9514 9772, Research.Ethics@uts.edu.au) and quote the UTS HREC reference number. Any complaint you make will be treated in confidence and investigated fully and you will be informed of the outcome.

9.2 Consent form – Chronic illness (clinical group)

CONSENT FORM UNIVERSITY OF TECHNOLOGY SYDNEY

I _____ agree to participate in the research project '*Investigating physiological association to brain (cognitive) function*' (Ethics approval no: UTS HREC REF NO. 2014000110)) being conducted at the Neuroscience Research Unit by Louisa Giblin of the University of Technology Sydney (UTS). Funding for this research has been provided by the School of Medical and Molecular Biosciences (UTS).

I understand that the purpose of this study is to find out if there are any associations of brain physiology to cognitive function. This has implications for development of any algorithms or cognitive management programs in the future.

I understand that my participation in this research will involve baseline measures (quiet sitting and/or math, word or neutral conversation type intervention). I also understand that I will be asked to complete questionnaires on lifestyle and behaviour. I also understand that non-invasive measurements such as blood pressure and electrocardiogram (using non-invasive methods) will be collected. I understand there will be minimal risk and/or inconvenience.

I also understand the study will involve screening for blood pressure and there is the possibility that I may be found to have high blood pressure. If my blood pressure is greater than 140/90 mmHg, I will be advised to consult a doctor. If my blood pressure is greater than 160/100 mmHg at any time during the study, I will be offered to be escorted to a doctor and/or advised to consult a doctor.

I am aware that I can contact Louisa Giblin on _____ or the supervisor Associate Professor Sara Lal ((02) 9514 1592 or Sara.Lal@uts.edu.au) if I have any concerns about the research. I also understand that I am free to withdraw my participation from this research project at any time I wish, without consequences, and without giving a reason.

I agree that Louisa Giblin has answered all my questions fully and clearly.

I agree that the research data gathered from this project may be published in a form that does not identify me in any way.

_____/_____/_____
Signature (participant)

_____/_____/_____
Signature (researcher or delegate)

NOTE:

This study has been approved by the University of Technology Sydney Human Research Ethics Committee. If you have any complaints or reservations about any aspect of your participation in this research which you cannot resolve with the researcher, you may contact the Ethics Committee through the Research Ethics Officer (ph.: 02 9514 9772, Research.Ethics@uts.edu.au) and quote the UTS HREC reference number. Any complaint you make will be treated in confidence and investigated fully and you will be informed of the outcome.

9.3 Emergency protocol

General Emergency Protocol

ALWAYS CALL SECURITY FIRST

UTS Contacts:

1. Dial/Call UTS Security: dial "6" on an internal UTS phone or 9514 1192
2. Dial/Call 000
3. Dial/Call Student medical Services (9514 1177)
4. Dial/Contact supervisor: Sara Lal (9514 1592) or other authority in the Department

Also if required:

Contact details for UTS medical centre:

Student Services Unit
 Tower building 1, Level 6, UTS
 Ph: 9514 1177

Contact details for external medical centre:

Broadway General Practice
 Level 1 Broadway Shopping Centre
 Ph:9281 5085

Hours of opening:

Monday: 8:30am-5:30pm
 Tuesday: 8:30am-5:15pm
 Wednesday: 8:30am-5:00pm
 Thursday: 8:30am-3:45pm
 Friday: 8:30am-4:45pm
 Saturday and Sunday: Closed

Hours of opening:

Monday-Wednesday: 8:30am-7:00pm
 Thursday: 8:30am-8:00pm
 Friday: 8:30am-7:00pm
 Saturday: 9:00am-6:00pm
 Sunday:10:00am-6:00pm

(Note: Hours of opening are approximations)

Emergency protocol (continued)

Addition to all research study protocols

Student/Researcher protocol

Inclusion criteria

Currently based on lifestyle questionnaire (Craig et al., 1996) per parent ethics approval for the study. That is to qualify for the study (per the lifestyle questionnaire) participants have to meet the following inclusion criteria: no severe concomitant disease, no history of alcoholism and drug abuse and no psychosis, psychological and intellectual problems likely to limit compliance.

Before commencement of any human related research study, after the participant/volunteer has had a 10-minute sitting (rest) period, take 3 sitting BP measurements from the arm.

A standard sphygmomanometer or a validated and reliable digital BP monitor (Omron etc.) should be used to take BP measurements.

After the measurements, if the average of the 3 BP readings are $>160/100$ mmHg or >160 mmHg for systolic alone or >100 mmHg for diastolic BP alone, the participant will not be included in the research study (see no chronic illness consent form (section 9.1)) and will be thanked for their time and offer to be escorted to the nearest medical centre. Student/researcher will/must advise participant of their BP and will/must urge them to seek medical attention.

In the clinical samples (see chronic illness consent form (section 9.2)), if refused to be escorted to a medical centre, the participant may continue with the study (so long as they feel well enough to do so) and are still advised to see a GP regarding their BP.

