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University of Dublin, Trinity College
School of Medicine,
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Autonomic influences on cognitive performance at a population level

PhD Thesis Submission
Submission date: September 2013
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Principal supervisor: Professor Rose Anne Kenny
Co-Supervisor: Dr Gerard Boyle

Declaration

I declare that no part of the material contained within my thesis has been submitted as an exercise for a degree in Trinity College Dublin or in any other institution.

The material of this thesis forms part of the cross-sectional data analysis from the ten year longitudinal study entitled 'The Irish Longitudinal Study on Ageing' (TILDA). I certify that I performed all work contained within this thesis, from analysis and interpretation of data to manuscript preparation. The hypotheses, design and governance of the TILDA study is under the direction of Professor Rose Anne Kenny. Professor Rose Anne Kenny and Dr Gerard Boyle provided guidance and direction to the issues addressed within this thesis and acted as supervisors. Dr Ciaran Finucane performed significant data processing of the neurocardiovascular signals obtained during the health assessment.

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Acknowledgements

I wish to acknowledge foremost the contribution of my supervisors Professor Kenny and Dr Boyle, for their time, guidance and expertise throughout my studies. Professor Kenny's talent and passion in the global field of Gerontology is an inspiration to pursue research of the highest international standard. I would also like to acknowledge the contribution of colleagues who assisted in subject recruitment, data collection and data processing within the TILDA study, especially;

Dr Ciaran Finucane

Dr George Savva

Dr Bellinda King-Kallimanis

Dr Hilary Cronin

Dr Claire O Regan

Dr Joanne Feeney

as well as the data management team, health assessment nursing team, and study administration team. I wish to thank Atlantic Philanthropies, the funding body supporting my Doctorate studies. Finally I would like to thank my parents for continually encouraging and supporting me throughout my studies.

Dissemination of Thesis

Publications accepted

1. Cognitive function is associated with impaired heart rate variability in ageing adults- The Irish longitudinal study on Ageing Wave one results -Clinical Autonomic Research (August 2013)
2. Cognitive performance in orthostatic hypotension: Findings from a nationally representative sample
   - Journal of the American Geriatric Society (August 2013)
3. Supine hypertension determines the association between orthostatic hypotension and cognitive performance
   -Journals of Gerontology Series A- Medical Sciences (September 2013)

Submitted for publication

4. Higher syncope burden is associated with poor cognitive function in an older adult population study- TILDA
   - Age and Ageing (February 2013)

Presentations

1. "Cognitive function is associated with impaired heart rate variability in ageing adults- The Irish longitudinal study on ageing wave one results"- (Poster) British Geriatric Society, April 2013, Belfast
2. "Higher syncope burden is associated with poor cognitive function in an older adult population study- TILDA"- (Platform presentation) European Society of Cardiology, August 2013, Amsterdam

3. "Supine hypertension determines the association between orthostatic hypotension and cognitive performance" (Platform presentation) European Union Society of Geriatric Medicine, October 2013, Venice

Overall summary

The principle aims of this doctoral investigation were to provide new insights into the relationship between cardiovascular disease (CVD) and cognitive performance, by investigating the function of the autonomic nervous system (ANS) in a population sample of older adults with varying degrees of cognitive function.

The rapidly ageing global demographic will likely augment the burden of age related health conditions in the coming years. Dementia is currently the second most burdensome chronic condition worldwide, and remains unpreventable and incurable. Risk factors for cognitive impairment have been established, however early intervention has yet to demonstrate its role in prevention.

Initially I reviewed the literature on the cross-sectional and longitudinal association between measures of autonomic function and cognition. A number of studies have reported an association between indices of autonomic function such as heart rate variability (HRV) and cognitive performance, in non-demented subjects. Others have reported a higher prevalence of conditions of neurovascular instability (NCVI) such as orthostatic hypotension (OH) and carotid sinus syndrome (CSS) in subjects with advanced cognitive impairment. No studies to date have investigated the relationship between autonomic function and cognition in a nationally representative population sample. Furthermore, no studies have investigated the association between cognitive performance and symptoms of autonomic dysfunction, such as syncope and likewise the association between cognitive performance and OH measured using continuous blood pressure (BP) monitoring.

The first study of my thesis investigated the association between HRV and cognitive performance, in The Irish longitudinal study on ageing (TILDA) - a nationally representative cohort of community dwelling older adults, living in the Republic of Ireland. We reported that lower overall variability and lower sympathovagal balance were associated with lower global cognitive performance, specifically in the domains of language and memory recall. The subsequent studies examined the association between conditions of NCVI/autonomic dysfunction (orthostatic hypotension and syncope) and cognition, again cross-sectionally. We defined OH using two measures- the first recorded BP in the seated and standing positions using a traditional cuff-based oscillometric device, and the second recorded BP on a continuous scale during orthostasis using photoplethysmographic equipment. Using the first measure, we reported an independent association between OH and lower performance, across cognitive domains of global function and memory. This association was confined to adult's ≥65 years of age, and was stronger in women. Using continuous data, we reported an association between early OH (sustained at 20-30 s following orthostasis) and poorer performance (in the domains of global and executive function), in subjects with baseline supine hypertension (SH) only. Finally we investigated syncope and cognitive performance and reported that subjects with a greater burden of syncope in the past year (two+ events) scored lower in global cognitive testing. This was also the case for subjects who had a history of unexplained falls in the past year- a potential surrogate for syncope with amnesia for loss of consciousness (A-LOC). We hypothesise that inflammation, neurochemical and neuroanatomical degeneration, and cerebral hypoperfusion each play roles in the relationship between autonomic dysfunction and cognitive performance.

In conclusion our findings represent an original contribution to the understanding of autonomic dysfunction and NCVI in the context of cognitive performance, in healthy older adults. Follow-up analysis of this cohort will expand our understanding of the relationship between these systems.

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Abbreviations

Ach = Acetylcholine

AD = Alzheimer's disease

Ad = Adrenaline

A-LOC = Amnesia for loss of consciousness

aMCI = Amnestic mild cognitive impairment

ANS = Autonomic nervous system

APOE = Apolipoprotein E

AS = Arterial stiffness

ATC = Anatomical therapeutic classification

BMI = Body mass index

BP = Blood pressure

BPV = Blood pressure variability

BRS = Baroreflex sensitivity

CAPI = Computer-assisted personal interview

CES-D = Centre for epidemiological studies depression scale

CBF = Cerebral blood flow

CNS = Central nervous system

CO = Cardiac output

CRT = The choice reaction time task

CSH = Carotid sinus hypersensitivity

CSS = Carotid sinus syndrome

CT = Computed tomography

CV = Coefficient of variation

CVD = Cardiovascular disease

DBP = Diastolic blood pressure

DLB = Dementia with Lewy bodies

DM = Diabetes mellitus

DP = Dietary pattern

ECG = Electrocardiogram

FFT = Fast fourier transform

FTD = Frontotemporal dementia

HADS-A = The hospital anxiety and depression scale

HDL = High density lipoprotein

HF = High frequency

HR = Heart rate

LDL = Low density lipoprotein

LF = Low frequency

LOC = Loss of consciousness

MCI = Mild cognitive impairment

MI = Myocardial infarction

MMSE = The Mini-Mental State Examination

MOCA = The Montreal Cognitive assessment

MRI = Magnetic resonance imaging

NAd = Noradrenaline

naMCI = Non-amnestic mild cognitive impairment

NCVI = Neurocardiovascular instability

NFT = Neurofibrillary tangles

OH = Orthostatic hypotension

PET = Positron emission tomography

PFC = Prefrontal cortex

PNS = Parasympathetic nervous system

PSD = Power spectral density

PWV = Pulse wave velocity

RCT = Randomised controlled trial

RSA = Respiratory sinus arrhythmia

SART = The sustained attention to response task

SBP = Systolic blood pressure

SCQ = Self-completion questionnaire

SD = Standard deviation

SDNN = Standard deviation of NN intervals

SNS = Sympathetic nervous system

SP = Senile plaques

TCD = Transcranial doppler

T-LOC = Transient loss of consciousness

TILDA = The Irish longitudinal study on ageing

TPR = Total peripheral resistance

TMT = Trail making test

ULF = Ultra low frequency

VaD = Vascular dementia

VCD = Vascular cognitive disorder

VLF = Very low frequency

VVS = Vasovagal syncope

WHO = World Health Organisation

WML = White matter lesions

Introduction

Literature review chapters one and two detail the background of the autonomic and cognitive systems – the subject of this thesis. Chapter one is a review of cognitive function and disorders of cognition. The epidemiology of major disorders of cognition is characterised alongside the underlying pathophysiology of each. I highlight the major burden of cognitive disorders and the need for preventative and interventional strategies- both of which are limited. Leading methods for measuring cognitive performance are described in relation to specific cognitive domains. A background to the established association between health behaviours, cardiovascular risk factors and cognition in both healthy and cognitively impaired subject groups is also performed. This review informs my thesis regarding the necessary adjustment for potential confounders in analysis.

A review of literature exploring the autonomic nervous system, common conditions of autonomic dysfunction and their relationship with cognition is reported on in Chapter two. The physiology underlying indices of autonomic function and the pathophysiology of common conditions of autonomic dysfunction are discussed, with a view to understanding their potential interaction with structures governing cognitive function. Methods for the optimal assessment of these indices and conditions are also explained, emphasising those which are practical to perform on a large scale.

The uses and advantages of population studies are summarised in Chapter three. Detail on The Irish Longitudinal Study on Ageing (TILDA) is outlined, including recruitment methodology and data acquisition. Data acquired in TILDA that is of interest to my thesis is outlined briefly. Finally, the objectives of my thesis are clarified with justification from the literature reviewed.

1 COGNITION: LITERATURE REVIEW

1.1 Cognitive function and dysfunction

1.1.1 Healthy age-related cognitive change

The majority of adults experience some decline in cognitive function over the course of their lifetime. In healthy ageing, this is largely confined to short term memory. Non-progressive age-related memory complaints include forgetfulness producing names or thinking of specific words and misplacing things. However memory for major events remains preserved and everyday activities are unaffected, as reported by both patients and informants. Recognition of early changes characteristic of cognitive disorders aids clinicians in differentiating pathology from age-related change. Decline in non-memory functions such as language, visuo-spatial perception and everyday functional activity suggests a cognitive disorder. However, short-term memory impairment is often an early marker of incident dementia, making diagnosis difficult. Subjective memory complaints often correlate poorly with objective impairment, and instead often represent a major symptom of depression [1].

Age-related physiological changes considered to underlie these observations include neuronal decline, neurochemical changes and cerebral atrophy; albeit to a low degree. Criteria used to define disorders of cognition include (i) the severity of cognitive impairment (ii) the domains of cognition affected (iii) the underlying pathological processes (often only established at autopsy) and (iv) functional impairment of everyday activities.

1.1.2 Mild cognitive impairment

Mild cognitive impairment (MCI) is defined as cognitive function worse than normative data for a set age and educational level, yet not severe enough to

meet the criteria defining dementia (see Table 1.1) [2]. It is a term often used to describe the intermediate state between healthy ageing and dementia. Reported memory problems may be subjective and/or objective, but their functional ability remains preserved. Functional ability is the feature that distinguishes MCI from dementia. Functional impairment refers to restrictions performing activities of daily living, e.g. eating, bathing and dressing [3]. Sub-classification distinguishes amnestic MCI (aMCI) and non-amnestic MCI (naMCI). Memory loss predominates in aMCI, whereas decline of executive function is greater in naMCI. Impairment within each sub-type may be confined to either a single or multiple cognitive domains (see figure 1.1). Approximately 50% of subjects with MCI will subsequently convert to dementia [4].

Winblad et al., 2004	Albert et al., 2011	Peterson et al., 2011	
Not normal, not dementia	Concern regarding change in cognition	**Core clinical criteria**	**Proposed research criteria**
Self and/or informant report and impairment on objective cognitive tasks	Impariment in one or more cognitive domains	Concern of cognitive change from patient, informant or clinician	Low cerebrospinal fluid or PET Aβ-42 levels
Evidence of	Preservation of	1-1.5 SD lower in	Signs of neuronal

decline over time on objective cognitive tasks	independence in functional abilities	one-plus domain relative to the normative mean for age and education	injury; high CSF tau levels, hypometabolism, cerebral atrophy, hypoperfusion on MRI, PET or spectroscopy, biochemical changes of cellular death or inflammatory cytokines
Preserved basic activities of daily living / minimal impairment in complex instrumental functions	Not demented	Preserved functional abilities, in spite of possible delays	
		No social or occupational impairment	

Table 1.1 Diagnostic criteria for Mild Cognitive Impairment (MCI).

The pathophysiology of MCI is heterogeneous and often characteristic of the incident dementia type diagnosed, in those who convert. Longitudinal analysis of subjects aged 70+ reported a prevalence of 11.6% and 9.9% for aMCI and naMCI respectively [5]. In the same study, prevalence increased with age in aMCI only. The conversion rate from MCI (aMCI and naMCI combined) to dementia is reported at 14% annually, with conversion rates similar between sub-types [6]. Although a number of studies report biomarker difference between *converter* and *stable* groups, few define cut-off values for predicting subsequent outcome [7]. Elevated biomarkers which increase the risk of conversion to dementia include cytokine biomarkers, magnetic resonance

imaging (MRI) analysis [8], decreased CSF-Aβ42, elevated CSF-tau protein [9], and PET detected amyloid plaques [10].

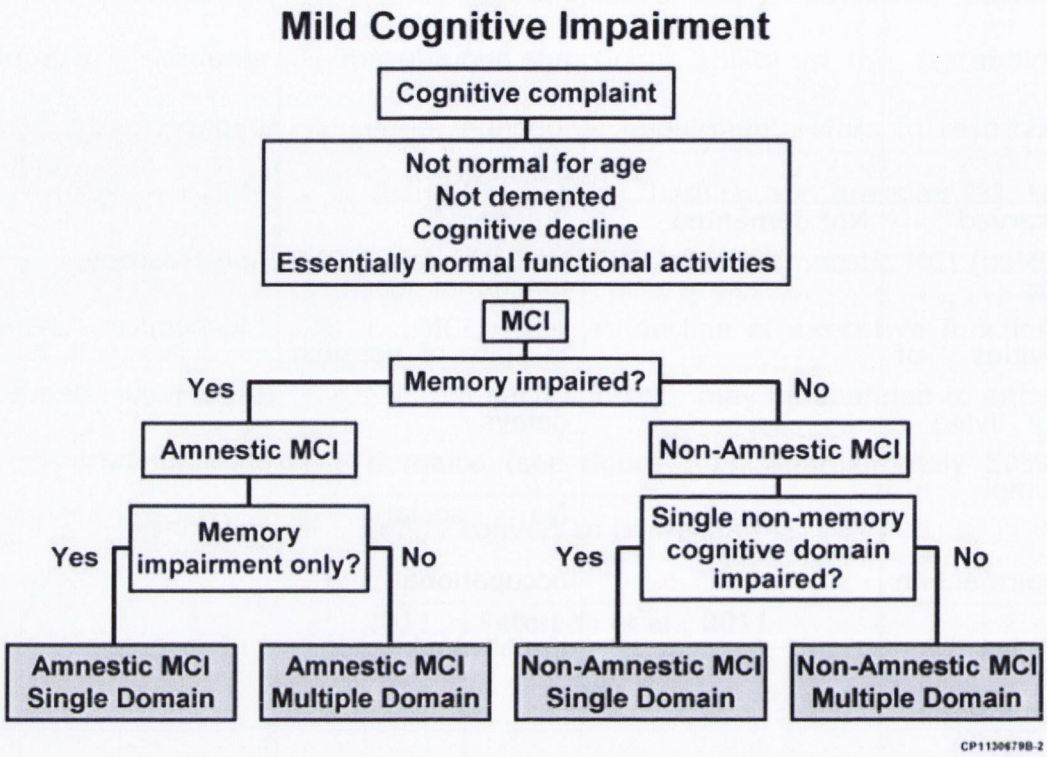


Figure 1.1 Sequential diagram of the diagnostic criteria used to categorize mild cognitive impairment sub-type [11].

1.1.3 **Dementia**

Dementia syndrome is an umbrella term describing cerebral damage that results in memory impairment, alongside reduced executive function, processing speed or language, as well as impaired functionality. There are a number of underlying pathologies, the most common of which are Alzheimer's disease (AD), vascular dementia (VaD), mixed type dementia (characteristics of both AD and VaD), and to a lesser extent dementia with Lewy bodies (DLB) and frontotemporal dementia (FTD) (see figure 1.2). AD is the most prevalent type of dementia, followed by VaD, while mixed type becomes more prevalent at older ages.

Dementia is the second most burdensome chronic condition worldwide [12]. It significantly impairs functional capacity [13], increases mortality [14], is responsible for significant burden on healthcare services [15], and most importantly, has lasting personal, emotional, financial and social effects on families and carers [16].

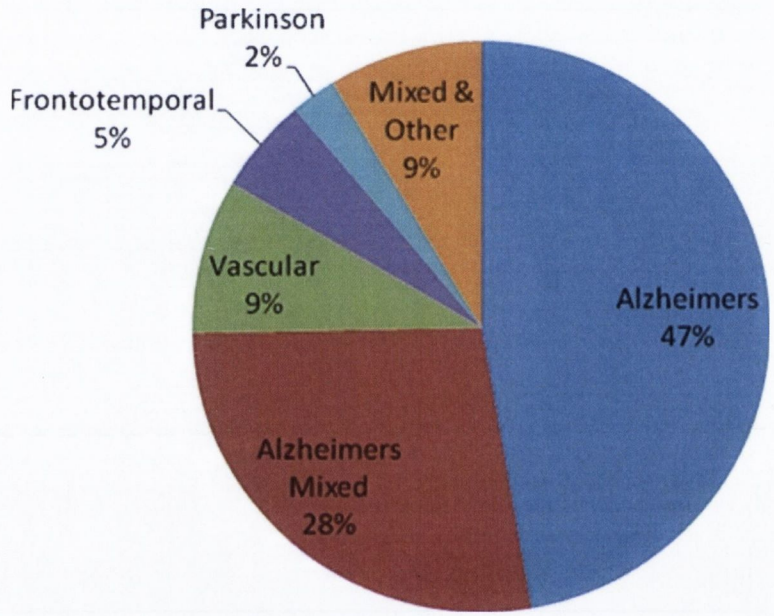


Figure 1.2 Dementia by type in a Canadian population [17].

The prevalence of dementia increases markedly with age, from an estimated 8% in people aged >64 years to 15-20% in those aged >80 years[18], the rate doubling every 6.3 years [12]. This results in a total population burden of 7.8 million across Europe alone [19], with Western Europe home to the highest number of people with dementia across the globe [12]. The aggregate cost of dementia services in this region is 1.29% of GDP- a significant proportion of the economy [15]. The worldwide burden of dementia (currently at 35.6 million) is doubling every 20 years, caused by the accelerating ageing demographic, with the forecast reaching 115.6 million by 2050 [12]. These estimates assume a

constant age-specific prevalence over time; however an increase in risk factor exposure secondary to sedentary lifestyles may amplify statistics. The burden of dementia is so significant that if it were a country, it would be the 18th largest economy worldwide (see figure 1.3) [15]. Furthermore, the prevalence of MCI that does not meet the defining criteria for dementia is reported to exceed double that of dementia [20, 21]. Hence, the actual burden of disease may far exceed current estimates.

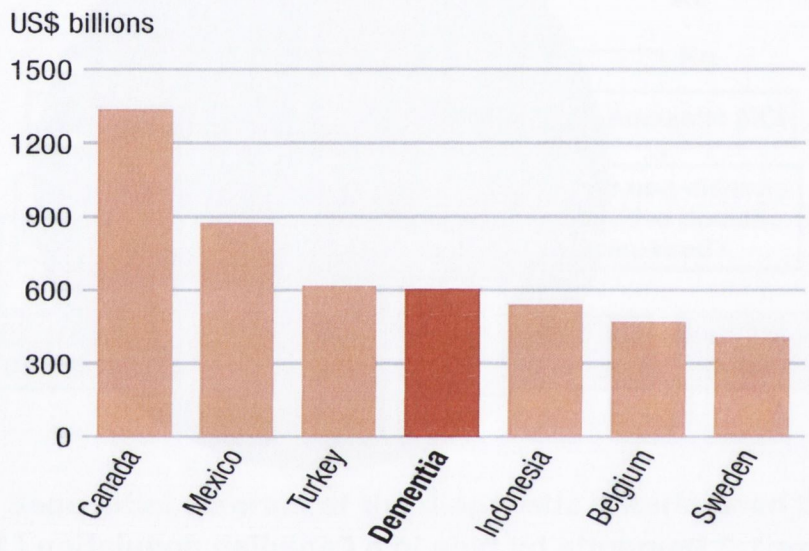


Figure 1.3 Cost of dementia compared to national economies [15].

Alzheimer's disease

AD is an acquired progressive neurodegenerative disorder, which markedly interferes with social and occupational functioning. AD prevalence is 9.7% at age 71+, and increases with age from 5% at 71-79 years to 37.4% at age 90+ [22]. Cognitive features of early AD include anterograde memory loss, visuo-spatial dysfunction, and mild anomic aphasia (word finding difficulties for speaking and writing). AD is staged as preclinical, mild, moderate, and severe, each defined by varying degrees of symptoms and functional impairment.

AD has characteristic hallmarks of neurofibrillary tangles (NFT) of hyperphosphorylated tau and β-amyloid plaques (also called senile plaques (SP)) [23]. SP accumulate prior to clinical onset, primarily in the cortices of association and hippocampus. These characteristics are not pathognomonic of AD as SP may present in normal ageing and NFT may present in other neuroprogressive disorders. Hence the distribution and quantity of these hallmarks, in tandem with clinical expression are used to define AD.

Oxidative damage caused by reduced protein synthesis often manifests early in AD [24], in areas responsible for cognitive function [25]. The production of β-amyloid is increased in the ischaemic state [26], and hypoxia induced factors stimulate β-amyloid production [27, 28]. Hence, cerebral ischemia secondary to hypoperfusion or infarction likely precedes AD [29].

Vascular dementia

Vascular dementia (VaD) encompasses syndromes of varying cerebrovascular pathology, resulting predominantly in damage to regions responsible for memory and executive function. Cerebrovascular changes are detected by neuroimaging, however no threshold of vascular damage is required for diagnosis [23]. VaD can be subcategorised according to the quantity and/or distribution of infarct or haemorrhagic lesions. Distribution may be diffuse, focal, or mixed; hypertension is a major cause of diffuse disease. A number of cardiovascular conditions responsible for cerebrovascular disease are modifiable; hence their early detection is important (described in further detail later). The prevalence of VaD is 1.6% (compared to 4.4% for AD), ranging from 0.3% at age 60-69 years to 5.2% at age 90+ [30].

Vascular ageing is contributed to by structural damage, including loss of elasticity and reduced arterial compliance [31]. This hinders the autoregulatory capability of cerebral arteries to maintain perfusion by controlling vessel diameter, in response to blood pressure (BP) changes. Sub-threshold BP may lead to cerebral hypoperfusion and consequently ischaemia [32], resulting in cerebral damage and vascular cognitive impairment.

Mixed dementia

Mixed dementia describes pathology of AD with cerebrovascular disease [33]. One-third of AD patients have underling vascular disease [34]. Risk factors common to the development of both VaD and AD (e.g. hypertension and diabetes mellitus) indicate a common vascular pathogenesis in mixed dementia. Apolipoprotein E (APOE), which plays a role in lipoprotein metabolism, also underlies both dementia sub-types. It increases the incidence of VaD in post-stroke patients, and is a risk factor for cerebral amyloid angiography in AD patients.

Vascular cognitive disorder (VCD) is an emerging term, used to describe the cognitive and functional impairment spectrum associated with vascular pathology. VCD ranges from vascular type cognitive impairment to subcortical VaD, post-stroke dementia, and mixed dementia [35].

Dementia with Lewy bodies

Dementia with Lewy bodies (DLB) is a progressive, degenerative dementia characterised by the deposition of Lewy bodies (protein aggregates) in the cerebral cortex. Psychotic symptoms in DLB commonly include; visual hallucinations (associated with hypoperfusion of the parietal and occipital association cortices), misidentification (associated with hypoperfusion of the

limbic-paralimbic structures) and delusions (associated with hypoperfusion of the frontal cortices) [36]. The accuracy of clinical diagnosis is poor, hence epidemiological data describing its prevalence is sparse. A French study reported the incidence of DLB to be 112/100,000 person-years, with incidence increasing with advancing age [37].

Anterograde memory loss characteristic of AD is less prominent here, whereas extrapyramidal features (e.g. bradykinesia and limb rigidity) are more common [38]. DLB is diagnosed using functional neuroimaging, via identification of reduced striatal dopamine transporter activity, and characteristic immunohistochemistry [39]. The absence of white matter lesions (WML) on brain MRI is used to distinguish DLB from its differential- VaD.

Frontotemporal dementia

Frontotemporal dementia (FTD) is often used as an umbrella term referring to clinical syndromes of frontal dementia or progressive aphasia (language and speech disorders). Frontotemporal lobar degeneration is the pathological feature underlying FTD. Prevalence of FTD is estimated at 15-22 per 100,000 individuals at ages 45-64 years [40], however its exact prevalence is unknown, given the complexity of syndromes defining FTD [40]. FTD characteristics include behaviour abnormalities such as disinhibition, impulsivity, and impersistance, as well as speech abnormalities, ideation, and memory retrieval impairment.

1.1.1 Risk factors for cognitive disease

Risk factors for cognitive impairment, MCI and dementia include advancing age, genetic predisposition, inflammation, health behaviours such as smoking, alcohol intake, diet and exercise, cardiovascular disorders such as high cholesterol (dyslipidaemia), atherosclerosis, obesity, arterial stiffness, glucose intolerance/

diabetes mellitus (DM), altered BP, and markers of autonomic dysfunction, such as heart rate variability, and orthostatic hypotension [41], all of which are described in further detail later.

1.2 Measurement of cognitive function

Tests measuring cognitive function are not mutually exclusive, given that cortical domains are multi-functional. Hence, tests usually measure more than one cognitive domain.

1.2.1 Global cognitive function

Global cognitive function is an overview of general performance, assessed across multiple cognitive domains. It is frequently measured in clinical settings where detailed assessment of individual domains is impractical, e.g. primary care. It is used predominantly as a screening tool for cognitive impairment. Quality and use of cognitive tests is dependent on factors including; sensitivity, adjustment for cultural and educational affects, language and simplicity of administration.

Mini-Mental State Examination

Several neuropsychological batteries measuring global cognitive function have been described. The Mini-Mental State Examination (MMSE) was the first major advance in screening instruments, first developed in 1975 [42], and remains the most widely used in clinical practice today [43]. Domains of orientation, registration, attention, recall and language are assessed here. A criticism of the MMSE is its relative lack of assessment of executive function. Individuals with a high pre-morbid level of intelligence or education display a ceiling effect, which results in a high false negative rate. Hence, normal scores require adjustment for age and educational attainment [44]. Test administration is standardised to

improve inter-rater variance. Meta-analysis indicates the use of MMSE in ruling out dementia, but concluded that it has little value in detecting MCI [45].

Montreal Cognitive assessment

The Montreal Cognitive assessment (MOCA) is a more comprehensive neuropsychological battery, evaluating executive function and executive memory in addition to domains assessed by the MMSE [46]. Encompassing more domains yields greater use for monitoring the transition from healthy ageing to MCI and early dementia. Its excellent psychometric properties (which have been validated in numerous studies) explain its increasing uptake in clinical practice [47-49]. MOCA is a one-page, 30-point test, which takes ~10 minutes to administer (see appendix 1).

When compared to the MMSE, MOCA has greater sensitivity (100% vs 90%), and specificity (78% vs 18%) [43]. The MOCA comprises five of the six most commonly used tools in screening for dementia [50]. Its authors suggest usability for individuals with cognitive complaints without functional impairment, as well as those with functional impairment, who score a normal MMSE score (see figure 1.4). In this way, the MOCA detects subtle cognitive decline, otherwise missed by the MMSE [46]. Figure 1.4 presents a paradigm accounting for the recommended use of each screening tools to detect different levels of cognitive impairment, i.e. MOCA for MCI/Mild dementia and MMSE for more advanced stages of dementia.

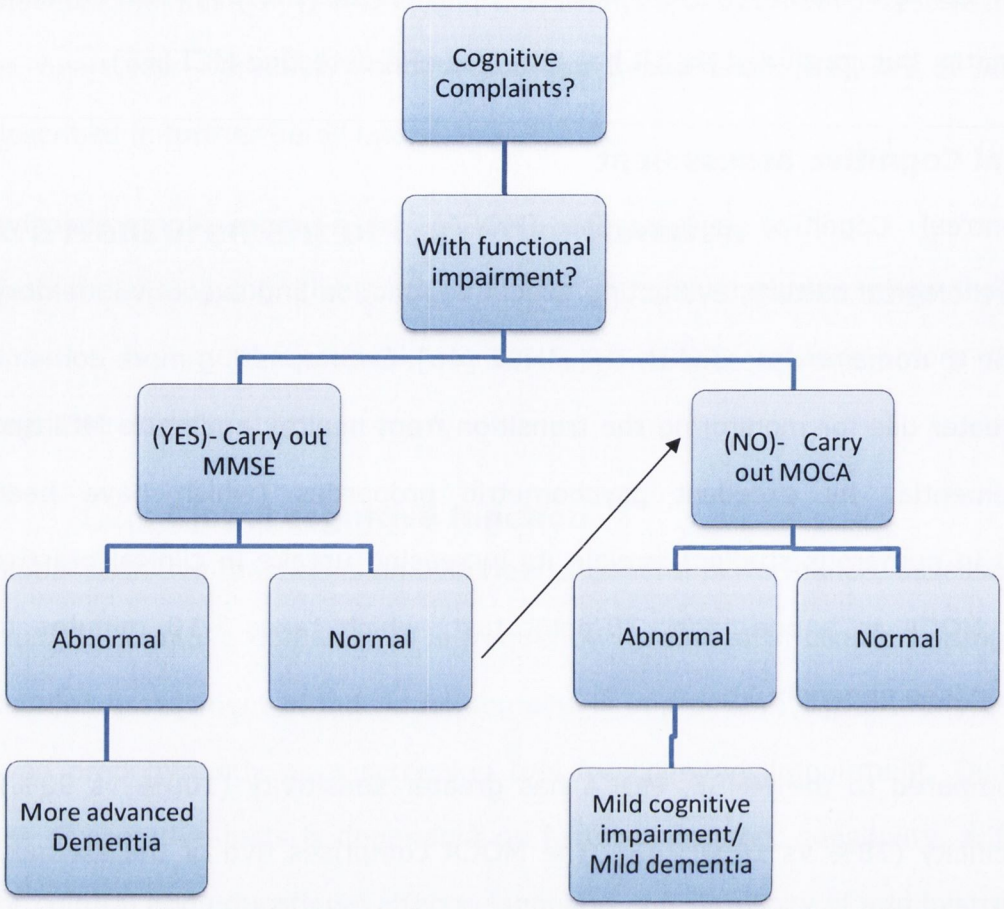


Figure 1.4 Paradigm recommended for the use of global cognitive tests, based on presenting complaints [46].

1.2.1 **Executive function**

Executive function describes the higher order cognitive ability to control, manage and prioritise tasks and abilities such as thoughts, behaviour, time and decisions. Executive function is considered a "macroconstruct" in which multiple subprocesses work in conjunction to solve complex tasks. In a sense, executive function can be considered as a "supervisory" function, overseeing organisation and execution of thoughts and behaviours [51].

). The prefrontal cortex has long been considered by some to govern executive function, however meta-analytical review of studies in this area does not support

a one-on-one relationship between executive function and frontal lobe activity [51]. Executive function decline may go undetected using basic attention tasks, but become apparent when tasks requiring alternating or divided attention are assessed.

Several tests such as verbal fluency, colour trails and visual reasoning assess executive function. Verbal fluency entails the generation of words within a category (semantic) e.g. animal type, or words beginning with a particular letter (phonetic) e.g. letter F fluency. Completion requires novel organising ability- an executive task.

The colour trials test is another measure of executive function, developed to overcome the language and cultural bias issues of the traditional Trail Making Test (TMT) [52]. It is a ten minute two part task that requires the respondent to connect different coloured and numbered circles. One is first asked to identify the digit '1' within a circle, and connect to subsequent ascending digits, up until the number 25. The second part requires connecting digits from 1-25 (as before), but doing so using numbers with alternatively coloured circles, that is, connecting a yellow circled 1 to a pink circled 2 (avoiding the yellow 3), etc (see appendix 2). Both parts are timed, and the part two time is an index of executive function, testing an individual's mental capacity to switch between functional task abilities.

Visual reasoning is another functional measure of executive function. Here the participant is shown 3 pictures, relating to each other in a pattern, followed by an empty box. The participant is asked to choose a 4^{th} picture from 6 options, that which best fits the pattern to complete the box. This is repeated over 6

patterns. This test forms part of the Cambridge Cognitive examination (CAMCOG), commonly used to diagnose dementia.

1.2.2 **Sustained Attention**

Selective and alternating attention are two attention types implicated in the manifestation of AD [53]. This may be explained by the need for functioning attention at multiple levels of higher order processing, in domains such as memory and learning- which have established associations with AD [54]. Sustained attention is defined as *"the ability to self-sustain mindful, conscious processing of stimuli, whose repetitive and non-arousing qualities would otherwise lead to habituation and distraction from other stimuli"* [55]. An example of sustained attention is the ability to perform everyday repetitive tasks such as reading the newspaper.

Cortical activity associated with sustained attention tasks is localised to the anterior cingulated and dorsolateral prefrontal and parietal cortical regions (i.e. the frontoparietal area) [56-58]. These regions are activated primarily, but not exclusively in the right hemisphere.

Factors determining the efficacy of sustained attention tests include; (i) successive (opposed to simultaneous) presentation of stimuli, (ii) a high event rate/ frequency of presentation, (iii) using dynamic stimuli, (iv) using stimuli with conditioned significance, to acquire higher order processing areas, and (iii) varying the point in space where the stimulus is presented [59]. These factors all impact on vigilance during testing.

Sustained attention to response task

The sustained attention to response task (SART) is widely used [55]. SART is sensitive to detecting differences in attention, in those with brain injuries and

controls alike [55]. In this computer based test, the numbers 1-9 appear on screen, consecutively and successively over five minutes. The respondent is instructed to click a button every time a number appears on screen, except for the number 3, in which case the individual is instructed not to click. A short trial is completed prior to the test itself.

Outcome variables include errors of omission (which refer to the number of times any number other than 3 was not clicked on) and errors of commission (which refer to the number of times the number 3 was clicked). Errors of omission reflect a break from task-engagement and lapsing attention. Errors of commission also reflect lapses of sustained attention, and to a lesser degree, deficits in response inhibition [60].

1.2.3 **Speed of processing**

Speed of processing is a measure of attention, processing, and motor functions. These account for the time taken to make (/process) a decision and the time taken to execute the decision ("motor"). To distinguish between processing and motor components, computer-based tasks are preferred over written tasks. In this way, results can be made attributable to the decision processing centre, via the time taken to consider a task once presented to the respondent, or the motor control centre, via the time taken to physically respond to the task. Hence speed of processing is a cognitive measure underpinning several domains.

Speed of cognitive processing can be assessed using the choice reaction time task (CRT). Here, the respondent is asked to press and hold down the 'start key'. The task begins once this key is held down. On the computer screen one of two options appears, YES or NO. The respondent is instructed to release the start (S) key and press either the corresponding yes or no key, to whichever

appears on screen. The time taken for the respondent to release the S key is defined as the decision/processing time, and the time between S key release and pressing the yes or no key is considered the motor time.

1.2.4 **Memory**

There are many categories of memory (summarised in figure 1.5), some of which remain relatively stable with ageing and others which exhibit a decline- as outlined briefly earlier. Semantic and procedural memory remain stable with age [61]. Others, such as episodic memory [61], prospective memory [61], and working memory (as defined by verbal and visuo-spatial memory, learning and working speed) [62], decline with advancing age.

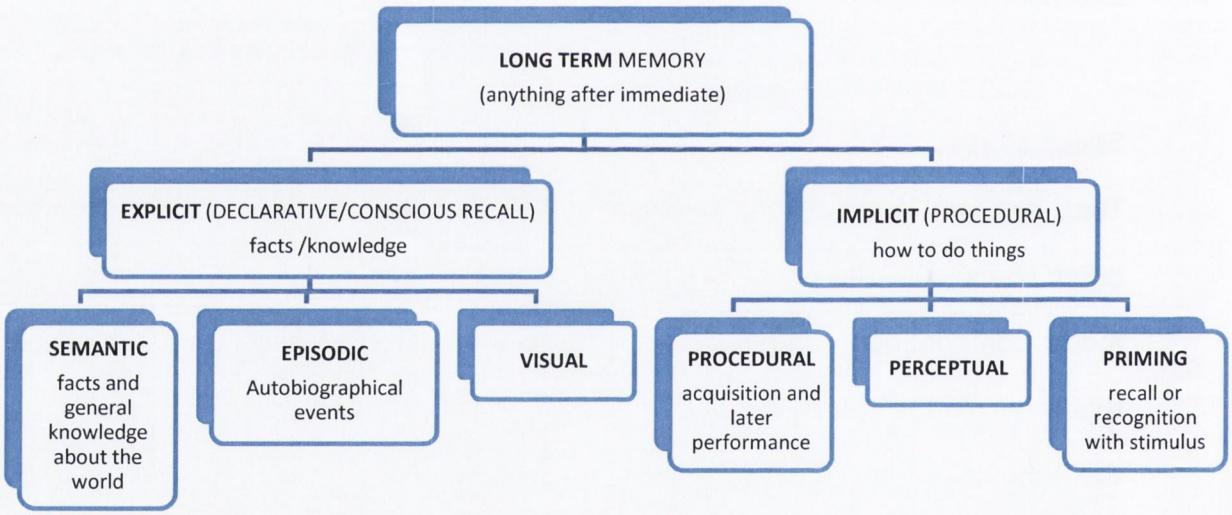


Figure 1.5 Memory hierarchy.

Verbal memory

Verbal memory describes the verbal recall of words presented following an interval. It can be measured by asking participants to listen to a list of ten words (e.g. one word every two seconds), and immediately recall as many of the words as possible. The participant may then listen to the same list again and recall as

many words as possible a second time. This is a type of explicit memory, as participants are aware of learning. Participants typically exhibit improved performance with the second recall, due to greater exposure. The left ventral prefrontal cortex (PFC) supports preferentially verbal working memory [63], while the right dorsal PFC has dominance over spatial working memory. After a period of time, delayed recall (a function of long-term memory) is recorded by asking participants to recall the words they remember.

Visual memory

Visual memory refers to storage and retention of visual stimuli that are no longer present. Processing of visual information occurs in the occipital cortex. The picture memory test can be used to assess visual memory. Participants are displayed with and asked to identify six common objects. They are later asked to recall as many of these images as they can remember (free recall). They are then shown images of 6 similar objects and asked to identify which objects were shown earlier (recognition). This test also exhibits a ceiling affect however, whereby results are negatively skewed, reducing the tests ability to discriminate between cognitively healthy and impaired individuals.

Prospective memory

Prospective memory refers to remembering to perform intended actions in the future. Prospective memory is controlled by frontal systems, especially in tasks that require planning and strategy to monitor the point of task execution. Tasks that require spontaneous retrieval of memory rely on medio-temporal and frontal lobe activity [64]. Prospective memory can be measured by asking participants to remember to complete a task after a period of time.

1.3 Health behaviours and cognition

Smoking

Systemic review of literature indicates that current smoking is a risk factor for both AD and VaD [65, 66]. An age-dependant relationship has also been reported, such that current smoking is associated with cognitive decline at older age only (>75 years) [67]. Recent former smoking appears related to decline in executive function, whereas individuals with a long-term former smoking history score similar to those with no smoking history (Sabia 2012). This relationship is reported in men only however, and no relationship is found amongst women. The authors propose that this may be due to greater tobacco volume smoked by men, or that smoking combines with existing risk factors differently for men and women. -

Alcohol

Low to moderate alcohol intake provides a neuroprotective effect against cognitive decline at older ages [68]. The protective effect is more established in preventing overall dementia and AD, than VaD and pre-dementia syndromes [69]. Excessive alcohol consumption has deleterious effects on cognitive function, which increases with age [68]. Memory and attention specifically decline with alcohol consumption over time [70]. Quantifying the optimal level of alcohol intake to protect against cognitive disease however remains contentious [69].

Diet

Specific nutrients within the diet have differing impact on cognition. Mono and poly-unsaturated fatty acids, along with low-fat dairy products have a neuroprotective role, while whole-dairy products impair performance [71, 72]. A

potentially more clinically relevant approach to the impact of diet on cognition is dietary pattern (DP) analysis [73]. A review of studies based on DPs (of which an example is the Mediterranean pattern), concluded that DPs characterised by a higher intake of fish, nuts, fruit and vegetables, and lower intake of meat, whole fat dairy, and sugars were associated with lower rates of cognitive disease [73]. This however has not been studied across a range of population settings.

Exercise

Resistance training is protective against cognitive decline [74], with mechanisms underlying the association hypothesised to include higher insulin-like growth factors-1 (IGF-1) associated with both resistance exercise and improved cognitive performance [75]. In addition, resistance training is associated with reduced homocysteine levels [76], higher levels of which are associated with cognitive decline [77].

Aerobic exercise in late life has a positive effect on cognitive performance [74]. A Cochrane review of studies investigating the effect of aerobic exercise on cognition reported the largest effects on cognition within the domains of motor function and auditory attention [78].

1.4 Cardiovascular Disorders and cognition

Dyslipidaemia

Studies investigating the impact of dyslipidaemia on cognition typically measure total serum cholesterol, with or without detail on triglycerides, high density lipoprotein (HDL) cholesterol and low density lipoprotein (LDL) cholesterol [79]. An inconsistent association between dyslipidaemia and cognition is reported [80]. One in two cross-sectional studies [81], and two in five longitudinal studies [82, 83] reported significant cognitive decline with measures of dyslipidaemia.

Conflictingly, two further studies reported significant positive associations between cholesterol and cognitive performance (processing speed and memory) in midlife [84, 85]. A moderate decrease in cholesterol level from mid to late life is a risk factor for subsequent cognitive decline [86]. The hypothesis that dyslipidaemia has a detrimental impact on cognition is supported by the aforementioned protective role of the Mediterranean diet, which is low in saturated lipids [86]. Figure 1.6 highlights the key factors associated with dyslipidaemia and their potential neuro-protective and neurodegenerative impact. Further research is needed to disseminate the impact of dyslipidaemia on cognition across the lifespan.

Atherosclerosis

Atherosclerosis refers to thickening of arterial vasculature, subsequent to the build-up of fatty material (plaques) [87]. Atheromatous plaques consist of an atheroma (nearest the vessel lumen) composed of macrophages, underlying cholesterol crystals, and calcification at the base of advanced lesions. Behavioural factors described above contribute to atherosclerosis. Other risk factors include DM, hypertension, obesity, and family history of cardiovascular disease (CVD). Atherosclerosis negatively impacts on cognitive function [88] and is correlated with all types of dementia (odds ratios 1.3-1.9) [89]. Atherosclerotic changes also facilitate cognitive dysfunction by causing strokes and silent cerebral infarctions [90].

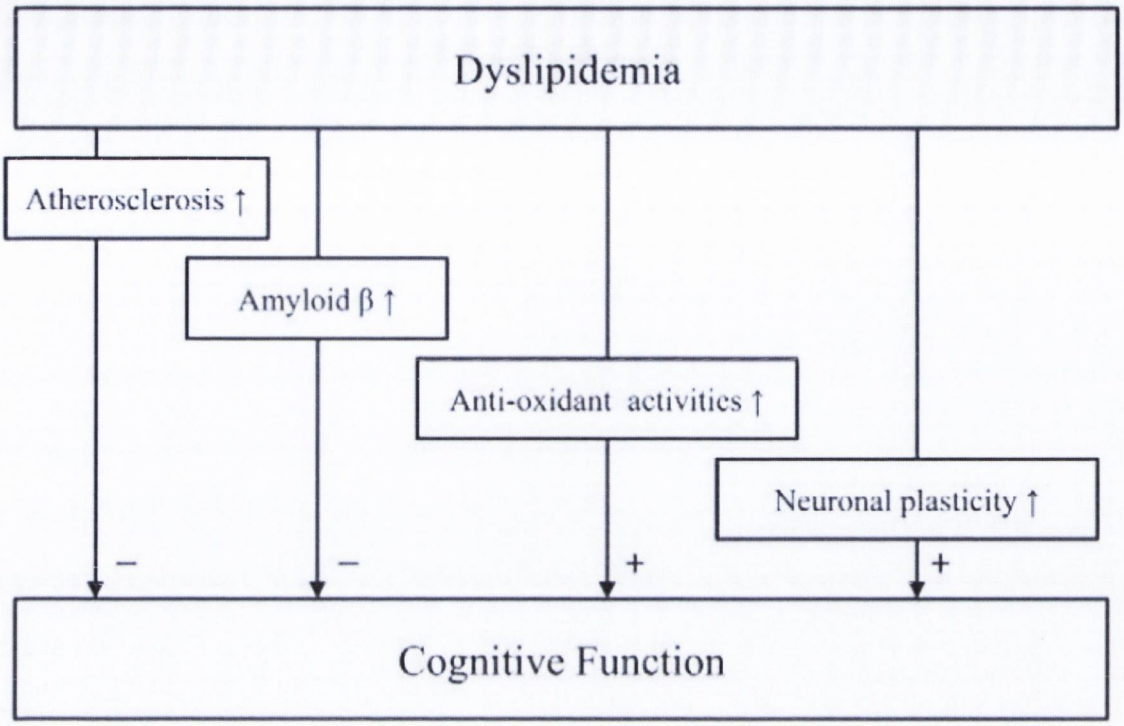


Figure 1.6 Potential factors linking dyslipidaemia to cognitive function. Arrows indicate direction of effect [90].

Obesity

Obesity is defined as a body mass index (BMI) ≥30 (World Health Organisation (WHO). BMI (kg/m^2) is defined as a person's weight (kg) divided by the square of his/her height (m). Obesity can also be estimated using indices of waist-hip ratio (WHR) and waist circumference, which in turn influences BMI. Obesity is caused predominantly by an imbalance between energy intake and energy expenditure. Hence, effective measures to reduce BMI include dietary modifications and increasing regular physical exercise (WHO).

Obesity predisposes to hypertension (five-fold risk), and DM type 2 [91-94], which in turn are associated with cognitive decline [95-97]. Obesity also exhibits an independent effect on cognitive decline [98]. BMI is associated with

pathological changes consistent with AD, including white matter disease and cerebral atrophy [99-103]. Studies reporting association between higher BMI and improved cognition may be explained by weight loss caused by impaired functional capacity, often seen in the prodromal stage of AD [104, 105].

Arterial stiffness

Age-related vascular changes result in arterial stiffening. This increased stiffness reduces the dispensability of the arterial walls, leading to increased velocity of blood flowing through the vasculature [106]. *'Pulse wave velocity* (PWV), *is a measure of arterial stiffness of the arterial territory between two measurement sites'* [107]. The systolic blood pressure (SBP) is augmented and the diastolic blood pressure (DBP) is reduced, creating a greater pulse-pressure. This increased pulse pressure causes blood to penetrate and damage microvasculature [108]. *Cerebral* vasculature is specifically exposed to the augmented pulse pressure effect of arterial stiffness [109]. Atherosclerosis is a primary risk factor for arterial stiffness.

Emerging evidence has indicated an association between arterial stiffness (AS) and cognitive decline [110]. Review of literature reported that AS (measured using PWV) predicts cognitive decline [111]. The need for research into the specific aetiology of arterial stiffening in the development of dementia has been highlighted [110].

Diabetes mellitus

Diabetes mellitus (DM) is a syndrome caused by a decrease in or total lack of insulin or diminished effectiveness of circulating insulin. It is associated with a 1.5-2.5-fold increase in incidence of dementia, with a multi-factorial underlying aetiology [112]. Inflammatory mediators, rheological factors, cerebral

microvascular changes, APOE4 allele carriers [113], and hypothalamic-pituatary-adrenal axis dysfunction may all be implicated in causing cognitive decline. DM remains the most consistent cardiovascular marker for cognitive dysfunction across mid and late life [90].

Hypertension

Hypertension is defined as a SBP ≥140mmHg, and/or a DBP ≥90mmHg. Hypertension increases the incidence of dementia in both middle-aged (≤69 years) and older age groups (≥70 years) [29, 114, 115]. A weaker association is reported in the oldest old (≥85 years) [116]. It is proposed that high BP in mid-life can have a cumulative effect over time, such that hypertension of longer duration has a greater impact on cognitive function. A significant association between lower BP and the onset of AD in older age groups has also been reported [117]. Hypotensive syndromes have a higher prevalence in dementia [118]. Hence, it is difficult to establish the causal relationship between blood pressure and cognition, as it appears that long-standing hypertension predisposes to cognitive decline, whereas hypotension may be a feature of cognitive decline occur prior to or following its onset.

Evidence indicates the role of treating BP in mid-life, as a protective measure against cognitive decline and dementia in later-life [18], however this may not be the case for older age groups [18, 119]. An optimal BP level to protect against cognitive decline has yet to be established. In RCTs (randomised controlled trials) investigating the effect of anti-hypertensives, cardiovascular outcomes are considered primary endpoints, and cognitive disorders are secondary endpoints. Consequently, trials are terminated once the benefits against primary endpoints are established. This limits the use of such trials for

investigating affects on cognitive function, as primary endpoints are often reached prior to observation of cognitive decline [119]. Hence, further research is needed to determine the impact of anti-hypertensive medications on cognition, where cognitive decline is considered as the primary endpoint.