Similarly, 3 BP readings are to be taken at the end of the study (if the participant qualified and underwent the study). Again if BP readings are $>160/100$ mmHg or >160 mmHg for systolic alone or >100 mmHg for diastolic BP alone, the participant is offered to be escorted to the nearest medical centre and advised to see a GP regarding their BP.

Note: In any case if BP levels of $>140/90$ mmHg are recorded, advise the participant to consult their GP.

NOTE:

According to the Australian Heart Foundation (AHF) (www.heartfoundation.org.au) new hypertension guidelines (2008):

Normal BP: $< 120/80$ mmHg

High to normal BP: 120-139/80-89 mmHg

Grade 1 (mild) hypertension: 140-159/90-99 mmHg

Grade 2 (moderate) hypertension: 160-179/100-109 mmHg

Grade 3 (severe) hypertension: $\geq 180/110$ mmHg

9.4 Disease State Questionnaire

Disease State Questionnaire (Giblin, 2013)

Do you suffer from any chronic illness such as hypertension, diabetes, mental illnesses (e.g. depression and/or anxiety)?

Hypertension (if applicable)

1. What type of hypertension do you have? E.g. primary/essential (no cause), secondary (due to another disease), mild, moderate, severe, isolated systolic/diastolic etc.

2. How long have you had hypertension and at what age were you diagnosed?

3. What medications (including dose) do you take for hypertension? E.g. chlorthalidone, verapamil, lisinopril etc.

4. Are there any other ways (apart from medication/s) you control your hypertension? E.g. reduced sodium intake, dietary interventions, acupuncture, exercise, complementary/alternative medications, etc.

5. Please circle below how you rate management of your hypertension? (Includes lifestyle and compliance to therapy):

Poorly managed

Well managed

0 1 2 3 4 5 6 7 8 9 10

6. Please list any hypertension-related symptoms/complications you present. E.g. cardiovascular disease, organ health etc.

7. Have you ever been hospitalised for a hypertensive-state emergency? If so, how many times?

8. Do you have a genetic link/positive family history for this illness?

Please list any further information regarding your hypertension:

Disease State Questionnaire (continued)

Diabetes (if applicable)

1. What type of diabetes do you have?

2. How long have you had diabetes and at what age were you diagnosed?

3. What medications (including dose) do you take for diabetes? E.g. Oral hypoglycaemic agents, insulin therapy.

4. Please state your fasting glycaemic level (mmol/L or mg/dL).

5. Please circle below how you rate your management of diabetes?
(Includes lifestyle and compliance to therapy):

Poorly managed		Well managed
0	1 2 3 4 5 6 7 8 9	10

6. Are there any other ways (apart from medication/s) you control your diabetes? E.g. dietary interventions, acupuncture, exercise, complementary/alternative medications, etc.

7. Please list any diabetes-related symptoms/complications you present. E.g. retinopathy, nephropathy, neuropathy etc.

8. Have you ever been hospitalised for a diabetic emergency? E.g. diabetic coma, seizure etc. If so, how many times?

9. Do you have a genetic link/positive family history for this illness?

Please list any further information regarding your diabetes:

Disease State Questionnaire (continued)

Mental illness (if applicable)

1. Which mental illness do you have? E.g. depression, bipolar disorder, generalised anxiety disorder, Parkinson’s disease etc.

2. How long have you had this illness and at what age were you diagnosed?

3. What medication/s (including dose) are you taking for you mental illness? E.g. lithium, valproate, fluoxetine, bupropion, imipramine, phenelzine etc.

4. Are there any other ways (apart from medication/s) you control your mental illness? E.g. Electroconvulsive therapy, psychotherapy/counselling, St John’s wort, repetitive transcranial magnetic stimulation, exercise, light therapy, complementary/alternative medicine etc.

5. Please list any mental illness-related symptoms/complications you present. E.g. apathy, weight change, fatigue/insomnia, decreased attention span, delusions.

6. Please circle below how you rate management of your mental illness?

(Includes lifestyle and compliance to therapy):

Poorly managed		Well managed
0	1 2 3 4 5 6 7 8 9	10

7. Have you ever been hospitalised for mental illness? If so, how many times?

8. Do you have a genetic link/positive family history for this illness?

Please list any further information regarding your mental illness:

Disease State Questionnaire (continued)

Other illnesses (if applicable)

1. What illness/es do you have?

2. How long have you had the illness and at what age were you diagnosed?

3. What medications (including dose) are you taking for your illness?

4. Are there any other ways (apart from medication/s) you control your illness? E.g. complementary/alternative medicine etc.

5. Please list any illness-related symptoms/complications you present.

6. Please circle below how you rate management of your illness?

(Includes lifestyle and compliance to therapy):

Poorly managed		Well managed
0	1 2 3 4 5 6 7 8 9	10

7. Have you ever been hospitalised for this illness? If so, how many times?

8. Do you have a genetic link/positive family history for this illness?

Please list any further information regarding your illness:

10. References

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