2 THE AUTONOMIC SYSTEM: LITERATURE REVIEW

2.1 The Autonomic Nervous System (ANS)

The autonomic nervous system (ANS) is the regulatory system responsible for control of the body's visceral functions, maintenance of homeostasis and adaptation to changing conditions. Anatomically, the ANS has both central and peripheral networks. The peripheral network is the point of sensory input and autonomic output. Divisions comprise of the sympathetic and parasympathetic nervous systems (SNS and PNS respectively), each of which perform opposing regulatory roles; the SNS enhances automaticity, while the PNS reduces automaticity. The right prefrontal cortex is considered by some to predominantly support SNS activity and the corresponding left counterpart predominantly supports PNS activity [120, 121]. However, this conceptualisation is considered untenable by others, and meta-analysis instead proposes that sympathetic and parasympathetic divisions have diverging roles, with the central autonomic network core governed by regions comprising the left amygdala, right anterior and left posterior insular, and midcingulate cortices, as evidenced using neuroimaging methods [122]. Afferent nerves signal towards and efferent nerves away from the central nervous system (CNS). The central network receives afferent inputs regarding visceral and somatosensory information, and is responsible for tonic, reflex and adaptive control in response to these signals via efferent outputs.

The SNS contains pre-ganglion neurons located in the spinal thoracolumbar cord, which use acetylcholine (Ach) for neurotransmission. Post-ganglion SNS neurons transmit NAd, with the exception of sweat glands, which transmit Ach. The parasympathetic division of the peripheral system contains pre-ganglion neurons

located in the brain stem and spinal cord. Its primary neurotransmitter is Ach, acting via muscarinic receptors. Figure 2.1 illustrates a schematic of the ANS structures, and their innervation targets. The SNS acts in response to stressful events, via increasing heart rate (HR) and BP, and decreasing blood flow to digestive organs. The opposing PNS functions in homeostasis and maintenance of *'rest and digest'* activities, via activation of digestive organs.

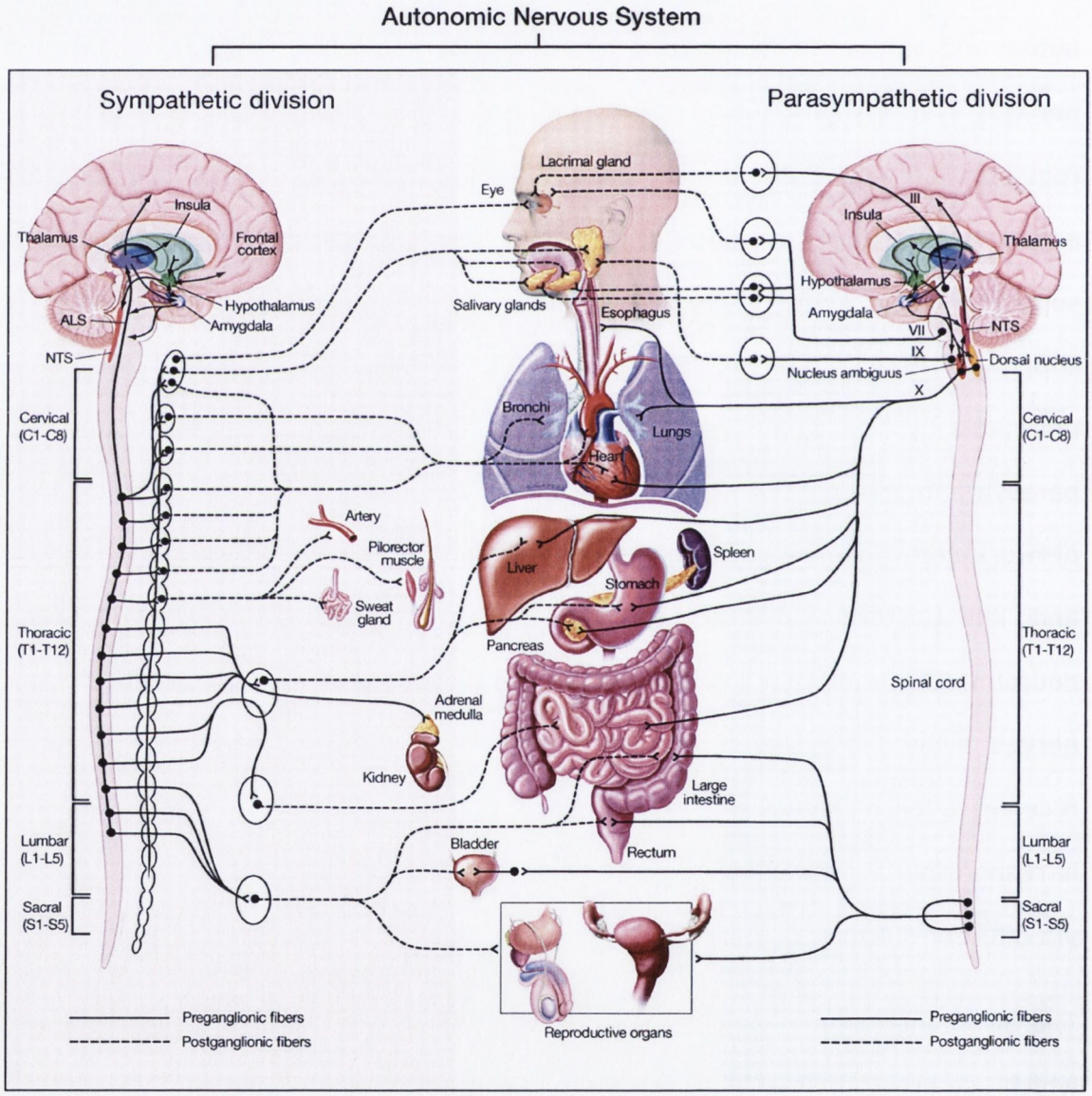


Figure 2.1 Schematic representation of the autonomic nervous system divisions and the systemic anatomical structures each innervate [123].

Roman numerals III, VII, IX, and X (vagus) represent cranial nerves. ALS = anterolateral system; NTS = nucleus tractus solitarius.

2.2 Cerebral autoregulation

Perfusion of non-autoregulatory tissues can be predicted from BP as the relationship is linear or curvi-linear [124]. In contrast, autoregulatory tissues have a non-linear pressure-flow relationship- expressed as the sigmoid autoregulation curve (see figure 2.2). Cerebral autoregulation refers to cerebral blood flow (CBF) adaptation in response to changing perfusion pressure. Perfusion pressure is the difference between arterial and either venous or cerebrospinal fluid pressure (the greater of the two). Intrinsic (originate within the CNS and innervate cerebral parenchymal vessels) and extrinsic (originate within the CNS but exit prior to cerebral innervation) components (including sympathetic, parasympathetic and trigeminovascular systems) control cerebral autoregulation.

Pressure autoregulation maintains a stable perfusion across the mean systemic pressures between 60-150 mmHg. Static autoregulation refers to long-term steady-state control, whereas dynamic autoregulation refers to beat-to-beat control in response to acute changes in BP [125]. Impaired autoregulation results in the relationship between CBF and BP becoming more linear, the BP range within which perfusion remains optimal is narrowed and the slope of the curve becomes steeper; with the effect that perfusion becomes more pressure dependent (also see figure 2.2). In this setting, vasodilatation in response to low BP is often reduced, and vasoconstriction in response to high BP is increased

[126]. Conditions that impair autoregulation include DM [127], smoking, vascular disease, stroke [128], hypertension [129] and hypotension [130].

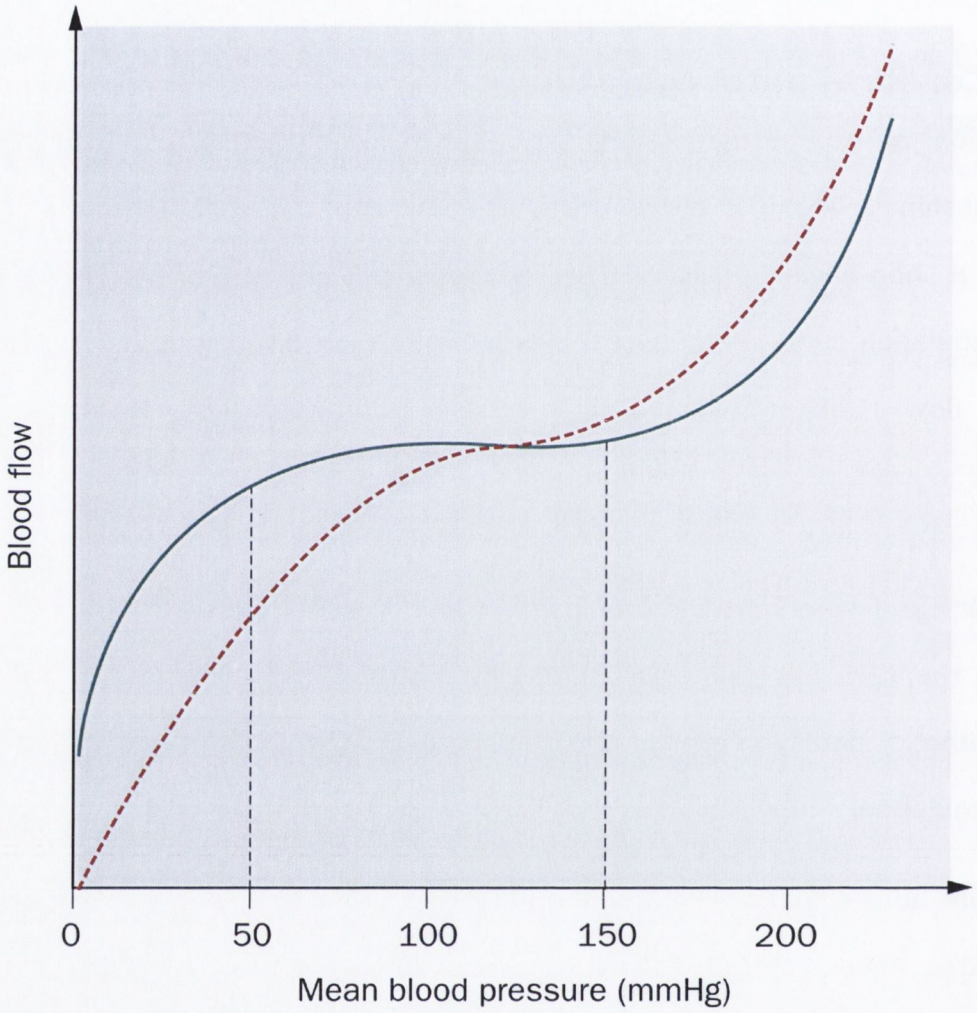


Figure 2.2 Normal cerebral autoregulation curve with its lower (50 mmHg) and upper (150 mmHg) limits of mean arterial pressure (green line), and a narrowed range with a steeper curve (red dashed line) [126].

2.3 Neurocardiovascular instability (NCVI)

Neurocardiovascular instability (NCVI) defines a group of disorders of the ANS, resulting in hypotension and/or bradycardia [118]. Prevalent NCVI conditions are

carotid sinus hypersensitivity/syndrome, vasovagal syncope, orthostatic hypotension and post-prandial hypotension. Causes include medications, dehydration and other disorders such as autonomic neuropathies [118]. Characteristic signs of NCVI conditions include periodic low BP, abnormal diurnal range in BP (e.g. loss of nocturnal dipping) and postural BP changes. Hypoperfusion both centrally and peripherally results in symptoms of NCVI, commonly including fatigue, muscle weakness, dizziness, falls and fainting/syncope (a transient, self-limited loss of consciousness and postural tone) [118].

Age related physiological changes in BP, heart rate and CBF, alongside comorbid conditions and concurrent medications account for some of the increase in prevalence of NCVI in older persons [131, 132]. Older people have lower intravascular volume due to increased salt wasting by the kidneys. When this is present with age-related diastolic dysfunction, cardiac output (CO) falls and OH or vasovagal syncope can result [27]. Pathological mechanisms underlying NCVI conditions originate in the ANS. In healthy individuals, baroreceptors found in the carotid sinuses of the neck are stimulated in response to BP change. The impulse response is relayed to the autonomic nuclei of the brainstem where responses are then sent to the peripheral vasculature and the heart. Sympathetic activation is initiated in response to low pressure, altering vascular resistance (increase in DBP, minimal decline in SBP), heart contractibility (increase) and heart rate (increase). The opposing parasympathetic response initiated in response to increased BP decreases heart rate. These mechanisms maintain an adequate CO for systemic and cerebral perfusion [118]. Changes in baroreflex function in response to static and dynamic manoeuvres may represent early stages of autonomic dysfunction and NCVI conditions.

Indices used to measure autonomic function include heart rate variability (HRV) and BP variability (BVP) which together estimate baroreflex sensitivity (BRS). Ewing's classification of autonomic dysfunction is used clinically and is based on detecting abnormalities during assessment of the following cardiovascular reflex tests; deep breathing, valsalva manoeuvre, orthostasis, cold-pressor test and sustained hand-grip[133]. The quantitative sudomotor axon test is used to assess the functional integrity of the postganglionic sympathetic sudomotor axon. Pupillometry assesses the size and responsiveness of the pupils light reflex- which is an index of central cholinergic activity.

A number of these measures of autonomic function and specific conditions of NCVI are described further next. A current understanding of their relationship with cognitive function is also summarised.

2.4 Heart Rate Variability (HRV)

Heart rate variability (HRV) is the temporal variation between consecutive heartbeats during sinus rhythm. HRV indices are calculated from the RR interval of an ECG [134]. The RR interval is the time period between two successive R waves (i.e. the peak of the QRS complex) (see figure 2.3).

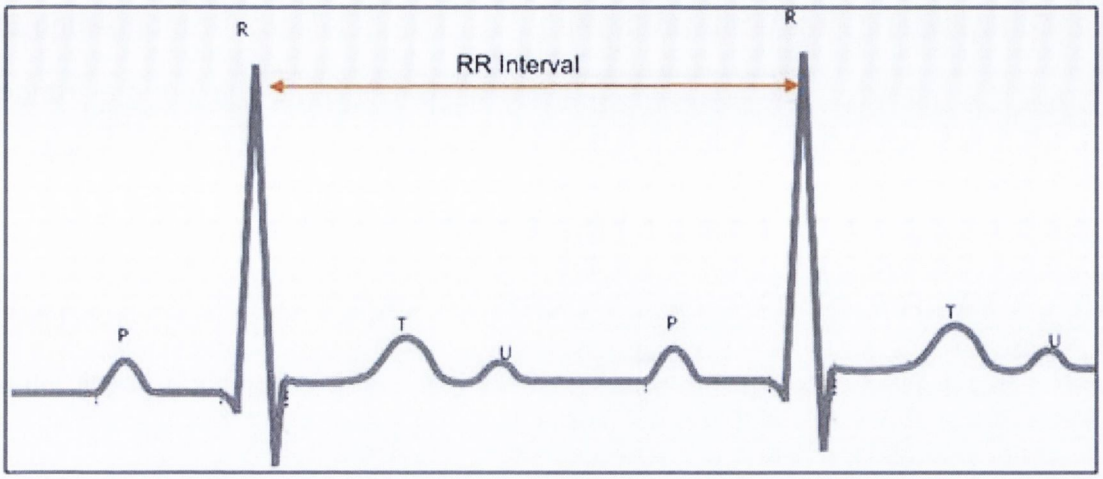


Figure 2.3 Waveform of electrocardiogram in normal sinus rhythm [135].

HRV is a marker of autonomic function [136, 137]. It is controlled predominantly by both limbs of the ANS- the SNS and PNS. Both systems influence heart rate by altering the ion channel permeability to ions, at the intrinsic control centre of the heart (the pacemaker). The resting/intrinsic heart rate is higher than the observed resting heart rate [138], due to tonic vagal inhibition.

Efferent vagal (parasympathetic) mediators apply their action relatively quickly on the heart via Ach release, affecting principally the high frequency (HF) component of the HRV spectrum [139]. This is due to the rapid hydroxylation of Ach at the sinus node. In contrast, sympathetic mediators exert their effect via adrenaline (Ad) and noradrenaline (NAd) release, over a longer period, reflected in both the low and HF powers of the spectra. The LF/HF ratio acts as a proxy to measuring the sympatho-vagal balance [140]. During sympathetic activation, there is normally a reduction in total power, whereas the opposite is true during vagal activation. Both limbs are modulated centrally (e.g. vasomotor and respiratory centres) and peripherally (e.g. oscillation in BP) [141]. As HRV

decreases, blood pressure variability increases. This is so because modulating BP results in a change in heart rate and control of BP within the optimal range. When HRV is diminished, capacity to modulate BP via the autonomic system is reduced- resulting in more uncontrolled BP.

Reduced HRV is associated with depression [142], DM [143], subclinical inflammation [144], carotid atherosclerosis [145], and hypertension [146], all of which are established risk factors for cognitive impairment.

HRV indices

HRV is calculated from both time and frequency (spectral) domains. Typical variables derived using the statistical method include the *standard deviation of the NN interval* (SDNN), i.e. the square root of the variance. The variance is equal experimentally to the total power in the spectral domain, indicating that SDNN reflects all cyclic components captured [140]. As HRV variance increases with recording duration, SDNN increases accordingly, such that recordings of varied length are not comparable [147].

Frequency domain analysis employs the use of power spectral density (PSD) to estimate the relationship between power (i.e. variance) and frequency. PSD is measured using parametric or non-parametric methods. Non-parametric methods use more simplistic algorithms (in most cases the Fast Fourier Transform (FFT)), and have a faster processing speed and generate smoother spectral components than non-parametric methods. Their disadvantage is the need for model verification. Short term PSD components comprise of very low frequency (VLF) (frequency range ≤0.4Hz), low frequency (LF) (0.04-0.15Hz), and HF (0.15-0.4Hz) components (see figure 2.4). VLF and ULF assessed from recordings less than 5 minutes is unreliable and should be avoided [148].

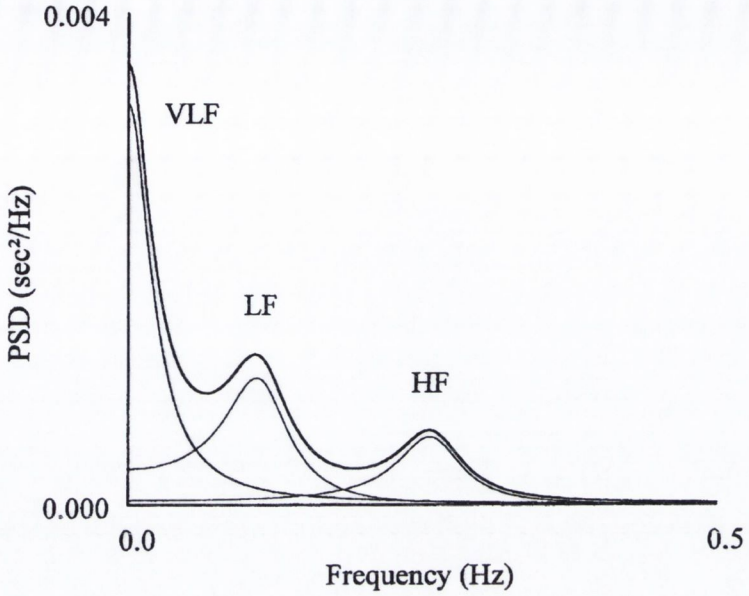


Figure 2.4 Graphical representation of heart rate variability- power spectral analysis.

HRV determinants

Physiological components such as ventilation are responsible for a cyclic fluctuation of HF power, mediated by changes in vagal outflow, termed respiratory sinus arrhythmia (RSA). During inspiration, there is a slight increase, and during expiration, a slight decrease in heart rate. A comparison of free and paced breathing measures of HRV reported that paced breathing at 12 cycles/min resulted in a stronger relationship between the $\log_e$ of HF (lnHF) and RR interval, indicating lnHF to be a valid index of vagal outflow (except in people with a very low resting heart rate), and hence a protocol of paced breathing is recommended [149]. Thermoregulation and baroreflexes are responsible for slower fluctuations of HRV. Circadian rhythms are responsible for the greatest variability of HR.

HRV absolute values decrease with age in healthy subjects [150], and studies are inconclusive regarding the role of gender in HRV [151] [150].

HRV measurement

The optimal sampling rate range is 250-500Hz [148]. The sampling rate must exceed twice the highest waveform frequency (also called the Nyguist frequency). Ectopic beats, arrhythmic events, noise, and missing data alter PSD estimation and interpolation corrects for abnormal beats. Preferentially, recordings free from ectopics, noise, and missing data should be used [148]. Visual checks and manual RR interval identification should be performed, and automatic filters should not be relied upon. The physiological environment should be described [140]. Adherence to recommendations is poor [152]. Recent improvements in the accuracy of fully automated HRV algorithm methods [153], suggest that current recommendations (e.g. for manual identification signal features) are outdated and should be updated to account for the era of fully automated methods [152]. In turn, clarification of measurement standards used is also needed, emphasising (i) The technical procedures used, (ii) The frequency bandwidths and normalization methods for spectral analysis, (iii) classification of the health-status of subjects, and (iv) recognition of normative HRV data for healthy populations [152].

HRV and cognitive decline

Two studies have to date investigated the direct association between HRV and cognition in healthy subjects [154, 155].

The Women's Health and Ageing Study (WHAS) study, investigated the association using HRV recorded for two hours at rest. Results reported that reduced HF (scoring in the lowest quintile) was independently associated with

lower cognition. Other HRV indices (SDNN, VLF, and LF) were also associated with lower cognition in the expected direction, however did not reach significance [154]. The cohort comprised of disabled females only, and sample size was small (n=311). Hence these results cannot be generalized to the healthy older population.

More recently, the Whitehall study investigated the longitudinal association between HRV and cognition, across several tests (verbal memory, reasoning, meaning (comprehension), and fluency). Reduced HRV was defined as one standard deviation below the mean, and cognitive decline was defined as scoring in the lowest quintile for each test. Results were inconsistent, with reduced LF showing the only association (significant in most cases) with cognitive decline, over each domain. This was not retained at follow-up. The larger sample size (n=4033), inclusion of both genders and follow-up analysis were strengths of this study. The cohort however consisted of middle-aged civil servants, thus under-representing those of older age and lower socio-economic status.

Studies investigating the association between HRV and cognition in cohorts with severe cognitive impairment have yielded results of stronger significance. Zulli et al compared HRV indices between groups (n=101 of AD, MCI, and healthy age-matched controls) and reported significant differences in SDNN, LF, and HF between groups [156]. Collins et al reported lower HF in MCI subjects compared to healthy controls [157].

HRV and cognitive performance have not yet been studied in a large nationally representative population sample. A larger sample size of older adults may be required to elucidate the relationship between HRV and cognition, both of which decline with increasing age. The above described studies did not use a paced

breathing protocol which controls for the aforementioned affect of respiratory sinus arrhythmia.

2.5 Blood Pressure Variability (BPV)

Blood pressure variability (BPV) represents short term components of BP control, which can be estimated by the standard deviation (SD) or coefficients of variation (CV) of BP values recorded over a defined time-period. 24-hour recordings are frequently used to compare day and night values [158-161]. Circadian components are estimated comparing the night:day BP ratio.

BP values used to calculate BPV are recorded using oscillometric devices or with a Finapres apparatus (beat-to-beat BP measurement). Similar to HRV computation, PSD derives the frequency domain component of BPV. There is one characteristic frequency peak- the Mayer wave.

24-hour monitoring reports the loss of a nocturnal dip in BP as characteristic of subjects with dementia [159, 161]. Studies investigating the role of night-time and short-term BPV indices in cognitive decline have reported conflicting results [162, 163]. Cross-comparison between studies measuring BPV over different time-periods is not recommended, and a standardised time for measuring BPV has yet to be established. Hence, it is difficult to elucidate a relationship between BPV and cognition from the literature to date.

2.6 Baroreflex Sensitivity (BRS)

Baroreflex receptors modulate the body's response to changes in systemic BP via heart rate, myocardial contractibility and peripheral resistance. Baroreflex sensitivity (BRS) is defined as the immediate change in heart rate (or RR interval), relative to the change in BP.

BP changes induce arterial wall deformation, which activate baroreceptors located at the carotid sinus and aortic arch. Increasing intravascular pressure activates baroreceptors resulting in sympathetic deactivation. This leads to a decrease in heart rate, vasoconstriction and peripheral resistance. A decrease in intravascular pressure induces the opposite effect, via sympathetic activation and parasympathetic withdrawal. The resultant increased total peripheral resistance (TPR) augments venous return and stroke volume. Serum NAd levels rise, increasing the HR response and cardiac contractibility. The baroreflex response time is dependent on the baseline HR i.e. the conduction time from baroreceptors to the heart is faster at lower heart rates (<75 beats per minute) [164]. Delayed conduction at increased heart rates is mediated by the SNS.

BRS can be estimated by several methods. The baroreceptor response to mechanical or pharmacological induced changes is used to estimate BRS dynamically, in an *open loop model*. Spontaneous fluctuations of arterial pressure and RR intervals can be used to estimate BRS in a *closed circuit system,* when all the reflexes and control mechanisms are intact. The advantage of spontaneous recording is that the length of recording is not limited by the duration of action of the external stimulus [165]. Two approaches to spontaneous BRS analysis are used; (i) time and (ii) frequency domain measurements.

Time domain analysis identifies sequences of consecutive cardiac cycles characterized by changes in both RR interval (by ≥6ms) and SBP (by ≥1 mmHg). BRS is estimated by computing the slope of the regression line between changes in RR interval and SBP [166], as illustrated in figure 2.5. The frequency domain approach involves the computation of spectral waveforms from

simultaneously obtained sequences of RR intervals and SBP. Similar to HRV bands, oscillations are grouped into LF and HF bands. Baroreflex gain is computed by dividing the amplitude of the RR oscillation, by the amplitude of the corresponding SBP oscillation, in the respective band. If RR interval and SBP are linearly related, the gain is measured as the square root of the ratio of the two components [165]. In this way, specific rhythms shared in the RR interval and SBP changes are detected in the BRS estimate, unlike during time domain estimation, where all interaction types account for BRS. Spectral BRS is typically recorded from subjects at supine rest, reflecting continuous autonomic modulation [165].

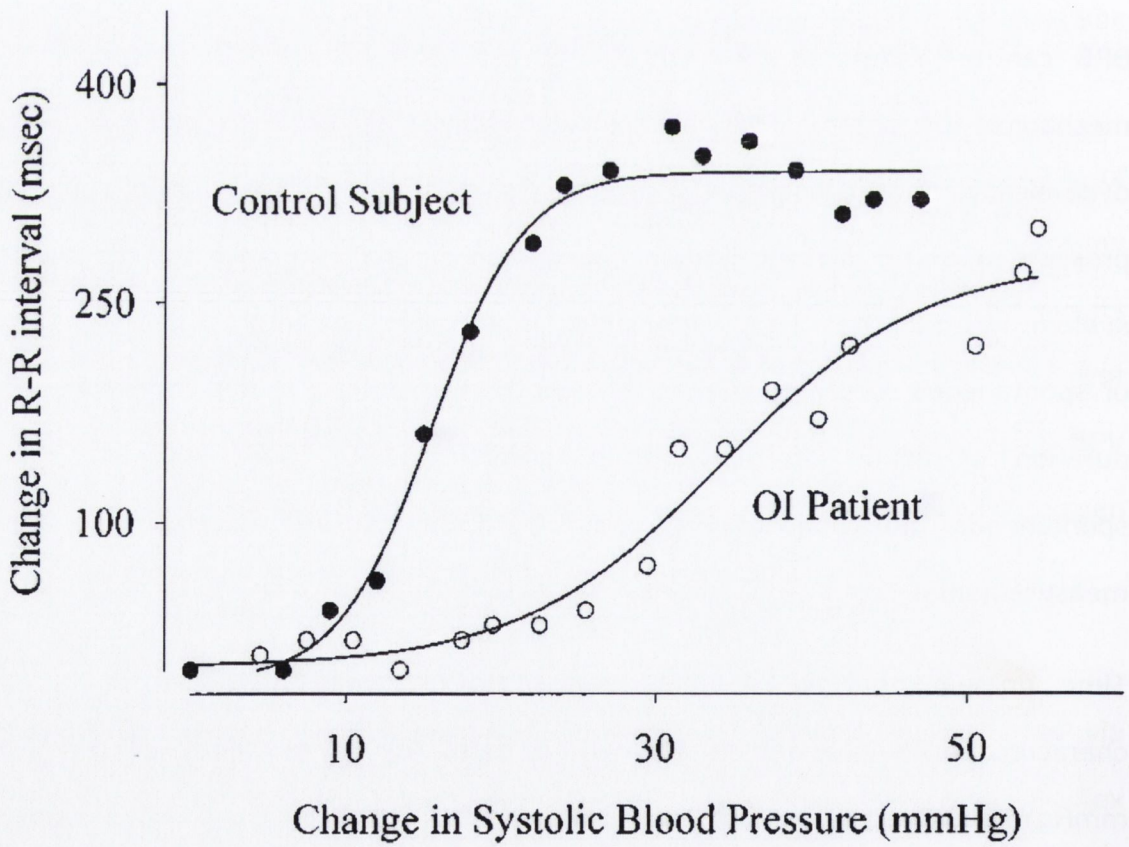


Figure 2.5 Baroreflex function (i.e. relationship between systolic blood pressure and R-R interval) in a subject with orthostatic intolerence (OI)

and a control subject. Note lower slope (cardiac vagal baroreflex gain) and R-R interval operating range in OI subject [167].

BRS and cognitive decline

Few studies have investigated the association between BRS and cognitive performance. The temporal association of baroreflex function with cognition has been investigated during cognitive testing. Results indicated that the relationship between BRS and cognition is dependent on tonic mean SBP. At higher SBP (greater than mean) an inverse relationship between BRS and cognitive performance is reported, in contrast to lower SBP (below the mean), which results in a direct relationship between BRS and cognitive performance [168]. Further study by the same group noted that this was confined only to women [169]. These findings must be interpreted cautiously as confounders were not adjusted for and the sample size was small (n=60). To the authors knowledge no other studies have investigated the impact of BRS on cognitive function.

2.7 Orthostatic Hypotension (OH)

Orthostatic hypotension (OH) is defined as a decrease in SBP by ≥20mmHg and/or a decrease in DBP by 10mmHg, within 3 minutes of standing from a supine position [170]. The prevalence of OH varies according to the population studied (e.g. the age range or institution), the population composition (e.g. healthy or select groups) and the use of concomitant medications: from 30% in the community dwelling population over 70 years [171], to 55% in geriatric outpatient clinics [172]. OH can be symptomatic or asymptomatic. Light-headedness is common, however more subtle symptoms include tiredness and difficulty concentrating [173]. Fainting can also occur, in which case syncope due to OH is diagnosed.

A number of mechanisms are responsible for haemostatic control following orthostasis. On standing, 500-700ml of blood is redistributed to lower extremities, splanchnic vessels, and pulmonary circulation [174]. This leads to a reduction in venous return and CO. Bodily response mechanisms to compensate for this fluid shift include (1) Ergoreflexes; mechano and metabo-receptor responses, which result in static contraction of skeletal muscle [175], (2) Arterial baroreceptor reflexes; pressure receptors located in the carotid sinus, intima of the aortic arch, and heart chambers which decrease their firing rate in response to a decrease in BP (described earlier) [176], (3) Neurohumoral changes; including activation of the Renin-angiotensin-aldosterone system (RAAS), adrenaline and dopamine β-hydroxylase release, and vasopressin release secondary to atrial/arterial stretch receptor activation (which function to increase blood volume) and (4) Cerebral autoregulation; adaptation of cerebral vasculature during orthostasis to maintain cerebral perfusion (described earlier) (see figure 2.6). Neurogenic, hypovolemic and drug-induced OH comprise the major sub-types of OH. Neurogenic OH is caused by primary dysautonomia or can be secondary to congenital, hereditary, inflammatory, infectious or metabolic diseases. A comprehensive list of established causes of OH are summarised in table 2.1. OH in the presence of primary autonomic failure can coexist with other conditions of dysautonomia, such as supine hypertension [177], complicating management practices [178].

Clinical assessment of OH can be performed using a number of methods [179]. Sphygmomanometer-based measurement is standard in primary care, whereby BP is measured after a rest period, the subject is asked to stand-up and BP measurement is repeated. More recent continuous monitoring methods, use infrared plethysmography to detect BP from the pulse of the digital artery [180].

Continuous methods are used during tilt-table testing in falls and syncope clinics to investigate the haemodynamic response to prolonged orthostasis, and determine the underlying cause of NCVI conditions. They allow for characterisation of the BP response to orthostasis, which is beyond the scope of oscillometric methods.

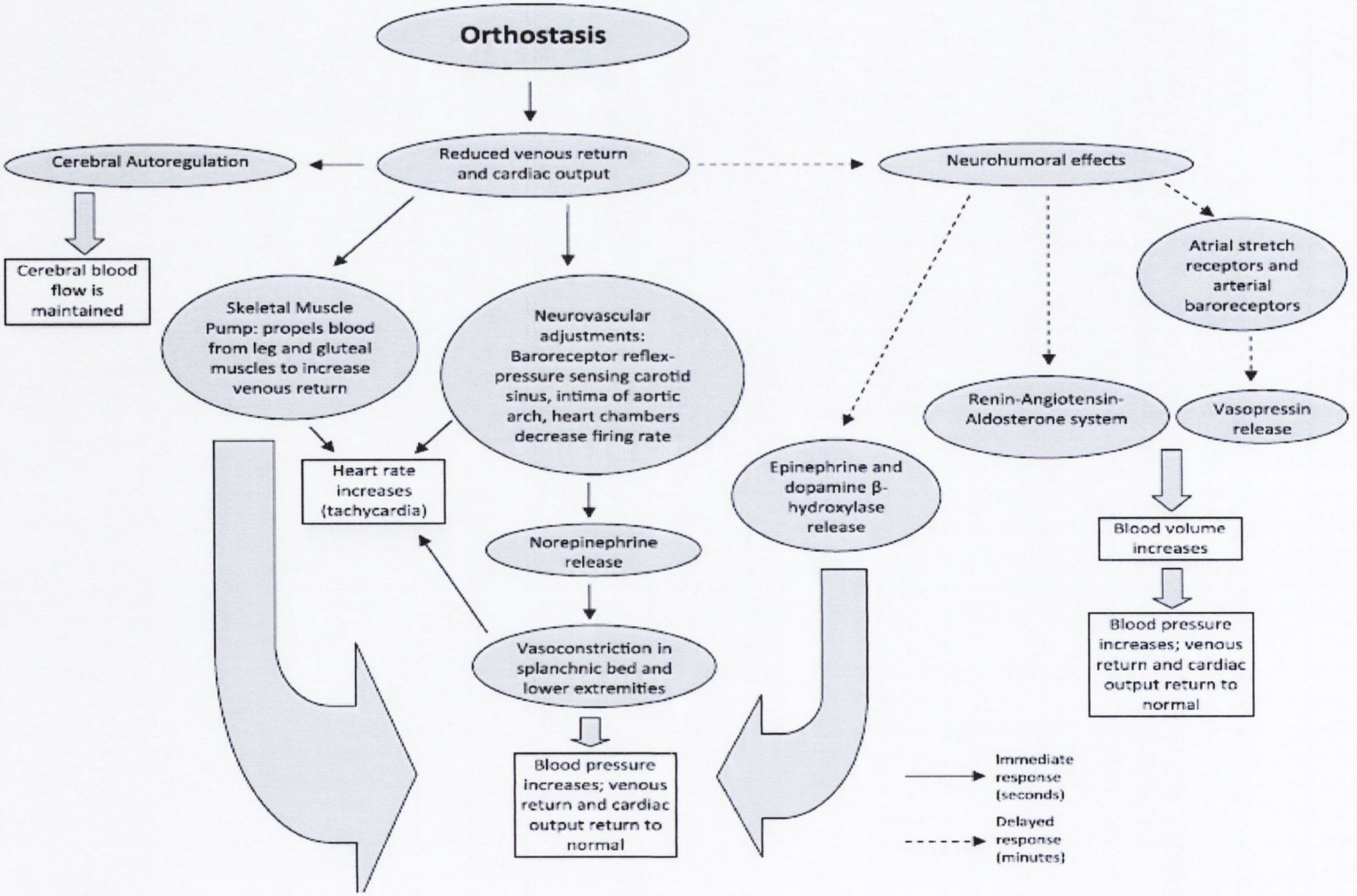


Figure 2.6 Overview of the mechanisms underlying orthostasis [176].

Table 2.1 Selected causes of orthostatic hypotension [177].

Volume depletion	*Cardiopulmonary*
Addison's disease	Pulmonary hypertension
Haemorrhage	Acute pulmonary embolism
Dehydration	Aortic stenosis
Autonomic failure	Hypertrophic cardiomyopathy
Acute (post-viral)	Cardiac failure
Pure autonomic failure	*Inflammatory*
Multi-system atrophy	Guillian-Barré syndrome
Paraneoplastic	Transverse myelitis
Congenital and hereditary	*Drugs*
Nerve growth factor deficiency	Calcium channel antagonists
Familial amyloid neuropathy	Levodopa
Familial dysautomia	Tricyclic antidepressants
Dopamine β-hydroxylase deficiency	Phenothiazines
Metabolic	Butyrophenones
Diabetes mellitus	Sildenafil
Chronic renal failure	Alpha adrenoreceptor antagonists
Infections	Nitrates
Tetanus	*Miscellaneous*
Septicaemia	Prolonged bed rest

There are four interrelated goals in the management of OH: to improve orthostatic BP without excessive supine hypertension; to relieve symptoms; to improve time-to-stand; and to improve the ability to perform activities of daily living. Pharmacological management alone is inadequate as symptoms are often time-dependent (e.g. occur post-prandially or at high temperatures). Patient education on orthostatic stressors and their mechanisms is crucial [181]. Fluid intake of 1.25-2.5L/day is essential but frequently neglected by older people. Elevation of the head of the bed to 10cm reduces nocturia and supine hypertension. Tight-fitting body stockings improve symptoms of OH by reducing venous capacitance. Physical counter-manoeuvres can lengthen the standing period that patients are capable of. These include leg crossing and thigh and

buttock contraction, which increase TPR and reduce venous capacitance (see figure 2.7).

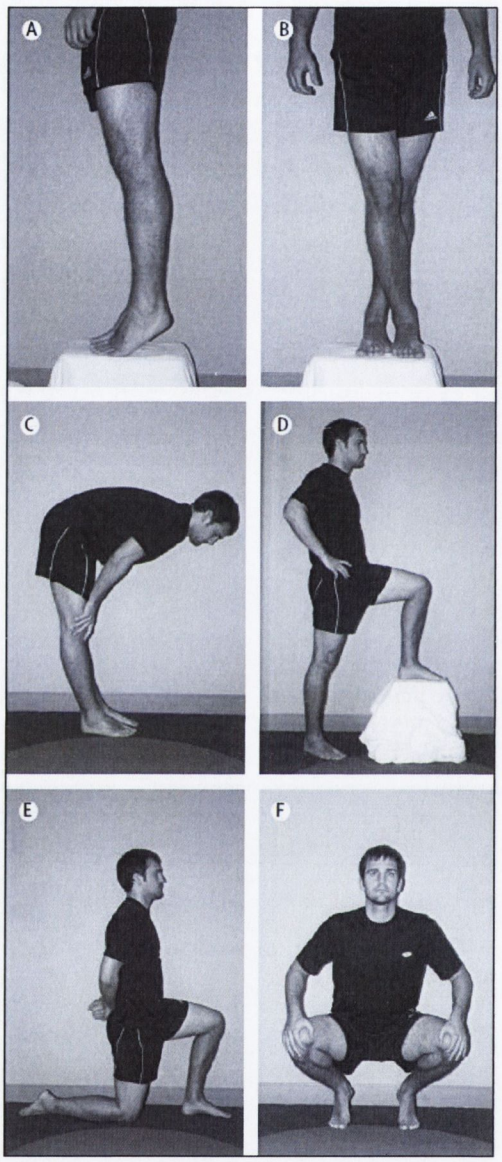


Figure 2.7 Physical manoeuvres that raise orthostatic blood pressure- (A) Toe raise. (B) Leg cross. (C) Forward lean. (D) Step up. (E) Genuflection contraction. (F) Squat. [181].

Pharmacological management options include Midodrine, Pyridostigmine, Droxidopa and Fludrocortisone. Midodrine is the only medication shown to

improve OH and related symptoms in a double-blind placebo controlled trial [182]. It is a direct a_1-adrenorecepter agonist, which is associated with side effects of parasthesis, supine hypertension and goosebumps. Hence patients are advised to avoid in the evenings, to reduce nocturnal supine BP. Pyridostigmine is a cholinesterase inhibitor indicated in mild OH cases, and does not aggravate supine hypertension [183]. Less evidence has indicated the therapeutic effect of other drugs on OH.

OH and cognitive decline

The prevalence of OH in dementia is 40-60%, compared to 4-33% in healthy subjects [118, 184, 185]. Presenting symptoms often differ between subjects with and without cognitive impairment. Presentation with syncope, falls and fractures is common in dementia, whereas typical symptoms in healthy individuals include unsteadiness of gait and complaints of dizziness with postural change [186].

Table 2.2 Overview of studies investigating orthostatic hypotension and cognitive function. CS=cross-sectional, L=longitudinal, HoTN= Hypotension.

Year	N	Cognitive measure	Author	Outcome	
1999	1159	MMSE	Viramo, P.	No longitudinal relationship	L
2007	36	MMSE, SVEBA (Italian cognitive scoring system)	Bendini, C	Weak association	CS
2008	2,321	MMSE	Yap, PL	No association CS. Associated L in HoTN gp	CS, L
2010 (1st)	12,702	Delayed Recall, Digit Symbol Substitution Test and Word Fluency	Rose, K. M.	No independent relationship	L
2010 (2nd)	74	Controlled Oral Word Association, Trail Making Test	Czajkowska, J.	Significant association reported.	CS
2010 (3rd)	495	cognitive efficiency profile (CEP)	Mehrabian, S.	Significant association reported.	CS

Several studies have investigated OH in the context of cognitive dysfunction both cross-sectionally [187, 188] and longitudinally [189, 190]- with conflicting results reported (see table 2.2). One study assessing the cognitive efficiency profile (CEP) scoring system on 495 participants with subjective memory impairment reported a significant association between low CEP score and OH [187]. Yap et al. Reported an association with reduced cognitive function (using MMSE) cross-sectionally in hypotensive subjects only, but was not sustained at follow-up [188]. Other longitudinal studies have reported similar findings [189,

190]. A recent review reported inconsistent results across studies [176]. Longitudinal studies to date have assessed OH at baseline and cognitive function at follow-up, however there remains a lack of evidence on the impact of cognitive function on subsequent OH. Studies assessing OH as an endpoint would broaden our understanding of the temporal relationship between OH and cognition. Assessment of OH in each of these studies used oscillometric based BP recording- none measured OH using continuous methods.

For these reasons I investigated the association using OH as defined using two measurement methods- traditional sphygmomanometer-based measurement and the more recently developed plethysmographic-based measurement. We investigated the association across multiple cognitive domains, in light of the limited cognitive testing applied in several previous studies.

2.8 Carotid Sinus Hypersensitivity (CSH)

Carotid sinus hypersensitivity (CSH) describes an abnormal reflex in response to stimulation of baroreceptors at the bifurcation of the common carotid artery [178]. The hypersensitive baroreceptors activate an inappropriate parasympathetic response. CSH is diagnosed by firm massage of the carotid sinus for 3-5 s, with continuous monitoring of HR and BP. When syncope occurs in the presence of CSH, carotid sinus syndrome (CSS) is diagnosed. Autonomic activity is similar between symptomatic and asymptomatic subjects which has led to the consideration that CSH is a generalized disorder, with dysautonomia present regardless of symptoms[191].

CSH is more common in subjects with dementia [192], particularly those with DLB (dementia with Lewy bodies). Cerebral autoregulation is impaired in CSS and neurodegeneration is considered the underlying cause of baroreflex

dysfunction in CSH, which may indicate a bidirectional relationship between CSH and cognitive impairment [193].

2.9 Syncope

Syncope is a transient loss of consciousness (T-LOC) due to global cerebral hypoperfusion, characterized by rapid onset, short duration and complete recovery [178]. A fall in BP to 60 mmHg or lower for 6-8 s is sufficient to cause global cerebral hypoperfusion (and specifically of the reticular activating system) resulting in complete LOC [194]. Classification of syncope is based on the underlying pathophysiology, emphasising groups of disorders with a common presentation and risk profile (see table 2.3). Systemic BP is controlled by CO and TPR, either of which can result in syncope if their function is impaired. CO is responsible for cardiac syncope and CO and/or TPR underlie both reflex syncope and syncope secondary to OH.

Reflex (neutrally-mediated) syncope covers conditions in which cardiovascular reflexes respond inappropriately to one or more triggers. It is the most prevalent syncope type, and its sub-classification can be based on the efferent pathway of the reflex implicated in the condition. *'Vasodepressor'* syncope occurs when hypotension predominates, and *'cardioinhibitory'* syncope occurs when bradycardia or asystole predominate- similar to CSH sub-classification [178]. Alternative classification based on the trigger is important in the clinical setting (table 2.3). *'Vasovagal'* syncope (VVS) is the clinical term for the common faint-occurring due to emotional or orthostatic stress. VVS is one of the main conditions of NCVI [118].

OH as a cause of syncope is described earlier. Cardiac syncope is caused mainly by arrhythmias, of which more severe forms of acquired atrioventricular block

are most linked to syncope. Delayed conduction via escape pacemaker sites in combination with their relatively low firing rate results in the reduced CO associated with syncopal events. Structural heart defects can also lead to syncope when CO is compromised. Cardiac syncope is the second most common syncope cause, and its incidence increases with age. OH as a cause of syncope also increases with age [178].

Diagnostic tests to determine the cause of syncope include carotid sinus massage, orthostatic challenge (both active stand and tilt-table testing), electrocardiographic monitoring and psychiatric and neurological evaluations.

Syncope treatment is dependent on the underlying cause. Reflex syncope and syncope caused by OH are managed using the pharmacological and non-pharmacological options outlined earlier. Cardiac syncope is treated according to the underlying cause, and may include cardiac pacing, catheter ablation or replacement of malfunctioning implanted devices.

'Pre-syncopal' or 'prodromal' signs and symptoms often precede syncopal events, and include sweating, pallor and dizziness. Amnesia for loss of consciousness (A-LOC) is prevalent in 28% of subjects with VSS when a syncopal event is induced during tilt-table testing [195]. Furthermore, the prevalence of A-LOC is higher amongst subjects presenting with unexplained falls (95%) than those presenting with syncope (27%), during carotid sinus massage [196]. This emphasises the importance of eyewitness accounts in addition to patient history. The prevalence of syncope amongst patients presenting with falls may therefore be higher than previously thought. For this reason, both history of syncope and non-accidental falls were examined in this thesis.

Table 2.3 Causes of syncope [176].

Reflex (neurally-mediated) syncope

Vasovagal:
- *mediated by emotional distress: fear, pain, instrumentation, blood phobia*
- *mediated by orthostatic stress*

Situational:
- *cough, sneeze*
- *gastrointestinal stimulation (swallow, defaecation, visceral pain)*
- *micturition (post-micturition)*
- *post-exercise*
- *post-prandial*
- *others (e.g., laught, brass instrument playing, weightlifting)*

Carotid sinus syncope

Atypical forms (without apparent triggers and/or atypical presentation)

Syncope due to orthostatic hypotension

Primary autonomic failure:
- *pure autonomic failure, multiple system atrophy, Parkinson's disease with autonomic failure, Lewy body dementia*

Secondary autonomic failure:
- *diabetes, amyloidosis, uraemia, spinal cord injuries*

Drug-induced orthostatic hypotension:
- *alcohol, vasodilators, diuretics, phenotiazines, antidepressants*

Volume depletion:
- *haemorrhage, diarrhoea, vomiting, etc*

Cardiac syncope (cardiovascular)

Arrhythmia as primary cause:

Bradycardia:
- *sinus node dysfunction (including bradycardia/tachycardia syndrome)*
- *atrioventricular conduction system disease*
- *implanted device malfunction,*

Tachycardia:
- *supraventricular*
- *ventricular (idiopathic, secondary to structural heart disease or to channelopathies)*

Drug induced bradycardia and tachyarrhythmias

Structural disease:

Cardiac: *cardiac valvular disease, acute myocardial infarction/ischaemia, hypertrophic cardiomyopathy, cardiac masses (atrial myxoma, tumors, etc), pericardial disease/tamponade, congenital anomalies of coronary arteries, prosthetic valves dysfunction*

Others: *pulmonary embolus, acute aortic dissection, pulmonary hypertension*

Syncope and cognitive decline

The increased prevalence of cognitive impairment in older age may attenuate recall of syncope and falls history [178]. To our knowledge, the direct relationship between syncope and cognitive performance has not been explored in the literature. It is hypothesised that the relationship is bidirectional however [197]. Neurochemical and neuropathological changes characteristic of dementia may result in dysautonomia. On the other hand, ishaemic damage caused by cerebral hypoperfusion, which is characteristic of syncope may also cause neurodegenerative and atrophic changes that result in cognitive decline. Due to the lack of research on this subject, there is a need for investigation of syncope and cognitive performance across multiple population groups.

3 Population studies

A population study refers to an investigation of all the subjects within a population, or a subset of the population that provide a reliable estimate of the entire population. In the latter case, a minimum proportion must be recruited to achieve reliability and validity. To confirm that the sample response represents the population, a comparison of the response group demographics with those of the total population is required. Similar demographics between groups provide a reliable estimate that the response group reflects the population as a whole. If responses inaccurately reflect the population, weighting methods can be derived and applied to the sample cohort. This requires highlighting the demographic features which differ between the sample and the population and applying a higher weight to underrepresented respondents and a lower weight to overrepresented respondents. Population studies incur greater costs relative to cohort studies, as greater efforts must be made to contact all members of the population studied.

There are many advantages to population studies. Analysis of population data provides reliable information regarding the health characteristics of a heterogeneous group, inclusive of both healthy subjects and those with health conditions. It allows for substantive research hypotheses to be examined, such as estimation of the true prevalence of health conditions and their epidemiological characteristics. Longitudinal analysis extends the scope of research to allow for investigation of the causal relationship between systems and understand the complete pathophysiology underlying disease development.

This can be undertaken by investigating the effect of exposure at one point in time on the incident outcome across exposed and non-exposed groups at a later stage. Adjusting for confounding factors allows for more accurate inferences of independent relationships between the variables of interest. However, one of the Bradford-hill criteria for establishing causation requires coherence of findings between study types, so by corroborating prospective cohort study findings with outcomes from experimental interventional studies, a clear causal relationship can be established. Interventional studies carry the benefit of withholding exposure to one group and comparing outcomes to an exposed group. Double-blinding of the assigned group, to both the study sample and to the researchers of the study exclude potential biases that cannot be controlled for in observational studies.

Combining the internal validity of prospective cohort experiments with the external validity of population groups is essential when extrapolating results from a study to a population. Population based studies are capable of providing policy-makers with greater confidence in their findings, when compared to case control studies [198].

3.1 The Irish Longitudinal Study of Ageing (TILDA)

The Irish longitudinal study of ageing (TILDA) is a population study set-up with the aims of (1) providing comprehensive baseline data of older people living in Ireland, (2) investigating the causal processes of age-related health conditions, (3) empowering older people to voice their opinions and (4) enhancing the infrastructure of gerontological research in Ireland. The TILDA study is multi-disciplinary, covering aspects of health, income, living conditions, social contact,

environment and family circumstances. This allows for a greater understanding of the web of causation between different domains.

TILDA is harmonized with leading international research in order to ensure adoption of best practice and to allow comparability of results. The Irish government, The Atlantic Philanthropies and Irish Life plc have funded the TILDA study. Ethical approval was obtained from the Trinity College Dublin Research Ethics Committee.

3.1.1 **Sampling methodology**

Recruitment for the TILDA study began in October 2009. The target population of the TILDA study is the population aged 50+ residing in the Republic of Ireland, and their partners of any age. The sampling frame used to select subjects was the RANSAM system, designed by the Economic and Social Research Institute of Ireland (ESRI) [199]. It uses a listing of all residential addresses in the Republic of Ireland, complied by the Irish postal service (An Post) and Ordnance Survey Ireland. The RANSAM program groups all of these addresses into one of 1433 clusters (townlands), each containing 500-1500 addresses. Clusters are stratified by socio-economic status and geographical location, ordered within each county based on a north/south pattern to preserve continuity. 640 clusters were selected, with the probability of selection proportional to the number of individuals aged 50+ living within the cluster (see figure 3.1).

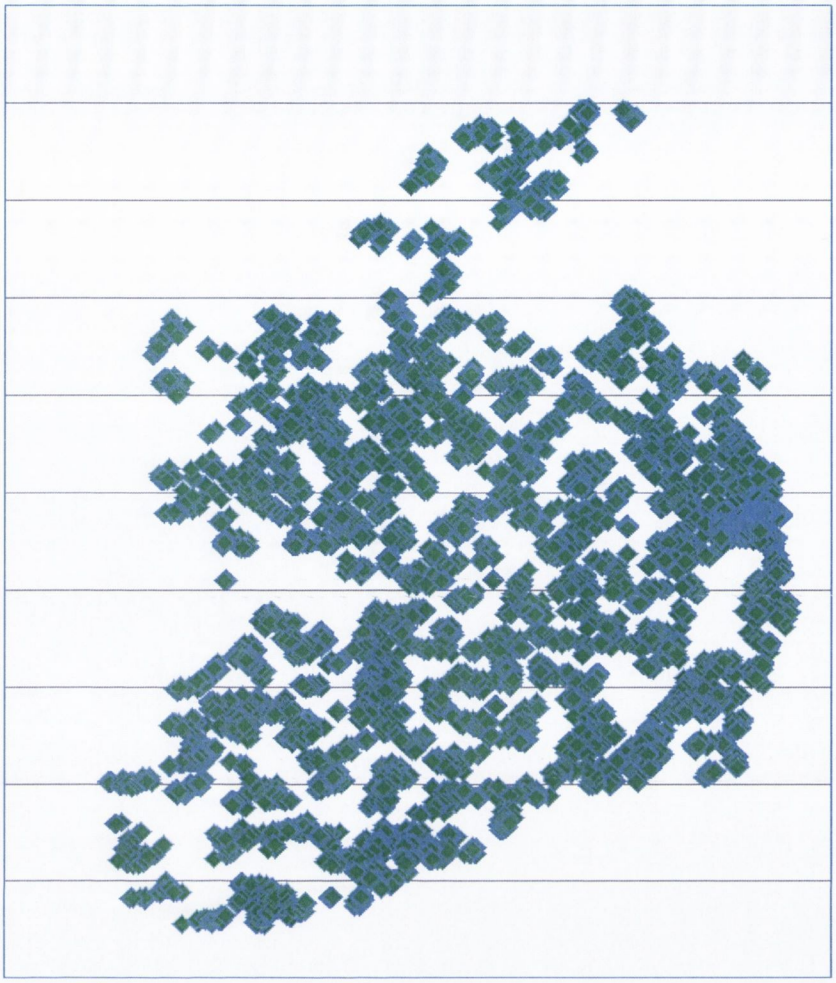


Figure 3.1 Location of clusters in the Republic of Ireland selected (at random) for inclusion in the TILDA study.

A sample of 50 addresses (40 used and ten in reserve- allocated at random) from each cluster was obtained (selected according to probability) and all persons aged 50+ in the selected households were asked to participate. Invitation letters were delivered by post to all unique addresses and hand delivered by interviewers to households with a non-unique address. A home visit was carried out one week later by field staff to determine eligibility of household members. At this point interviewers screened for dementia, at their discretion. There was no formal criterion applied to screen for dementia. The interviewers

judged competency at the point of contact, based on competency to engage conversation and secondly, cases were identified following voluntary disclosure by the spouse, where applicable. The response rate was 62% and over 8000 people responded and consented to participation. For this reason, the reserve list was not utilised. Bias introduced by non-random response rate variation was adjusted for using calibration weights, derived using data from the Quarterly National Household Survey. Each TILDA participant is representative of 142 members of the population aged ≥50 years. Further detail of the study design is described elsewhere [200].

3.1.2 **Data acquisition**

Three modes of data collection were used in the TILDA study (see figure 3.2). The computer-aided personal interview (CAPI) component was undertaken in the participants home by trained professional social interviewers. Detail on demographics, lifestyle, social support, attitudes to ageing and behavioural, mental and physical health was collected here (see Table 3.1).

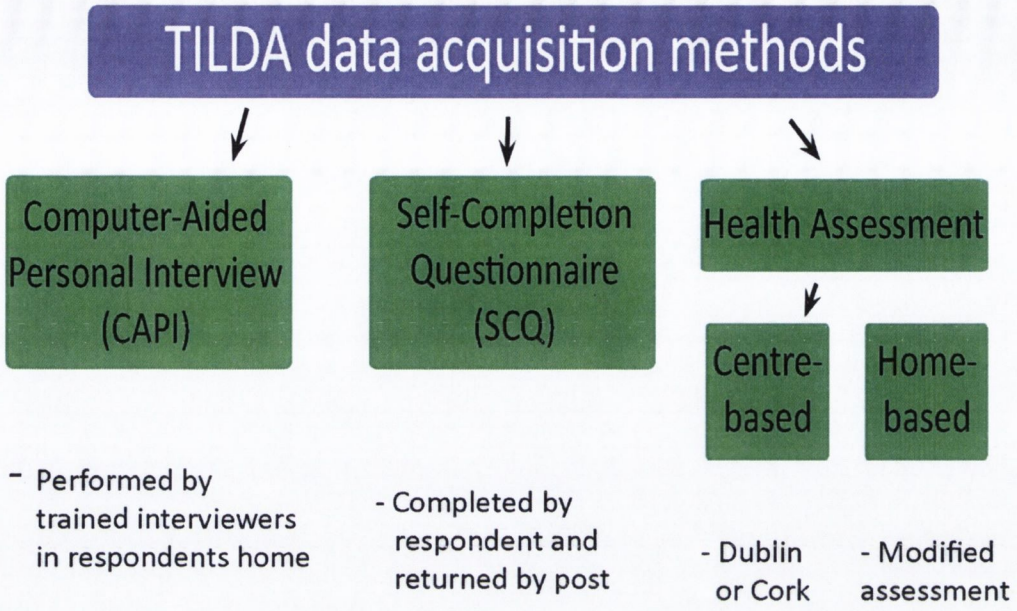


Figure 3.2 Methods of data collection used in the TILDA study.

Clinical health assessment was carried out to acquire objective measures of health. Assessment duration was ~150 min and subjects who were unwilling or unable to undergo centre-based assessment were offered an in-home assessment, where a subset of features was measured. The following measures were examined in-centre; anthropometric measurements (height, weight, waist circumference), clinical profile (blood pressure, blood cholesterol level), cardiovascular measurements (electrocardiogram and pulse wave velocity) autonomic measurements (heart rate variability recording and BP monitoring in response to orthostasis) and neurocognitive testing (covering domains of global function, executive function, processing speed, sustained attention and memory). Standardised protocols were used during assessment to enable comparability with previous studies. In-home assessments were essential in order to capture to objective health profile of subjects who may have been

unable to attend centre-based assessment due to health-related relations. The modified in-home assessment measured antropometric data, clinical profile, BP response to orthostasis and neurocognitive measurements. Other measures were omitted due to practical and financial constraints.

Data collected during the first wave of the TILDA study allowed for investigation of the point-in-time association between multiple domains of cognitive function and a number of autonomic indices. Heart rate variability generated from electrocardiogram data was used as an index of general autonomic function. Orthostatic hypotension, defined using BP measurements from both cuff-based (recorded in both centre and home-based assessments) and continuous monitoring (centre only) were also studied, as it is indicative of autonomic dysfunction. Finally history and burden of syncope and non-accidental falls (assessed during the CAPI) were examined to investigate the differential effect of burden of autonomic disorders on cognition.

As clinically diagnosed MCI requires one of either individual subjective complaints of cognitive dysfunction, informant reported changes, or clinician reported changes, it was unjustified to define an MCI group in the TILDA dataset, as such information was not available. Furthermore, cross-sectional wave one data (analysed here) does not allow for computation of declining scores over time.

Table 3.1 Summary of data collected in TILDA and Self-completion Questionnaire (SCQ) [198].

Demographic data	**Physical health**
Education	Self-rated health
Childhood health	Limiting long-standing illness/disability
Migration history	Sensory function
Marital status and marriage history	Cardiovascular disease
Social circumstances	Non-cardiovascular chronic illness
Transfers to (and from) children	Falls/fear of falling/steadiness
Transfers to (and from) parents	Chronic pain
(Instrumental) activities of daily living	Incontinence
Helpers	Medical screening
Social connectedness	**Mental health**
Participation in social/recreation activities	Self-reported mental health
Relationship quality (SCQ)	Depression
Employment and lifelong learning	Life satisfaction
Employment situation	Anxiety (SCQ)
Job history	Worry (SCQ)
Lifelong learning	Loneliness (SCQ)
Retirement and expectations	Perceived stress (SCQ)
Planning for retirement	Stressful life events (SCQ)
Expectations	Quality of life (SCQ)
Income and assets	**Cognitive health**
Sources of income	Self-rated memory
Assets	Orientation
Transport	Word-list learning (immediate and delayed recall)
Transportation	Verbal fluency
Driving	Prospective memory
Medications	**Behavioural health**
Health-care utilization	Smoking
	Physical activity
	Sleep
	Alcohol (SCQ)
	Ageing perceptions (SCQ)

3.2 Conclusion

There is ample research evidence to suggest an association between indices of autonomic function, conditions of autonomic dysfunction and cognitive impairment. The mechanisms through which we hypothesise the relationship between autonomic dysfunction and cognition are summarised in Figure 3.3.

Many studies report conflicting results, and few investigate the association in large population based cohorts. No studies have investigated HRV and cognition in a large community-representative cohort. There is a complete absence of literature describing the association between syncope and cognitive performance. Similarly, the association between cognition and continuously monitored BP during orthostasis has not been explored in a large population

based cohort. Disorders of NCVI are more prevalent in dementia; however the temporal relationship between autonomic dysfunction and cognitive impairment has not yet been established.

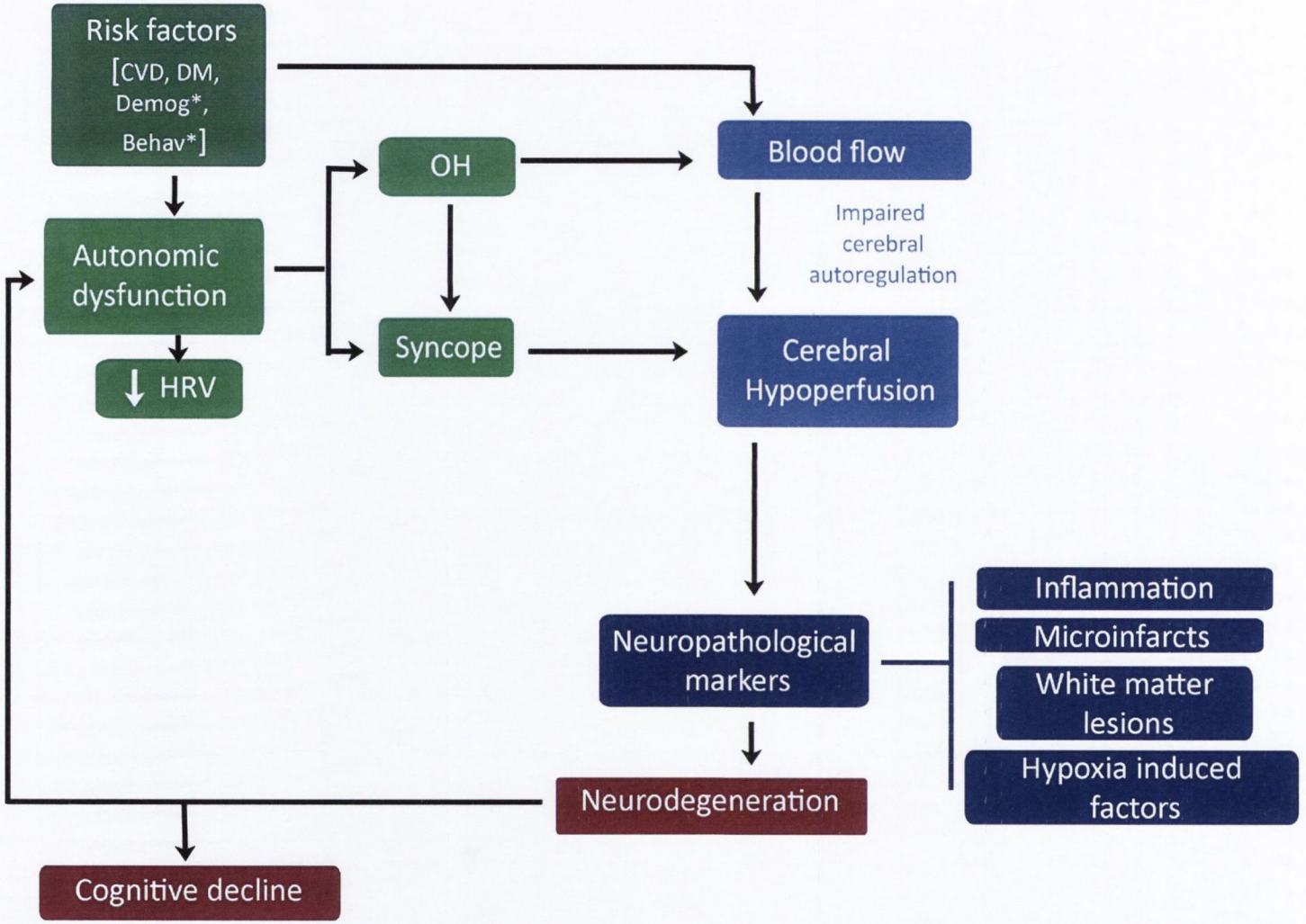

Risk factors
[CVD, DM,
Demog*,
Behav*]
OH
Blood flow
Impaired
cerebral
autoregulation
Autonomic
dysfunction
↓ HRV
Syncope
Cerebral
Hypoperfusion
Inflammation
Microinfarcts
White matter
lesions
Hypoxia induced
factors
Neuropathological
markers
Neurodegeneration
Cognitive decline

Figure 3.3 Schematic of the proposed relationship between autonomic dysfunction and cognitive decline.

Demog*= demographics, Behav*=behavioural health, HRV= heart rate variability, OH= orthostatic hypotension.



3.3 Objectives of my Doctorate thesis

The objectives of my thesis, using data from the first wave of the TILDA study, are to investigate

4. The cross-sectional association between heart rate variability and global cognitive performance. Attention was focussed exclusively on global function given that few studies to date have investigated HRV in relation to cognition. Therefore the aim here was to establish if an overall association does exist.
5. The cross-sectional association between orthostatic hypotension,
   i) measured using traditional oscillometric recording and cognitive performance, and
   ii) measured using photoplethysmographic recording.

   As numerous previous studies have investigated OH in relation to cognition, the aim here was to expand the investigation by analysing the association between OH and several domains of cognitive function.
6. The cross-sectional association between history and burden of syncope, non-accidental falls and cognitive performance. Finally, as no previous studies have investigated the association between syncope and cogntion, the aim here was to investigate its relationship with global function.

4 Cognitive function is associated with impaired heart rate variability in ageing adults- The Irish longitudinal study on Ageing Wave one results

4.1 Abstract

Objective

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

Methods

Cross-sectional analysis of wave 1 data from the Irish longitudinal study on ageing (TILDA) was performed. A subset of 4763 participants who underwent ECG recording during resting and paced breathing periods, were used for analysis. HRV indices were divided into quintiles for comparison of values and cognitive performance was defined using the Montreal cognitive assessment (MOCA) score. Multivariate linear regression was used to model the association between cognition and different quintiles of each HRV index, after adjustment for covariates.

Results

The mean age was 61.7 ± 8.3 years and 2618 (55%) were female. Lower quintiles of SDNN (P=0.01 -paced), LF (P=0.001-paced), and LF:HF ratio (P=0.049 -paced) were significantly associated with lower MOCA scores (during both recording periods), independent of confounders. Sub-domains of MOCA

responsible for the relationship were predominantly memory recall and language.

Interpretation

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

4.2 Introduction

Ageing is associated with a reduction in cognitive performance. The average incidence rate of mild cognitive impairment (MCI) is 12-15 per 1000 person years in persons aged 65 and older [201]. The conversion rate from MCI to dementia is 14% annually [6]. Predictors of conversion from MCI to dementia currently include cerebrospinal fluid biomarkers, neuropsychological tests and structural MRI morphometry [202-204].

The ageing demographic shift will likely increase the global burden of cognitive disorders in the coming years. In light of this, there is an urgent need for interventional strategies targeting modifiable determinants of MCI, dementia and conversion from MCI to dementia. Factors associated with cognitive decline include age, lower education, lifestyle (lower physical activity, smoking and high alcohol consumption), genetic predisposition, metabolic dysregulation (obesity, impaired glucose tolerance, diabetes), cardiovascular disease (hypertension, atherosclerosis, stroke) and inflammatory markers- many of which are evidently modifiable [68, 205-208].

Many of these factors are also precursors to reduced heart rate variability (HRV); including smoking, high alcohol intake, obesity, diabetes, hypertension, and inflammation [144, 209, 210]. This suggests that HRV and cognition have common risk factors. HRV is a marker of cardiac autonomic function, and involves the interaction of activity from the sympathetic (SNS) and parasympathetic nervous systems (PNS). Emerging evidence suggests an association between cognitive impairment and autonomic dysfunction. This relationship may be bidirectional with autonomic dysfunction causing systemic

hypotension that leads to cognitive impairment [211], while neurodegenerative processes influence autonomic pathways, causing autonomic dysfunction [212].

Studies investigating the association between HRV and cognitive function have to date reported conflicting results [154, 213], however none have been conducted in large population based samples. The aim of this study was to investigate the independent association between HRV and global cognitive function, in a nationally representative sample of older adults. HRV acquired during two breathing protocols was applied, in order to limit respiratory bias. The role of sub-domains assessed within global cognition on the association was also examined.

4.3 Methods

Study design

Data from the first wave of The Irish Longitudinal Study on Ageing (TILDA) was analysed. TILDA is a large prospective cohort study of ageing, comprised of community dwelling adults aged 50 and over, resident in the Republic of Ireland. A nationally representative sample was selected using the regularly updated RANSAM sampling technique [199]. Further detail of the study design is published elsewhere [200]. Data collected within TILDA is composed of three parts; (i) Computer-assisted personal interviewing (CAPI), (ii) Self-completion questionnaire (SCQ), and (iii) a physical health assessment. Participants unwilling to undergo centre based health assessment were offered an in-home health assessment, where a sub-group of measures were recorded. Electrocardiograms were conducted in the health centre assessment but not the home assessment. Ethical approval was obtained from Trinity College Dublin and all participants provided signed informed consent prior to the study. All experimental procedures adhered to the Declaration of Helsinki. This study uses data from the first wave of TILDA, collected between July 2009 and June 2011.

Cognitive assessment

Cognitive function was assessed in the TILDA study using a battery of cognitive tests [200]. This included the Montreal cognitive assessment (MOCA) [46], which was administered during the health assessment and used in the present study. MOCA is a measure of global cognitive function (score range; 0-30), comprised of the sub-domains i) memory ii) visuospatial function, iii) executive function, iv) sustained attention, v) language, and vi) orientation. It was chosen for analysis over the mini mental state examination (MMSE) due to its higher

predictive value for MCI [46] and less ceiling effect in a population-representative sample.

Measurement of RR interval variability

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

The ECG was acquired and subsequently band-pass filtered (0.01-1000Hz). A proprietary algorithm was used to detect the R peak of each heart beat recorded on the ECG signal [214]. Its accuracy is described elsewhere [214]. Supra-ventricular ectopic beats and noise were excluded from the signal using linear interpolation. All recordings were screened for atrial fibrillation (AF) using criteria from the European society of cardiology (ESC) [215], and those identified with AF were subsequently excluded from analysis. Other arrhythmias were detected and excluded by the Darwin software system. Heart rate was recorded and controlled for in study analysis.

300-second epochs of RR interval data were analysed. Statistical methods were used to derive the time domain index; the *standard deviation of NN intervals* (SDNN). Frequency domain (FD) features were calculated from spectral

estimates derived using an autoregressive (Burg method) algorithm, with assignment of 256 discrete frequency bins. FD features were derived by integrating the power spectrum across bands using the Fast Fourier Transform (FFT) as recommended by the Task Force for HRV measurement [140]. *Low frequency power* (LF, 0.04-0.15Hz, ms^2) and *high frequency power* (HF, 0.15-0.4Hz, ms^2) were calculated and expressed as a ratio LF:HF also.

A number of recordings (n=424) were unsuitable for analysis of paced breathing data due to technical error or protocol non-compliance. These were flagged by the Darwin software system. The group with erroneous paced data were compared to those with complete data, using chi-squared tests for continuous normally distributed variables and rank-sum tests for non-normally distributed variables. The erroneous group were found to have lower educational attainment and lower median MoCA scores when compared to those with complete paced data.

Measurement of covariates

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

The Centre for Epidemiological Studies Depression (*CES-D*) scale was used with a cut-off score of 16 or above, to define subjects as depressed [216]. The Hospital Anxiety and Depression (*HADS)* scale was used to define subjects as having anxiety, using a cut-off criteria score of 11 or above [217]. This was obtained through a self-completion questionnaire. Self-reported cardiovascular diseases were documented and included: history of angina, myocardial infarction (MI), heart failure, diabetes mellitus (DM), stroke, transient ischaemic attack (TIA), and cardiac arrhythmias.

Medication use was recorded during the home interview (CAPI) and confirmed by cross-checking the medication labels. The Anatomical Therapeutic Classification (ATC) codes were subsequently recorded for categorisation [218]. Medication categories adjusted for in analysis were alpha-blockers ('CO2CA', 'CO2LE'), beta-blockers ('C07*'), calcium channel blockers ('CO8*'), cardiac glycosides ('C01A*'), midodrine ('C01CA'), anticholinergic agents ('N04A*'), and anticholinesterase agents ('N06DA*, N07AA*').

Statistical analysis

Statistical analysis was performed using Stata version 12 (StataCorp, College Station, TX). Distribution of continuous variables was assessed qualitatively using Q-Q plots and histograms, and quantitatively using statistical tests of kurtosis and skewness. For quantitative tests, $P<0.05$ was considered indicative of non-normal distribution. Normally distributed variables were described as means and standard deviations (SD), and were compared across groups using independent t-tests. Non-normally distributed variables were described as medians and percentiles and compared using Mann-Whitney tests, and categorical variables were compared using Chi-squared tests. HRV indices were

divided into quintiles for analysis, in order to investigate the non-linear association between HRV and cognition. Multivariate linear regression was used to assess the relationship between HRV indices and MOCA score (continuous scale). Indices measured during spontaneous and paced breathing periods were compared. Significance was taken as $P<0.05$. For each quintile increase in HRV, the standardised regression coefficient (β) corresponded to the associated change in MOCA cognitive score. A core model (A) was first tested; adjusting for age, gender and education level, to observe the role of baseline demographics on the HRV-cognition association. A subsequent model (B) was tested to explore the additional role of physiological factors which may confound the relationship between HRV and cognitive performance, namely; adjusting for these three variables, along with all remaining covariates described above, namely behavioural health (smoking, alcohol and physical activity), clinical profile (BMI, cholesterol, height, seated blood pressure), mental health (CES-D and HADS-A scores), cardiovascular disease (angina, MI, heart failure, DM, stroke, TIA, arrhythmias) and medications listed above. Adjusted predictive MOCA scores across quintiles of HRV indices were fitted.

4.4 Results

In total 8175 participants aged 50 years and older were recruited to the TILDA study [200]. Of these 5036 agreed to undergo an in-centre health assessment, 4763 of whom had technically adequate data for HRV analysis (see Figure 4.1). A subset of 424 subjects had spontaneous-breathing HRV data only.

The mean age was 61.7 (±8.3 SD) and 2618 (55%) were female. HRV patterns of the sample for both spontaneous and paced breathing periods are outlined in Table 4.1, together with subject characteristics. Men had higher levels of alcohol consumption, former smoking, physical activity, BMI, SBP, DBP, and prevalence of cardiovascular disease. Women had higher levels of cholesterol and prevalence of anxiety and depression. Minimum, mean and maximum HR values were greater during paced breathing. HRV indices LF and HF were greater during spontaneous breathing, while SDNN and LF:HF ratio were greater during the paced breathing period.

The association between HRV (measured as quintiles) and MOCA score is summarized in Table 4.2, according to spontaneous or paced breathing. In Model A (adjusted for age, gender, and education) lower (quintiles of) LF:HF ratio during spontaneous breathing, lower HF and higher mean HR during paced breathing, and lower SDNN and LF during both periods, were significantly associated with a lower MOCA score.

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

association between higher mean HR and lower MOCA score remained significant in Model B, during paced breathing only.

There was a dose response in the multivariate adjusted effect size between HRV and MOCA score, for the indices LF and LF:HF ratio. MOCA scores were fitted across quintiles of paced LF, with adjustment for covariates, to illustrate this dose response (see figure 4.2). Subjects in the lowest LF quintile group had an adjusted estimated MOCA score of 25 (95% CI; 24.8-25.3), whereas subjects in the highest LF quintile group scored 25.7 (95% CI; 25.5-26).

Figure 4.3 illustrates the HRV changes associated with poor cognitive performance. $SDNN^2$ is shown instead of SDNN as it is indicative of total power and yielded identical significance to SDNN in analysis. Regression analysis using a dichotomised MOCA score, according to the criteria for cognitive impairment (scores below 24) [48, 219] yielded broadly similar results (not shown). Further sub-analysis stratifying by gender yielded similar results between men and women.

Analysis of the sub-domains of MOCA score was performed to determine the component responsible for the effect of HRV on cognitive function. Confounders included in Model B above were adjusted for here (see table 4.3). Domains of memory recall and language predominantly accounted for the association between HRV and MOCA score.

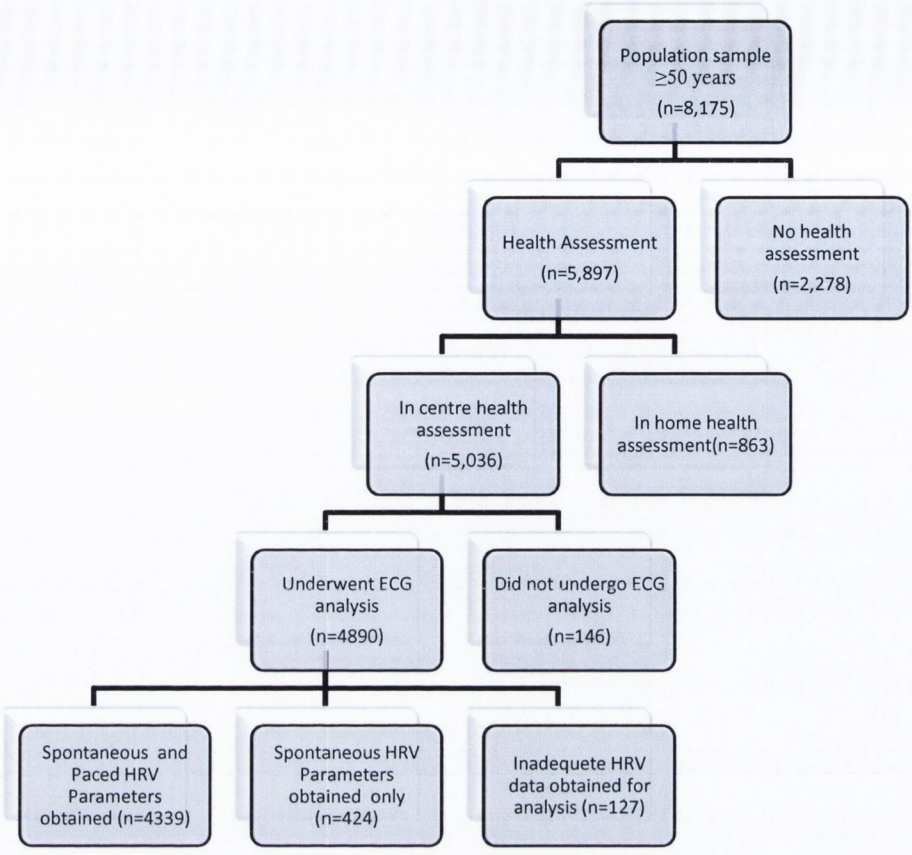


Figure 4.1 Flowchart of TILDA study participants eligible for ECG recording in TILDA.

Characteristics	Men (n=2145)	Women (n= 2618)	P-value
Age, mean ± SD	61.8 ± 8.3	61.5 ± 8.3	0.29
Education, % (n)			
Primary	23.4 (502)	19.6 (512)	
Secondary	41.5 (890)	42.2 (1105)	0.0001
Tertiary	35.1 (753)	38.2 (999)	0.0001
MOCA score [a]	26 (23, 28)	26 (24, 28)	0.11
Smoking status, % (n)			
Never	38.3 (821)	52.5 (1374)	
Former	46.5 (998)	32.4 (849)	0.0001
Current	15.2 (326)	15.1 (395)	0.0001
Standard drinks consumed weekly [a]	4.5 (0.48, 12)	1.5 (0, 6)	0.0001
Level of physical activity (IPAQ), % (n)			
Low	23.1 (490)	31 (804)	
Medium	32.6 (694)	39.5 (1026)	0.0001
High	44.3 (942)	29.5 (770)	0.0001
Body mass index (kg/m^2), mean ± SD	29.1 ± 4.4	28 ± 5.2	<0.0001
Total cholesterol (mmol/L), mean ± SD	4.9 ± 1.1	5.4 ± 1	<0.0001
Systolic blood pressure (mmHg), mean ± SD	139 ± 18.3	131 ± 19.6	<0.0001
Diastolic blood pressure (mmHg), mean ± SD	83.7 ± 11	81.2 ± 11.1	<0.0001
Mental health, % (n)			
Anxiety (HADS-A ≥11)	15.3 (328)	19.1 (500)	<0.0001
Depression (CES-D ≥16)	7 (149)	12 (312)	<0.0001
Disease prevalence, % (n)			

Angina	6 (129)	2.8 (72)	<0.0001
Myocardial infarction	6.6 (142)	1.7 (44)	<0.0001
Heart failure	1.3 (27)	0.3 (8)	<0.0001
Diabetes	8.6 (185)	4.4 (115)	<0.0001
Stroke/TIA	2.8 (61)	2.5 (65)	0.44
Cardiac arrhythmia	6.2 (133)	5.5 (145)	0.33

Heart rate variability	**(n=4339)**		**P-value**
	Spontaneous breathing period	**Paced breathing period**	
Minimum heart rate, mean ± SD	57.6 ± 9.6	58.1 ± 9.6	<0.0001
Mean heart rate, mean ± SD	64 ±10.1	66.4 ±10.6	<0.0001
Maximum heart rate, mean ± SD	75 ± 16.3	77.9 ±15.2	<0.0001
SDNN (ms) [a]	34.6 (25.5, 47.3)	41.1 (30, 55.7)	<0.0001
LF (ms^2) [a]	164.4 (104.1, 288.8)	148.3 (74.4, 298.8)	<0.0001
HF (ms^2) [a]	215.2 (140.2, 330.8)	160.9 (72.2, 354.6)	<0.0001
LF:HF ratio [a]	0.73 (0.57, 1.13)	0.94 (0.52, 1.66)	<0.0001

[a] Summarized as median (25^{th} percentile, 75^{th} percentile), because of skewed distribution.

SD = standard deviation.

Table 4.1 Characteristics of the study population.

			MOCA score					
			Spontaneous breathing (n=4763)			Paced breathing (n=4339)		
HRV Variable & Model number	Range of values within each quintile	Quintile	β	95% CI	P	β	95% CI	P
Mean HR	40.78-55.52	Q_1	-	-	-	-	-	-
Model A	55.65-60.69	Q_2	-0.017	-.28, .25	0.06	-0.274	-.55, .01	**<0.001**
	60.78-65.56	Q_3	-0.129	-.4, .14		-0.301	-.58, -.02	
	65.68-72.1	Q_4	-0.182	-.45, .09		-0.434	-.72, -.15	
	72.25-102.2	Q_5	-0.363	-.64, .09		-0.631	-.91, -.35	
Model B	42.04-57.6	Q_1	-	-	-	-	-	-
	57.75-63.1	Q_2	-0.067	-35, .22	0.3	-0.362	-.66, -.06	**<0.001**
	63.18-68.17	Q_3	-0.119	-.41, -.17		-0.316	-.62, -.01	
	68.28-74.82	Q_4	-0.220	-.52, .08		-0.582	-.89, -.27	
	74.96-104.3	Q_5	-0.306	-.61, -.01		-0.646	-.97, -.34	
SDNN	6.5-24	Q_1	-	-	-	-	-	-
Model A	24.2-31.2	Q_2	0.237	-.03, .5	**<0.001**	0.525	.25, .8	**<0.001**
	31.5-40	Q_3	0.455	.19, .72		0.654	.37, .93	
	40.2-52.9	Q_4	0.485	.22, .76		0.439	.16, .72	
	53.4-157.7	Q_5	0.728	.45, 1		0.574	.28, .87	

Model B	8.2-28.1	Q_1	-	-	-	-	-	-
	28.3-37.3	Q_2	0.019	-.27, .31	**0.001**	0.465	.16, .77	**0.01**
	37.5-47.3	Q_3	0.334	.04, .63		0.506	.19, .82	
	47.5-62.1	Q_4	0.283	-.03, .56		0.276	-.05, .6	
	62.5-162.6	Q_5	0.599	.27, .93		0.435	.08, .79	
LF	10.7-94.5	Q_1	-	-	-	-	-	-
Model A	95.4-141	Q_2	0.238	-.03, .5	**<0.001**	0.430	.15, .71	**<0.001**
	142-208.7	Q_3	0.467	.2, .73		0.687	.41, .97	
	210.9-363.7	Q_4	0.455	.19, .72		0.575	.92, .86	
	369.2-4712.2	Q_5	0.861	.58, 1.14		0.78	.49, 1.1	
Model B	2.1-64.5	Q_1	-	-	-	-	-	-
	65.1-119.8	Q_2	0.197	-.1, .49	**<0.001**	0.324	.02, .63	**0.001**
	121-205.4	Q_3	0.411	.11, .71		0.507	.2, .82	
	207.5-381.6	Q_4	0.455	.15, .76		0.470	.15, .79	
	385.4-5013.2	Q_5	0.846	.52, 1.2		0.697	.36, 1	
HF	5.9-123.3	Q_1	-	-	-	-	-	-
Model A	125-189.9	Q_2	-0.001	-.27, .26	0.2	0.351	.08, .63	**0.003**
	191.3-260.1	Q_3	0.045	-.22, .31		0.402	.13, .68	
	261.6-389.3	Q_4	0.115	-.15, .38		0.438	.16, .72	
	392.1-3129.2	Q_5	0.309	.03, .59		0.554	.26, .85	
Model B	2.7-61.3	Q_1	-	-	-	-	-	-
	62.4-127.7	Q_2	-0.095	-.38, .19	0.6	0.067	-.23, .37	0.7
	129-237.3	Q_3	-0.007	-.3, .28		0.106	-.21, .42	
	240-473.6	Q_4	0.023	-.28, .33		0.151	-.17, .48	
	486-4395.7	Q_5	0.165	-.2, .49		0.239	-.1, .58	

LF:HF	0.17-0.54	Q_1	-	-	-	-	-	-
ratio	0.54-0.66	Q_2	0.171	-.1, .44	**<0.001**	0.055	-.23, .34	0.2
ModelA	0.67-0.84	Q_3	0.212	-.06, .48		0.159	-.13, .44	
	0.84-1.44	Q_4	0.454	.18, .73		0.319	.03, .61	
	1.49-11.58	Q_5	0.566	.3, .84		0.186	-.1, .48	
Model B	0.07-0.45	Q_1	-	-	-	-	-	-
	0.45-0.74	Q_2	0.213	-.07, .5	**<0.001**	0.035	-.27, .34	**0.049**
	0.75-1.17	Q_3	0.229	-.06, .52		0.186	-.12, .49	
	1.18-1.92	Q_4	0.533	.24, .83		0.314	.01, .62	
	1.94-12.67	Q_5	0.583	.29, .87		0.404	.09, .72	

Model A included age, gender and education

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

HR=heart rate, SDNN= standard deviation of NN intervals, LF=low frequency, HF=high frequency

Statistically significant relationships are in boldface

β : Standardized regression coefficients

Table 4.2 Adjusted regression coefficients and 95% Confidence Intervals of cognitive performance comparing quintiles of HRV indices during spontaneous and paced breathing.

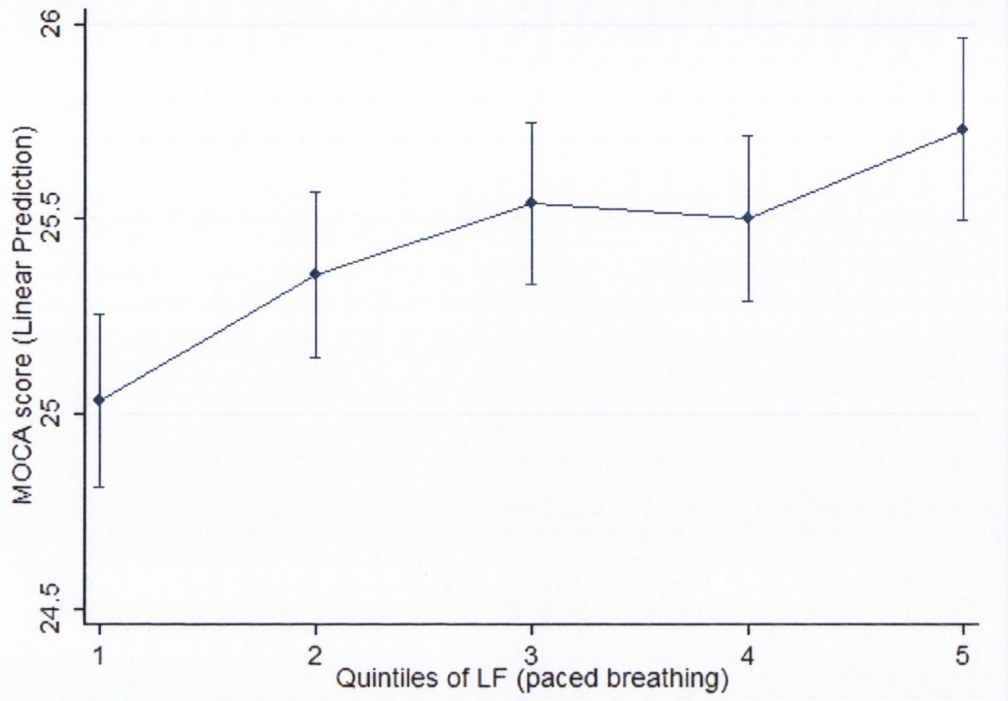


Figure 4.2 Fitted MOCA scores across quintiles of Low Frequency HRV with 95% CIs. **Analysis adjusted for age (both linear and non-linear effects), gender, education, smoking status, alcohol consumption, exercise level, body mass index, total cholesterol level, height, systolic blood pressure, diastolic blood pressure, CES-D depression score, HADS-A anxiety score, angina, myocardial infarction, heart failure, diabetes mellitus, stroke/transient ischaemic attack, cardiac arrhythmias, mean heart rate, and the following medications: alpha-blockers, beta-blockers, calcium channel blockers, midodrine, anti-cholinergics, and anti-cholinesterases. MOCA= Montreal cognitive assessment, HRV= heart rate variability, LF= low frequency.**

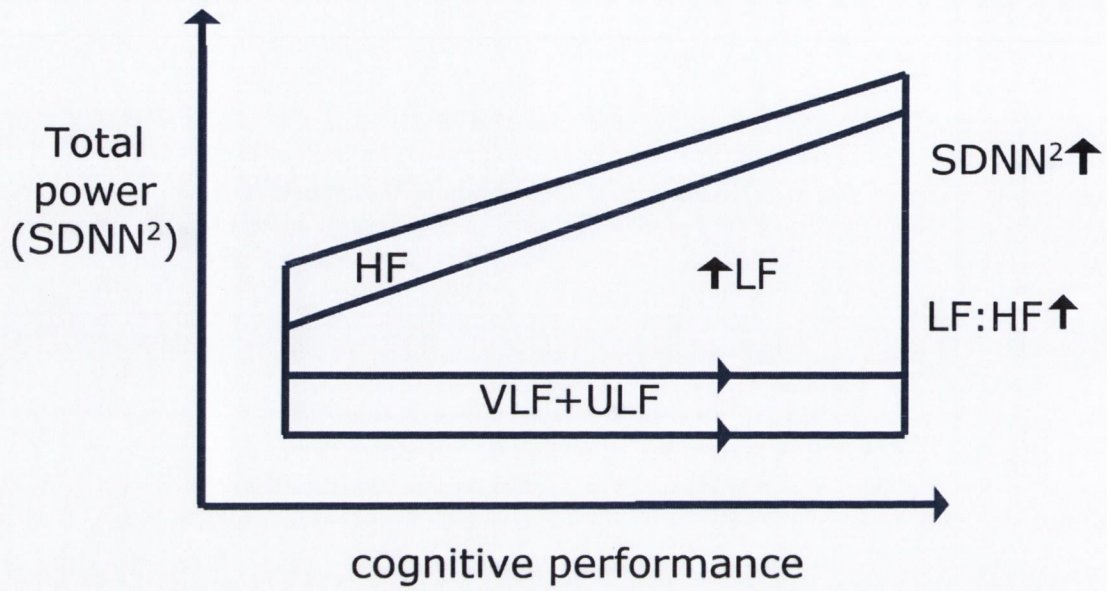


Figure 4.3 Schema explaining the HRV changes independently associated with cognitive decline. **SDNN= Standard deviation of NN intervals, ULF = Ultra low frequency, VLF= Very low frequency, LF= Low frequency, HF= High frequency.**

MOCA subdomain	Breathing period	Mean HR		SDNN		LF		HF		LF:HF	
		Q_5		Q_5		Q_5		Q5		Q_5	
		β	SE	β	SE	β	SE	β	SE	β	SE
Memory recall	Spont[a]	-0.086	0.078	**0.249**	**0.084**	**0.435**	**0.084**	0.155	0.082	**0.224**	**0.074**
	Paced	**-0.154**	**0.082**	**0.273**	**0.09**	**0.335**	**0.085**	0.066	0.088	0.169	0.08
Visuospatial function	Spont[a]	**-0.064**	**0.039**	**0.108**	**0.043**	0.085	0.043	0.007	0.042	0.05	0.038
	Paced	**-0.125**	**0.042**	-0.02	0.046	0.073	0.043	0.062	0.045	0.013	0.041
Executive function	Spont[a]	-0.035	0.048	0.057	0.052	0.051	0.052	-0.027	0.051	0.097	0.046
	Paced	-0.139	0.051	0.026	0.056	0.041	0.053	0.058	0.055	0.031	0.05
Sustained attention	Spont[a]	-0.071	0.043	0.079	0.047	0.102	0.047	-0.022	0.046	**0.122**	**0.041**
	Paced	-0.097	0.046	0.058	0.05	0.103	0.048	0.069	0.049	0.033	0.045
Language	Spont[a]	-0.026	0.059	**0.166**	**0.063**	0.184	0.063	0.008	0.062	**0.174**	**0.056**
	Paced	**-0.163**	**0.062**	**0.153**	**0.068**	**0.167**	**0.065**	0.011	0.067	**0.153**	**0.061**
Orientation	Spont[a]	-0.019	0.015	0.02	0.016	0.012	0.016	-0.027	0.016	**0.027**	**0.014**
	Paced	-0.016	0.016	0.019	0.018	0.017	0.017	0.007	0.018	-0.005	0.016

Model included age (both linear and non-linear effects), gender, education, smoking status, alcohol consumption, exercise level, body mass index, total cholesterol level, height, systolic blood pressure, diastolic blood pressure, CES-D depression score, HADS-A anxiety score, angina, myocardial infarction, heart failure, diabetes mellitus, stroke/transient ischaemic attack, cardiac murmurs, cardiac arrhythmias, mean heart rate, and the following medications: alpha-blockers, beta-blockers, calcium channel blockers, midodrine, anti-cholinergics, and anti-cholinesterases.
Statistically significant relationships are in boldface.
Spont[a] = spontaneous (n=4863)
Paced n =4339
β : Standardized regression coefficients
Statistically significant relationships are in boldface (ANOVA across all quintiles).

Table 4.3 Model B regression coefficients and standard errors of MOCA sub-domains, comparing 1st to 5th quintiles of HRV indices.

4.5 Discussion

HRV was independently associated with poor global cognitive performance in a large representative population sample of community dwelling, non-demented persons over 50 years. Furthermore, there was a graded association between degrees of impaired cognitive performance and spectral indices of LF and LF:HF ratio, which was independent of respiration, indicating impaired baroreflex function and sympathovagal homeostasis in early cognitive ageing. This is the first such study in a population sample of both men and women detailed with information on co-medications and co-morbidities. Memory recall and language were most strongly associated with lower HRV values, suggesting implication of a common neuro-anatomical pathway- possibly the fornix, which is the predominant outflow tract of the hippocampus and functions in autonomic control [220]. The direction of causality will be explored in futures waves of this longitudinal study.

The interpretation of LF as an index of sympathetic function is debated, with recent evidence suggesting LF to be more reflective of baroreflex function than sympathetic function [221, 222]. LF:HF ratio is considered a measure of sympathovagal balance, however it may be more closely associated with cardiac autonomic modulation, a term more inclusive of complexities of the autonomic system [223]. In light of this, findings from this study suggest that reduced overall HRV (SDNN), baroreflex function (LF), and cardiac autonomic modulation (LF:HF) are all associated with poor cognitive performance in the community dwelling population. The methods and details applied in TILDA differ from previous studies which have examined this association. Kim et al. reported an association between low LF and HF and poor global cognition in a convenience sample of 311 female participants [154]. In the Whitehall study, which was a

younger cohort of civil servants, no association was noted either cross-sectionally or longitudinally [213]. A possible explanation for this difference is social class.

The MOCA sub-domains of memory recall and language were most strongly associated with lower HRV values. This is in accordance with previous studies reporting significant associations between HRV and verbal memory recall [224]. The integrity of the fornix, which is the predominant outflow tract of the hippocampus, is predictive of memory performance and progression from MCI to AD [212]. This region is also implicated in autonomic control [220], suggesting that the fornix may form the anatomical location underlying the relationship between HRV and cognition.

The cholinergic anti-inflammatory pathway may also explain the association between reduced HRV and cognitive decline. Efferent vagal nerve activity inhibits pro-inflammatory cytokine release, protecting against systemic inflammation [225]. Reduced LF, HF, and SDNN, along with increased HR are associated with higher levels of C-reactive protein (CRP) [144, 226, 227], and IL-6 [226], both of which are associated with cognitive decline; thus inflammation may mediate the relationship between reduced HRV and cognitive performance [228-230]. Inflammatory markers were unavailable for analysis in the current study.

Another hypothesis implicates Noradrenaline (NAd). Up-regulation of NAd is proposed to optimize function of the key elements of cognitive reserve- namely educational level, IQ, mental and social engagement- which together lengthen the period between onset of pathological changes consistent with AD and symptoms of the disease [231]. Reduction in NAd and acetylcholine (Ach) function (neurotransmitters of the SNS) results in lower HRV values.

Hypertension is an established predictor of cognitive decline [232], and is also associated with reduced HRV [233], indicating a possible role in the relationship of HRV and cognition. We controlled for resting blood pressure however, demonstrating that the presence of hypertension does not account for our findings.

Our analysis adjusted for both linear and non-linear effects of chronological age; however the role of unidentified biological ageing processes cannot be excluded. Hence, such factors may account for decline in both HRV and cognitive function, without the two systems being causally related. For example, physiological elements underlying frailty may have a role to play in this relationship.

A standardized protocol for recording HRV describing the optimal duration, environment, and respiratory rate for recording has yet to be established. Adherence to procedure recommendations [140] remains sub-standard, limiting the interpretive value of absolute HRV data between studies [152]. Re-test reliability of HRV measures is poor [234], however paced breathing data collection protocol improves reliability and so its use is encouraged [235, 236]. For this reason, a paced breathing protocol was implemented here. The association between HRV and cognitive function, adjusted for respiration, indicates that a stronger relationship possibly exists than previously reported, as studies to date have recorded HRV during spontaneous breathing only. Given the practicality of delivering comprehensive assessments to participants nationwide it was not possible to ask participants to fast or to standardize the time of day that health assessments were performed. Time of day however was recorded and subsequently analysed to determine its effect on HRV. It was not independently associated with HRV indices. This study is limited by the cross-

sectional analytical approach, and so we were unable to investigate the causal relationship between the two systems. The subgroup with incomplete paced breathing HRV data had lower cognitive scores, which limited comparability between spontaneous and paced data analysis. However the independent association reported using the paced breathing data is indicative of an association in this marginally cognitively healthier sub-sample. The MOCA coefficients attributable to differences in HRV values were less than one, across each test, indicating that changes in HRV are unlikely to be related to clinically meaningful changes in cognitive function. Nonetheless, the independent association reported here indicates the need for further studies to understand the relationship between HRV and cognitive disorders, the latter of which represents an area of growing burden worldwide.

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

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

Conclusion

In light of the ageing population demographic predicted in the coming years, interventional strategies to combat the associated rise in burden of cognitive disorders is imperative. This study has for the first time reported an association

between HRV (as a measure of cardiac autonomic function) and global cognitive performance at a population level. Reduced overall HRV (SDNN), baroreflex function (LF), and cardiac autonomic modulation (LF:HF) are all independently associated with reduced cognitive performance. This may reflect shared anatomical pathways or mechanistic pathways such as inflammation or depletion of NAd reserves. Longitudinal follow up will help to explain our observations, by studying the role of exposure to lower HRV with subsequent cognitive decline. However, experimental studies are needed to determine the role of modifiable factors adjusted for here, on the reported associations.

5 Cognitive performance in orthostatic hypotension: Findings from a nationally representative sample

5.1 Abstract

OBJECTIVES: To describe the cognitive profile in a population representative sample with orthostatic hypotension compared to those without.

DESIGN: Cross-sectional analysis of a prospective nationally representative population study.

SETTING AND PARTICIPANTS: 5936 participants of the Irish longitudinal study on ageing (TILDA) were studied.

MEASUREMENTS: OH was defined as a drop of ≥20mmHg in systolic blood pressure or a drop of ≥10mmHg diastolic pressure on standing from a seated position. Cognitive performance was assessed using comprehensive cognitive tests, measuring domains of global function, executive function, processing speed, attention and memory - from which composite standardized scores were computed. Multivariate analysis controlling for potential confounders was carried out to compare cognitive performance by OH status.

RESULTS: In this Irish population, mean age 63±9 years (54% women), the prevalence of OH was 6.1% (95% confidence Interval 5.4-6.7%). After adjustment for demographics, mental health, cardiovascular disease, and medications (anti-hypertensives and anti-psychotics) a significant negative association between OH status and global cognitive function (β=-0.21, p=0.01) and memory (β=-0.26, p=0.002) among females aged 65 and older was observed, but other specific cognitive domains were not affected.

CONCLUSION: OH was associated with poorer global cognitive function and poorer memory, independent of potential confounders, in older females in a large population based sample of older adults. Longitudinal studies with concomitant assessment of cerebral perfusion are needed to determine causal relationships.

5.2 Introduction

Orthostatic hypotension (OH) describes an exaggerated or prolonged blood pressure (BP) drop in response to standing. The current consensus definition of OH is a drop in systolic BP (SBP) of ≥20 mmHg or a decrease in diastolic BP (DBP) ≥10 mmHg within 3 minutes of orthostasis [170]. OH has a higher prevalence in dementia patients [118], and the importance of vascular risk factors in the pathogenesis of cognitive disorders has gained research momentum in recent years [237]. Cardiovascular risk factors that affect cognitive impairment include high cholesterol, smoking, hypertension and type 2 diabetes mellitus [238]. These factors are associated with cerebral hypoperfusion [239], which may be explained by compromised vascular integrity. Cerebral hypoperfusion is in turn associated with cognitive impairment [240]. The presence of OH, its chronicity, and severity of orthostatic BP drops may all influence cerebral perfusion and cognitive decline.

A number of studies have investigated the association between OH and cognitive function, however results have been mixed [187-190, 241, 242]. This may be due to small sample size [241, 242], variable sample age range [189], lack of adjustment for potential confounders [187], and the use of cognitive tests with low sensitivity and specificity (e.g. MMSE alone) [188, 190]. Here we overcome these limitations by comprehensively assessing the cognitive function (across multiple domains) of both middle aged and older people with and without OH using a well-controlled design. Data is analysed from a large nationally representative study sample of community dwelling adults aged 50 and over.

5.3 Methods

Study population

Data from the first wave of The Irish Longitudinal Study on Ageing (TILDA) was analysed (collected June 2009-June 2011). TILDA is a large prospective cohort study on ageing, comprising of community dwelling adults aged 50 and over resident in the Republic of Ireland. A nationally representative sample was selected using the regularly updated RANSAM sampling technique, from a listing of all residential addresses in the Republic of Ireland (The Irish Geodirectory) [199]. Detail of the study design is published elsewhere [200]. Data collected within TILDA comprises of (i) Computer-assisted personal interviewing (CAPI), carried out in the participant's home, (ii) Self-completion questionnaire, and (iii) a physical health assessment carried out by trained study nurses in one of two dedicated health centres. Participants unwilling to undergo centre-based assessment were offered an in-home health assessment (where all measures for this study were also recorded). The response rate to the in home interview was 62.0%, and comparison of the sample age distribution with that of the population suggests very little differential non-response with respect to age. The proportion agreeing to health assessment component was 75% among those aged 50-64 years, 72% among those aged 65-75 and 60% among the over 75s. Study weights are applied to prevalence estimates to correct for any potential bias associated with differential non-response [243]. Ethical approval was obtained and all respondents provided signed informed consent prior to participation. All experimental procedures adhered to the Declaration of Helsinki.

Measurement and classification of blood pressure response to orthostasis

Participants underwent a sit-to-stand orthostatic stress test. *Seated blood pressure:* Two seated SBP and DBP measurements were obtained separated by 1 minute using an automatic digital BP monitor (OMRON™, Model M10-IT). The means of both SBP and DBP readings were calculated. Participants had been seated for ≥30 minutes and were ≥1 hour pre or post lunch when measurements were obtained. *Standing blood pressure:* After 1 minute the participant was asked to stand and a single SBP and DBP measurement was obtained, using the same monitor with the cuff at heart level. OH was defined as a drop of at ≥20 mmHg SBP or ≥10 mmHg DBP on standing [170].

Assessment of cognitive function

Cognitive function was assessed using a cognitive battery of tests. The cognitive domains assigned represent the areas of cognition predominantly affected (and hence clinically assessed) in disorders of cognitive function. Composite scores for each cognitive domain were derived from a combination of test scores.

The composite score for global cognition was derived from the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MOCA) test. MOCA and MMSE scores were added, then transformed using log((60 - sum score) +3) to eliminate skew and approximate a normal distribution.

Composite scores for all other domains were created based on an equally unit-weighted approach using standardized scores (*z*-scores), that is composite z-score for tests A, B and C was calculated by standardising the sum of the z-scores for each test individually. Tests were chosen for each domain based on the function each is considered to represent, according to the founders of the

test. Additionally, assignment of each test to its domain was concordant with methods applied commonly in cognitive research studies.

The composite score for executive function was derived from verbal fluency and visual reasoning tasks, and Color Trail 2 time. Two verbal fluency tasks were assessed; participants were asked to name as many animals as possible in 1 minute (word fluency) and during the MOCA, were asked to list as many words beginning with the letter "F" as possible in 1 minute (letter fluency) . In the visual reasoning test, 3 boxes were shown with objects inside and one empty box. Participants were asked to identify the missing object to complete the pattern, from 6 options. This was repeated over 6 sequences allowing a maximum score of 6. The Color Trails Test is a cultural and language bias free alternative to the Trail Making Task. In Color Trail 1, participants drew a line connecting circles numbered 1-25 in consecutive order. In Color Trail 2, participants connected these numbered circles but alternated between pink and yellow circles i.e. pink 1, yellow 2, pink 3 etc.

The composite score for processing speed was derived from the Color Trails 1 time and the cognitive reaction time (RT) of the choice reaction time (CRT) task. In the computer based CRT task, participants depressed a button and waited for a stimulus (YES/NO) to appear on screen. This occurred approximately 100 times and participants were required to press a corresponding YES/NO button on the keyboard in response. Cognitive RT was the time taken to release the button in response to the stimulus.

The Sustained Attention to Response Task (SART) was used to measure sustained attention. Participants were presented with a repeating sequence of the numbers 1-9 for approximately 4 minutes. Digits appeared for 250ms,

followed by a 900ms mask, resulting in a total sequence of 225 numbers. Participants were instructed to click in response to each number except 3. Mean and SD of response times were used for the composite score. The number of commission errors (number of times participant clicked mouse when a number 3 appeared) and omission errors (number of times participant did not click mouse when a number other than 3 appeared) were used only for adjustment during analysis of sustained attention.

The composite score for episodic memory was derived from a word recall test and a picture memory test. Following auditory presentation of 10 words, participants were asked to recall as many words as possible immediately and at a later time during the interview. In the Picture Memory test, participants were asked to name 6 well known objects shown to them in picture format. At a later stage (and without forewarning), they were asked to recall these objects (picture recall). They were also asked to identify each object when presented alongside two similar objects (picture recognition).

Covariates

Other variables that were considered potential confounders of the association between OH and cognition were also collected. These included age, gender, educational attainment (primary, secondary or tertiary), smoking status (never smoked, former or current), physical activity (using the International physical activity questionnaire (IPAQ) short form, classified as low, medium, or high), height (cm), body mass index (BMI) (kg/m^2), and total blood cholesterol (mmol/L).

The Centre for Epidemiological Studies Depression (*CES-D*) scale was used with a cut-off score of 16 or above, to define subjects as depressed. Self-reported

cardiovascular diseases (CVD) were documented: history of angina, myocardial infarction, heart failure, diabetes mellitus, stroke, transient ischaemic attack (TIA) and cardiac arrhythmias.

Medication use was recorded during the home interview (CAPI) and confirmed by cross-checking with medication labels. Anatomical Therapeutic Classification (ATC) codes were subsequently recorded for categorisation. BP modifying medications were anti-adrenergic agents ('C02*'), diuretics ('C03*'), beta-blockers ('C07*'), calcium channel blockers ('C08*'), angiotensin-converting-enzyme inhibitors/ angiotensin-receptor blockers ('C09*') and combinations of the above ('C02*'). Anti-psychotic medications ('N05A') were also classified and controlled for in analysis.

Statistical analyses

Statistical analysis was performed using Stata version 12.1 (StataCorp, College Station, TX). Intercorrelation of composite scores within each cognitive domain was assessed using Cronbach's alpha coefficient. Values >0.5 were considered adequate reliability between variables. Time based test scores were inversed prior to standardization, resulting in positive values correlating with higher performance. Distribution of continuous variables was assessed using Q-Q plots and histograms. For descriptive analyses, normally distributed continuous variables were described as means and standard deviations (SD), and were compared by OH status using independent t-tests. Non-normally distributed continuous variables were described as medians and percentiles and compared using Mann-Whitney U tests, and categorical variables were compared using Chi-squared tests. Data on cognitive tests was largely complete (no more than 11%

missing for any test) and missing data was not significantly more common among subjects with OH, hence was excluded on a case-wise basis.

Differences in cognitive domains between OH and non-OH groups were tested using multiple linear regression. A model for each domain was tested separately using its standardised composite score (as described above) as a dependent variable and OH along with potential confounding variables as predictor variables. Covariates were entered in three blocks, first age, sex and educational attainment, (to determine the influence of demographic on the association) second additional health behaviours, clinical profile, CVD, and mental health, (to study the additional role of physiological biomarkers and conditions) and finally additional medications (to investigate the role of iatrogenic cause), however findings from these models did not differ substantially and so only the final model including all covariates is reported.

The effects of OH across age groups and by sex were estimated by the marginal effects of OH from a single regression model including the interactions of age group (50-64 vs 65 and older) and sex with OH and all other covariates. The statistical significance of any differences found between age and sex groups was tested using a single Wald test for each cognitive measure, testing the hypothesis that the effect of OH was constant across the four age and sex groups. Additional tests were performed using models including only the interactions between OH and age group and between OH and sex separately.

5.4 Results

The study population consisted of 5936 subjects aged 50 years and older. Mean age was 63±9 and 54% (n=3191) were female. Weighted prevalence of OH was 6.3% (n= 359) overall; 4.1% (n=140) in subjects aged 50-64 years, and 9.3% (n=219) in subjects aged 65 and older. Demographic and clinical characteristics according to OH-status are presented in table 5.1. Individuals with OH were older, more frequently female and had lower educational attainment. Cardiovascular disease prevalence was similar between groups. OH subjects had lower BMI but higher systolic and diastolic blood pressure, and were more likely to be taking anti-hypertensive and anti-psychotic medications.

Table 5.1 also describes the cognitive performance of OH and non-OH groups. OH subjects performed significantly less well across all tests of global cognitive function, processing speed, sustained attention and memory. OH subjects also performed less well in all tests of executive function; however scores were not significantly different between groups for verbal (letter) fluency.

Table 5.2 shows the relationship between OH and domains of cognitive function in the whole study population (all aged 50 and over) and stratified by age group and sex, with all differences adjusted for covariates described above. Only global cognitive function and memory were different in those with OH. When results were stratified by age and sex, these differences were restricted to females over 65, with a strong effect on memory (b=-0.26; 95% CI=-0.43,-0.10; p=0.002) and general cognitive function (b=-0.210; 95% CI=-0.37,-0.05; p=0.010). However none of the interaction effects we tested were statistically significant, meaning that while the association between OH and cognitive function appeared

to be restricted to older women in our sample, this finding should be treated with caution.

Characteristics	Without OH (n= 5577)	With OH (n=359)	P-value
Age, mean ± SD	61.9 ± 9.3	67.2 ± 9.6	0.0001
Female, % (n)	53.8 (2977)	59.6 (214)	0.03
Education (≤8 years), % (n)	25.8 (1429)	31.7 (114)	0.01
Smoking status (Current), % (n)	15.7 (872)	19.2 (69)	0.3
Level of physical activity (IPAQ), % (n)			
Low level of activity	30.1(1650)	33.2 (119)	0.49
Body mass index (kg/m^2), mean ± SD	28.7 ± 5	28 ± 5.4	0.01
Total cholesterol (mmol/L), mean ± SD	5.1 ± 1.1	5.1 ± 1.1	0.58
Mental health, % (n)			
Depression (CES-D ≥16)	10.4 (575)	10.9 (39)	0.77
Disease prevalence, % (n)			
Angina	5.3 (293)	4.7 (17)	0.65
Myocardial infarction	4.6 (257)	3.9 (14)	0.52
Heart failure	1 (56)	0.6 (2)	0.4
Diabetes	7.3 (403)	7.2 (26)	0.98
Stroke/TIA	3.5 (193)	4.2 (15)	0.49
Cardiac arrhythmia	7.6 (422)	7.8 (28)	0.9
Seated systolic BP, mean ± SD	134.9 ± 19.6	147.4 ± 19.6	<0.0001
Seated diastolic BP, mean ± SD	82 ± 12.1	87.1 ± 12.1	<0.0001
Taking anti-hypetensive medications, % (n)	36.1 (2000)	46 (165)	<0.0001
Taking anti-psychotic medications, % (n)	1.25 (69)	2.51 (9)	0.04

Cognitive performance			
	Without OH	**With OH**	**P-value**
Global cognition	**(n= 5577)**	**(n=359)**	
MOCA [†]	29 (28, 30)	29 (27, 30)	0.0001
MMSE [†]	25 (23, 27)	25 (22, 27)	0.0004
Executive function			
Colour Trail 2 (s) [†]	103 (82, 132)	115 (88, 147)	0.0001
Trail time diff (s), mean ± SD	55 ± 26	60 ± 28	0.0005
Letter fluency, mean ± SD	12 ± 5	11 ± 5	0.28
Word fluency, mean ± SD	21 ± 7	20 ± 7	0.003
Visual reasoning, mean ± SD	3 ± 1.4	2.9 ± 1.3	0.048
Processing speed			
Colour Trail 1 (s) [†]	51 (39, 68)	56 (43, 75)	0.0001
Cognitive RT (ms) [†]	490 (436, 556)	508 (446, 586)	0.009
Attention			
Mean SART (ms) [†]	369 (305, 447)	386 (324, 456)	0.009
SD SART (ms) [†]	98 (69, 151)	108 (75, 206)	0.0004
Memory			
Picture recall, mean ± SD	3.2 ± 1.1	2.9 ± 1.2	0.0001
Picture recognition [†]	6 (5, 6)	6 (5, 6)	0.003
Immediate recall, mean ± SD	5.8 ± 1.7	5.5 ± 1.7	0.002
Delayed recall, mean ± SD	6.1 ± 2.3	5.6 ± 2.3	0.0001

[a] Summarized as median (25th percentile, 75th percentile), because of skewed distribution.

SD = standard deviation, TIA= transient ischaemic attack, BP= blood pressure.

Table 5.1 Characteristics and cognitive performance of the study population according to presence of absence of OH.

	All aged 50 and over β (95% CI)	Male		Female		P-value for interaction effect [a]
		50-64	65+	50-64	65+	
Global Function	-0.096 (-0.19,0.00) *	-0.057 (-0.29,0.18)	-0.066 (-0.25,0.12)	-0.013 (-0.20,0.17)	-0.210 (-0.37,-0.05) *	0.428
Executive Function	-0.022 (-0.11,0.07)	0.046 (-0.18,0.27)	-0.097 (-0.28,0.09)	-0.055 (-0.24,0.13)	0.038 (-0.12,0.20)	0.661
Processing Speed	-0.012 (-0.12,0.09)	-0.078 (-0.33,0.18)	0.085 (-0.12,0.29)	-0.180 (-0.40,0.03)	0.079 (-0.11,0.26)	0.218
Attention	-0.073 (-0.18,0.03)	-0.067 (-0.33,0.19)	-0.196 (-0.40,0.01)	-0.115 (-0.34,0.11)	0.042 (-0.14,0.23)	0.466
Memory	-0.150 (-0.24,-0.06) **	0.072 (-0.16,0.31)	-0.133 (-0.32,0.06)	-0.168 (-0.36,0.02)	-0.262 (-0.43,-0.10) **	0.167

Table 5.2 Regression coefficients (with 95% confidence intervals) corresponding to the difference in cognitive function between participants with OH and participants without OH. Negative coefficients correspond to worse cognitive

performance among those with OH. All estimates are adjusting for age (including an age-squared term), gender and education, smoking status, height, body mass index, total cholesterol levels, systolic blood pressure, angina, myocardial infarction, heart failure, stroke, transient ischaemic attack, heart arrhythmias and depression, anti-hypertensive and anti-psychotic medications. (Estimates for the effect on sustained attention was additionally adjusted for errors of omission and commission).

5.5 Discussion

In the TILDA study, subjects with OH performed more poorly across all cognitive domains than those without OH. This association remained statistically significant for global cognition and memory following adjustment for all confounders (demographics, cardiovascular diseases, health behaviours and mental health, anti-hypertensive and anti-psychotic medications). The difference in adjusted co-efficient of determination values between the first and final models tested were relatively small (e.g. Global cognition regression adjusted R^2 difference= 0.05), highlighting that covariate factors have a minor role in improving the fit between observed and modelled values. On stratification across age groups this association was only apparent in the over 65s. These results align with several previous studies [187, 241, 244, 245]. However the current study is the first to demonstrate this association in a large population representative cohort including a comprehensive assessment of potential confounders and a range of cognitive outcomes. A previous population based study by Rose et al did not report a significant association between OH and cognitive function cross-sectionally nor longitudinally, in a larger sample than used here [189]. The older cohort in our study (OH subjects mean age 67.3 vs 57.2) may explain this difference, and we found no effects among those aged 50-64 years.

The association between OH and cognitive impairment is possibly mediated by leukoaraiosis (LA) triggered by cerebral hypoperfusion. Cerebral autoregulation may become impaired, improved or remain intact in OH [130]. Irrespective of this, rapid BP changes remain capable of substantially altering cerebral blood flow [246], and cerebral hypoperfusion is pronounced in OH [247]. Other studies

have demonstrated reduced cerebral perfusion in areas of LA [248] and alongside reduced cognitive function [240]. A review of pathological mechanisms underlying neurodegeneration in cognitive impairment and dementia supports this hypothesis [238].

The causality of the relationship between OH and cognitive function remains poorly understood but may be bidirectional. Longitudinal studies to date have reported mixed results [189, 242]. Autonomic dysfunction secondary to neurodegeneration in demented subjects may result in impaired orthostatic BP control, which would account for the stronger association with memory than other cognitive domains. Subsequent cerebral hypoperfusion may further compound detrimental effects on cognition.

Management of OH includes modification of culprit medications, particularly anti-hypertensives and anti-psychotics [181]. Other intervention strategies range from physical counter-manoeuvres, added salt and increasing fluid intake, to medications such as midodrine, pyridostigmine, fludrocortisone and octreotide. If a causal association were established, interventions to treat OH may prevent cognitive decline. Clearly this is speculative and would require a prospective experimental study. Nonetheless, the result of a clear association between OH and cognitive function emphasises the need for future investigation of causality and possible intervention.

The cross-sectional design is the main limitation of this study. Future follow-up of the TILDA cohort will allow for investigation into the longitudinal relationship between OH and cognitive function. BP was recorded on one occasion following orthostasis. It is known that measurement of BP is variable; hence the classification of OH/non-OH in our study is uncertain, however this would only

reduce the estimate of any true effect and so our findings are conservative from this perspective. The duration of OH is also not known. Hence, we were unable to adjust for the potential biological gradient that relates long-standing OH with greater degrees of cognitive impairment. Individuals living in residential care were excluded from this study. Hence the effects reported in this study may be underestimated, given that health conditions such as OH and cognitive impairment have a higher prevalence in residential care institutions. Detailed medication information obtained allowed for correction of possible confounding effects of medication on the association between OH and cognition, and results did not vary whether or not medications were included in the models. Underlying blood pressure was controlled for in analysis; however we were unable to control for duration of hypertension. It is recognised that hypertension predisposes to both OH and cognitive decline, so it may be the case that longer duration of hypertension increases the likelihood of developing OH and/or cognitive decline, whereby the two conditions are affected by BP without being causally related to one another.

Although the benefits of certain cognitive tests have been recognised over others, e.g. MoCA has greater discrimitory power over the MMSE, all tests governing each cognitive domain were weighted equally, as higher accuracies in some tests above others have not been objectively quantified in the literature to date. It also must be acknowledged that interpreting composite scores carries its own limitations. The inclusion of the chosen tests per domain was based on the representing function, as considered by the originators of each test. Cognitive tests are multi-dominal, and so grouping by the predominant function such tests are considered to represent, results in a loss of a proportion of the tests power, when using this approach.

Our results should be considered in light of the large number of hypothesis we tested, although it should be noted that these tests were not independent and in a whole-sample analysis we detected an association between OH, memory and global cognitive change. As data was reanalysed five times for each cognitive domain, the type-1 error rate may have been inflated. Adjusting for this, using Bonferroni adjustment, we can consider significance as $P<0.05/5$ i.e. $P<0.01$. In this setting, the association remains significant for OH and memory function, alongside a trend towards lower cognition for OH groups across all domains. Given that $P<0.01$ was considered significant, 1 in 100 subjects in this group were likely to have been falsely reported. This is true for all statistical tests, and only studies replicating analysis performed here have the potential to determine if the findings here represent false-positive cases. Interaction tests were not statistically significant; therefore the finding that effects are restricted to females over the age of 65 should be treated with appropriate caution. Nonetheless, emerging evidence indicates sex differences in aetiological factors underlying cerebral ischaemia [249]. The molecular mechanisms underlying stroke in men and women are distinct [250], which are thought to account for the epidemiological difference between sexes. Men have a higher incidence of stroke until an advanced age, after which rates rise significantly in women [251]. Estradiol is a recognized neuroprotectant, and depleted levels in older women may account for elevated rates of stroke and other cerebrovascular disorders. These sex differences in cerebral pathology may account for our finding of a stronger association between OH and cognitive performance in older women. However, further research is warranted to investigate this hypothesis.

In conclusion, this study has for the first time reported an association between OH (using traditional oscillometric BP measurement) and global cognitive

function and memory among a general older population. Further investigation of the longitudinal association between OH and cognition is underway.

6 Supine hypertension determines the association between orthostatic hypotension and cognitive performance

6.1 Abstract

Objectives

This study investigated the association between orthostatic hypotension (OH), supine hypertension (SH) and cognitive performance.

Methods

4690 participants of the Irish longitudinal study on ageing (TILDA) were studied. Supine hypertension (SH) was defined as systolic blood pressure (SBP) ≥140mmHg and/or diastolic blood pressure (DBP) ≥90mmHg, measured following supine rest (10min). OH was defined as a sustained drop of ≥20mmHg SBP or ≥10mmHg DBP at 20, 30, 60 and 90-seconds following orthostasis. Cognitive performance tests assessed global function, executive function, processing speed, attention and memory - from which z-scores were computed. Multivariate adjusted analysis was performed comparing cognitive scores by OH status overall and in SH/non-SH groups separately.

Results

Thirty-nine percent had baseline SH (n=1868), and demonstrated a greater orthostatic fall in SBP ($P<0.0001$) and DBP ($P<0.0001$), had a higher prevalence of OH at all time-points, and scored lower in tests across all cognitive domains. No overall association between OH and cognitive performance was seen. However, SH subjects with OH scored significantly worse (adjusted) than SH subjects without OH, in domains of global cognition (30-seconds post-stand β=-

0.15; 99% CI -0.29, -0.14; P=0.004) and executive function (20 seconds post-stand; β=-0.11; 99% CI -0.22, -0.01; P=0.006). There was also an indication towards lower cognition in all non-significant analyses. OH was not associated with cognitive performance in non-SH subjects.

Conclusion

In conclusion individuals with SH (defined as BP> 140/90 mmHg), coupled with OH measured using phasic BP, had lower global and executive cognitive performance than those with SH but without OH.

6.2 Introduction

Orthostatic hypotension is a highly prevalent age-related condition in both the community and health-care settings; from 30% in older-aged community dwelling adults [171], to over 50% in the geriatric ward setting [252]. OH is a strong predictor of all-cause mortality [253]. The global aging demographic is likely to result in an increased healthcare burden of OH and other age-related conditions such as cognitive impairment, in the foreseeable future.

Vascular risk factors for cognitive impairment and dementia are well recognised, however preventative or curative strategies have yet to be established. Emphasis is placed on identifying potentially modifiable risk factors for cognitive decline. The association between hypertension and cognitive dysfunction is well recognised, however a U-shaped relationship may exist, such that both low and high blood pressure are associated with cognitive decline [254]. Ample evidence indicates hypertension as a predictive factor for cognitive decline, however evidence for the role of hypotension is less conclusive, with a recent review unable to determine whether hypotension is a cause or consequence of cognitive impairment in old age [255].

The current consensus-based definition of Orthostatic Hypotension (OH) is a drop in Systolic Blood Pressure (SBP) of ≥20 mmHg or a decrease in Diastolic Blood Pressure (DBP) ≥10 mmHg within 3 minutes of orthostasis [256]. More recently, a refinement of this definition to ≥30mmHg SBP drop for subjects with baseline SBP ≥160mmHg has been proposed [256]. BP and heart rate recovery are generally complete by 30 seconds post-stand, such that the early stage of stabilisation has been attained [257]. Continuous methods for BP assessment detect beat-to-beat haemodynamic changes in response to orthostasis, and have

demonstrated a stronger association with clinical outcomes than traditional cuff-based BP measurement [258]. Continuous methods also exhibit increased sensitivity to postural BP responses, and improved identification of episodes of transient OH [258].

Studies which have examined the association between OH and cognition indicate conflicting results [187-189], and few have measured OH using continuous methods [259]. The prevalence of OH is higher in hypertension [260] and Supine Hypertension (SH), which may indicate a dysautonomic pathogenesis when these conditions present together [177].

This study sought to investigate the association between OH (measured using continuous BP assessment) and cognitive performance, and the influence of SH on the association, in a representative sample of community dwelling older adults.

6.3 Methods

Study population

Data from the first wave of The Irish Longitudinal Study on Ageing (TILDA) was analysed (2009-2011). TILDA is a large prospective cohort study of ageing, comprising of community dwelling people aged 50 and over resident in the Republic of Ireland. Detail of the study design is published elsewhere [200]. Data collected within TILDA comprises of (i) Computer-assisted personal interviewing (CAPI), carried out in the participant's home, (ii) Self-completion questionnaire, and (iii) a physical health assessment carried out by trained study nurses in one of two dedicated health centres. Ethical approval was obtained and all respondents provided signed informed consent prior to participation. All experimental procedures adhered to the Declaration of Helsinki.

Measurement and classification of blood pressure response to orthostasis

The BP response to orthostasis was recorded using the volume clamp method (Finometer® MIDI, Finapres Medical Systems, Arnhem, The Netherlands). Recordings were obtained in a comfortably lit, quiet room at ambient temperature (21-23°c). Following ten minutes of supine rest, baseline SBP and DBP were measured as the mean of values recorded between 60 and 30 seconds prior to postural change. Physiocal was switched off immediately prior to standing. BP was subsequently recorded for 120 seconds in the standing position. The nadir was used to calculate the maximum orthostatic BP fall from baseline. BP was estimated at 10-second intervals using five-second moving averages around each point [258]. OH at each time-point after standing was defined as a *sustained* drop of ≥20 mmHg SBP or ≥10 mmHg DBP from baseline up to that point. Since a 10 second averaging window with 50% overlap (5

seconds) was used, the point at 120 seconds in most individuals would include edge effects. Time points at 10 second intervals beginning at 20 seconds post orthostasis were tested in initial analysis. It was subsequently decided to report results for time-points at 30 second intervals once the observable effects stabilized. Hence, data at 20, 30, 60, and 90 seconds was used in analysis- which also delineates the initial response to the period of early BP stabilisation in healthy individuals [257]. Baseline SH was defined as SBP ≥140mmHg or DBP ≥90mmHg, as measured during 60 to 30 seconds before standing. This is the first stage of hypertension to confer a cardiovascular disease risk, modifiable by therapeutic management [261].

Assessment of cognitive function

Cognitive function was assessed using a battery of cognitive tests. Composite scores for each cognitive domain were derived from a combination of test scores. The cognitive domains assigned represent the areas of cognition predominantly affected (and hence clinically assessed) in disorders of cognitive function. Further detail on all cognitive tests administered is described elsewhere [243].

The composite score for global cognition was derived from the Mini-Mental State Examination (MMSE) [42] and the Montreal Cognitive Assessment (MOCA) test [46]. MMSE and MOCA scores were summed, then transformed using log((60-sum score) +3) to reduce the skew and approximate a normal distribution. This calculation was applied to eliminate zero scores, which cannot be used to derive standardised values. The negative form of each standardised score was computed resulting in lower values corresponding with lower performance.

Composite scores for all other domains were created based on an equally unit-weighted approach using standardized scores (*z*-scores), that is composite z-score for tests A, B and C was calculated by standardising the sum of the z-scores for each test individually. Tests were chosen for each domain based on the function each is considered to represent, according to the founders of the test. Additionally, assignment of each test to its domain was concordant with methods applied commonly in cognitive research studies.

The composite score for executive function was derived from verbal fluency and visual reasoning tasks, and Color Trail 2 time.

The composite score for processing speed was derived from the Color Trails 1 time and the cognitive reaction time (RT) of the choice reaction time (CRT) task [262].

The composite score for episodic memory was derived from a word recall test and a picture memory test.

The Sustained Attention to Response Task (SART) was used to measure sustained attention.

Covariates

Other acquired measures included age, gender, educational attainment (primary, secondary or tertiary), smoking status (never smoked, former or current), alcohol intake (units weekly), physical activity (using the International physical activity questionnaire (IPAQ) short form- classified as low, medium, or high according to the standard scoring protocol [263]), body mass index (BMI) (kg/m^2), and total blood cholesterol (mmol/L).

The Centre for Epidemiological Studies Depression (*CES-D*) scale was used with a cut-off score of 16 or above, to define subjects as depressed [216]. SBP and DBP were recorded during seated rest, using a digital automatic BP monitor (OMRON™) as the mean of two readings. Self-reported cardiovascular diseases (CVD) were documented: history of angina, myocardial infarction, heart failure, diabetes mellitus, stroke, transient ischaemic attack (TIA), and cardiac arrhythmias.

Medication use was recorded during the CAPI and confirmed by cross-checking the medication labels. Anatomical Therapeutic Classification (ATC) codes were subsequently recorded for categorisation [218]. BP modifying medications were anti-adrenergic agents (2nd level ATC code 'C02'), diuretics ('C03'), beta-blockers ('C07'), calcium channel blockers ('C08'), angiotensin-converting-enzyme inhibitors/ angiotensin-receptor blockers ('C09') and combinations of the above ('C02'). Anti-psychotic medications ('N05A') were also classified and controlled for in analysis.

Statistical Analysis

Statistical analysis was performed using Stata version 12 (StataCorp, College Station, TX). Intercorrelation of composite scores within each cognitive domain was assessed using Cronbach's alpha coefficient. Values >0.5 were considered adequate reliability between variables. Time based test scores were inversed prior to standardization, resulting in positive values correlating with higher performance for all cognitive measures. Distribution of continuous variables was assessed using Q-Q plots and histograms. For descriptive analyses, normally distributed continuous variables were described as means and SD, and were compared by sex using independent t-tests. Non-normally distributed continuous

variables were described as medians and percentiles and compared using Mann-Whitney tests, whereas categorical variables were compared using Chi-squared tests. Data on cognitive tests was largely complete (no more than 11% missing for any test) and subjects with missing data were subsequently excluded on a case-wise basis.

Multivariate linear regression analysis was performed to compare cognitive performance between OH and non-OH subjects. Z-scores for each cognitive domain were used as outcome variables to allow comparison of performance between groups on a common scale for all cognitive domains. Subjects without OH at 20 seconds (i.e. those whose blood pressure had recovered before 20 seconds post standing) were considered the reference group. A single model was fitted for each cognitive outcome, adjusting for age (linear and non-linear effects), sex, education, smoking, alcohol intake, exercise, BMI, cholesterol level, history of CVD, depression, and medications. Errors of omission and commission were additionally adjusted for in analysis of sustained attention. OH and non-OH subjects were first compared in the whole cohort, and subsequently according to baseline SH. In our analysis we only considered tests as significant where $P<0.01$, due to the large number of independent hypotheses being considered, and report 99% confidence intervals for estimates of effects. Bonferroni adjustment was conducted yielding the significance level of interest of 0.05/5 (5= number of tests applied per cognitive outcome) i.e. $P<0.01$.

6.4 Results

In total 8175 participants aged 50 years and older were recruited to the TILDA study [200]. Of these 5036 agreed to undergo an in-centre health assessment, 4690 of whom had technically adequate data for orthostatic BP analysis. They were younger and had healthier physical, behavioural and cognitive characteristics than others who underwent home-based assessment or no health assessment [243].

The mean age was 60.9 and 2599 (55%) were female. Demographic and clinical characteristics of the study cohort are outlined in Table 6.1. Thirty-nine percent of subjects had baseline SH (n=1868). These subjects were older and had a higher BMI, cholesterol level, seated BP and anti-hypertensive medication use. They demonstrated a greater orthostatic fall in SBP (-44.4 vs -35.6; P<0.0001) and DBP (-27.2 vs -24.8; P<0.0001) on standing (nadir-baseline). Oscillometric recorded SBP and DBP were also higher in this group. The non-SH group had higher education and history of smoking (current and former) and heart failure. Gender, alcohol consumption, physical activity, depression and prevalence of other CVD were similar between groups.

Cognitive performance across all tests used to derive z-scores is reported in Table 6.2. Test scores for MMSE, word fluency, visual reasoning, Color trails 1 & 2, immediate and delayed memory recall and SART were poorer amongst subjects with SH. These differences only remained statistically significant for SART however, following adjustment for age.

The proportion of subjects with OH at each time-point is listed in Table 6.3. Overall, 15% of subjects had sustained OH at 30 seconds, which fell to 4.6% at 90 seconds. Subjects with SH had a higher prevalence of OH at all times. At 20

seconds post-stand 37.2% (n=695) of supine hypertensive and 23.9% (n=673) of non-hypertensive subjects had OH, which decreased to 6.7% (n=125) and 3.2% (n=91) by 90 seconds post-stand, respectively.

Figure 6.1 presents the standardized z-scores for OH subjects across the five domains of cognition stratified by OH at each time-point relative to non-OH subjects. Analysis was adjusted for all covariates, covering demographics, behavioural and mental health, clinical profile, CVD and medication use. Overall, there was a trend towards lower cognitive performance amongst OH subjects, however this was not significant at $P<0.01$ in any domain at each time. Subjects with OH at 20 seconds scored worse overall in domains of executive function (β=-0.052; 99% CI -0.12,0.02; CI P=0.06) and sustained attention (β=-0.06; 99% CI -0.14,0.01; P=0.03).

Stratified analysis in subjects with and without baseline SH is also illustrated in Figure 6.1. SH subjects with OH scored significantly worse than SH subjects without OH, in domains of global cognition (at 20 and 30 seconds post-stand; 30-secondβ=-0.15; 99% CI -0.29,-0.01; P=0.004) and executive function (at 20 seconds post-stand; β=-0.11; 99% CI -0.22,-0.01; P=0.006).

We compared the magnitude of cognitive performance between OH and non-OH groups with modelled age coefficients, to determine the equivalent age-related difference in cognition. This was performed comparing the OH regression coefficients presented in figure 6.1 with the age coefficient in the same model. The age coefficient corresponding to the association model between sustained OH at 20 seconds in the SH group, and global performance was -0.02. Hence the effect of OH (β=-0.13) is equivalent to approximately 6 years of cognitive ageing in non-OH subjects with SH.

Across all other domains and at each time, there was some evidence of lower cognition in this group (significant at $P<0.05$ in five tests), with results generally consistent with the effect among those with OH at 20s. However none had sufficient power available to detect a statistically significant difference from the non-OH group. There was no evidence of lower or higher cognition in OH subjects in the non-SH group. Regression models including terms for interactions showed that the difference between SH and non-SH groups in terms of the association between global cognitive function and OH at 20 seconds ($p=0.004$) was statistically significant and there remained a trend at 30 seconds ($p=0.02$). As a sensitivity analysis, participants were also stratified based on cuff-measured hypertension and again hypertensive subjects with OH consistently scored poorer across all tests, with comparable significance (data not shown).

The data was also analysed based on redefined OH classification (≥30mmHg SBP drop for subjects with baseline SBP ≥160mmHg) [256]. Results were similar to the analysis shown, with significance confined to the association of lower global cognitive performance. As the number of subjects with OH according to this definition was fewer, the CI of each point estimate was wider.

Characteristics	Total cohort (n=4690)	No supine hypertension (n=2822)	Supine hypertension (n=1868)	P-value ∞
Age, mean ± SD	60.9 ± 5.8	59.7 ± 8.5	62.8 ± 8.7	<0.0001
Female, % (n)	55.4 (2599)	54 (1533)	57 (1066)	0.06
Education, % (n)				
Primary	20.4 (955)	18.5 (521)	23.3 (434)	
Secondary	42.2 (1980)	42.4 (1195)	42.1 (785)	0.003
Tertiary	37.4 (1753)	39.2 (1105)	34.7 (648)	<0.0001
Smoking status, % (n)				
Never	45.8 (2150)	43.5 (1227)	49.4 (923)	
Former	39.1 (1830)	39.7 (1120)	38 (710)	0.008
Current	15.1 (710)	16.8 (475)	12.6 (235)	<0.0001
Standard drinks consumed weekly †	3 (1.2, 7.5)	3 (0.24, 7.5)	3 (0.12, 8.8)	0.6
Level of physical activity (IPAQ), % (n)				
Low	27.6 (1283)	27.6 (775)	27.5 (508)	
Medium	35.7 (1661)	34.9 (978)	37 (683)	0.4
High	36.7 (1708)	37.5 (1051)	35.6 (657)	0.5
Body mass index (kg/m^2), mean ± SD	28.5 ± 4.9	28 ± 5.1	29 ± 4.7	0.03
Total cholesterol (mmol/L), mean ± SD	5.2 ± 1.1	5.1 ± 1.1	5.2 ± 1	0.0005
Seated SBP* (mmHg), mean ± SD	134 ± 19	126 ± 16	144 ± 19	<0.0001
Seated DBP* (mmHg), mean ± SD	82 ± 12	79 ± 9.7	87 ± 11.1	<0.0001
Mental health, % (n)				
Depression (CES-D ≥16)	9.4 (442)	9 (254)	10.1 (188)	0.2
Disease prevalence, % (n)				
Angina	4.2 (198)	4.2 (118)	4.3 (80)	0.8
Myocardial infarction	3.8 (176)	4.2 (118)	3.1 (58)	0.06
Heart failure	0.8 (36)	1.1 (31)	0.3 (5)	0.001
Diabetes	6.3 (294)	5.7 (162)	7.1 (132)	0.07
Stroke/TIA	2.6 (123)	2.5 (71)	2.8 (52)	0.5
Cardiac arrhythmia	6.9 (325)	6.7 (189)	7.3 (136)	0.4
On anti-hypertensive medication, % (n)	31.6 (1482)	29.8 (842)	34.3 (640)	0.001
On anti-psychotic medication, % (n)	1 (49)	1.24 (35)	0.8 (14)	0.1
Supine SBP, mean ± SD	135.9 ± 22.2	121.6 ± 12.6	157.4 ± 15.3	<0.0001

Supine DBP, mean ± SD	73.2 ± 11.2	68 ± 8.5	81 ± 10.2	<0.0001
Maximum orthostatic SBP difference, mean ± SD	-39.1 ± 17.8	-35.6 ± 9.9	-44.4 ± 19	<0.0001
Maximum orthostatic DBP difference, mean ± SD	-25.7 ± 10.3	-24.8 ± 9.9	-27.2 ± 10.8	<0.0001

† Summarized as median (25th percentile, 75th percentile), because of skewed distribution.

∞ P-values based on test statistics comparing subjects with and without supine hypertension.

*** Measured using oscillometric blood pressure equipment.**

SD =standard deviation, IPAQ =International Physical Activity Questionnaire, SBP =systolic blood pressure, DBP =diastolic blood pressure, CES-D =Centre for Epidemiologic Studies Depression scale, TIA =transient ischaemic attack.

Table 6.1 Characteristics of the study sample, and according to supine blood pressure.

Cognitive performance	Total cohort (n=4690)	No supine hypertension (n=2822)	Supine hypertension (n=1868)	P-value ∞
Global cognition				
MMSE †	29 (28, 30)	29 (28, 30)	29 (28, 30)	0.2
MOCA †	26 (24, 28)	26 (24, 28)	26 (23, 28)	0.4
Executive function				
Word fluency, mean ± SD	21.7 ± 6.9	22 ± 7	21.4 ± 7	0.3
Letter fluency, mean ± SD	12.3 ± 5	12.3 ± 5	12.4 ± 5	0.2
Visual reasoning, mean ± SD	3.2 ± 1.3	3.2 ± 1.3	3.1 ± 1.3	0.6
Colour Trail 2 (s) †	98 (80, 124)	96 (78, 121)	102 (83, 128)	0.9
Processing speed				
Colour Trail 1 (s) †	48 (38, 63)	47 (37, 61)	50 (40, 66)	0.9
Cognitive RT (ms) †	484 (433, 547)	482 (431, 544)	489 (434, 550)	0.4
Memory				
Immediate recall, mean ± SD	6 ± 1.6	6.1 ± 1.6	5.9 ± 1.6	0.5
Delayed recall, mean ± SD	6.3 ± 2.2	6.4 ± 2.2	6.2 ± 2.2	0.3
Picture recall, mean ± SD	3.2 1.1	3.2 ± 1.1	3.2 ± 1.1	0.4
Picture recognition †	6 (5, 6)	6 (5, 6)	6 (5, 6)	0.23
Sustained attention				
Mean SART (ms) †	364 (301, 437)	358 (298, 427)	375 (309, 451)	0.003
SD SART (ms) †	92 (66, 134)	91 (65, 133)	94 (68, 137)	0.09

† Summarized as median (25th percentile, 75th percentile), because of skewed distribution.

∞ P-values based on test statistics comparing subjects with and without supine hypertension, adjusted for age.

SD = standard deviation, MMSE = Mini-Mental State Examination, MOCA = Montreal Cognitive Assessment test, RT =reaction time, SART =Sustained Attention to Response Task.

Table 6.2 Cognitive performance of the study sample and according to supine blood pressure.

	Total cohort (n=4690)	No supine hypertension (n=2822)	Supine hypertension (n=1868)	P-value ∞
	Orthostatic Hypotension, % (n)			
Sustained at 20 seconds	29.2 (1368)	23.9 (673)	37.2 (695)	<0.0001
Sustained at 30 seconds	15 (702)	11.4 (321)	20.4 (381)	<0.0001
Sustained at 60 seconds	6.6 (308)	4.6 (130)	9.5 (178)	<0.0001
Sustained at 90 seconds	4.6 (216)	3.2 (91)	6.7 (125)	<0.0001

∞ P-values based on test statistics comparing subjects with and without supine hypertension.

Table 6.3 Number of subjects with orthostatic hypotension at time-points following orthostasis, according to baseline blood pressure.

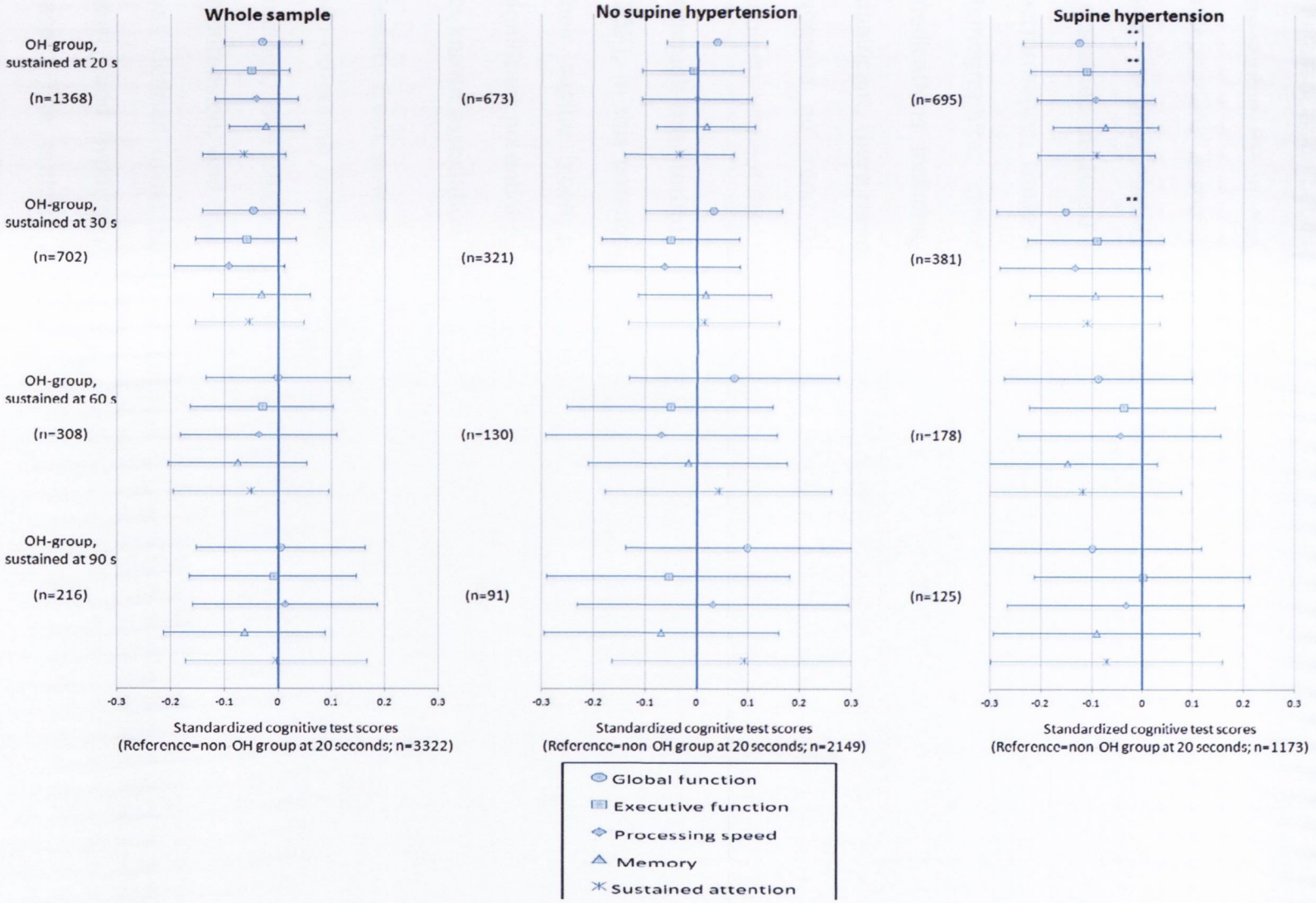

Whole sample
No supine hypertension
Supine hypertension
OH group, sustained at 20 s
(n=1368)
(n=673)
(n=695)
OH-group, sustained at 30 s
(n=702)
(n=321)
(n=381)
OH-group, sustained at 60 s
(n=308)
(n=130)
(n=178)
OH-group, sustained at 90 s
(n=216)
(n=91)
(n=125)
-0.3 -0.2 -0.1 0 0.1 0.2 0.3
Standardized cognitive test scores
(Reference=non OH group at 20 seconds; n=3322)
Standardized cognitive test scores
(Reference=non OH group at 20 seconds; n=2149)
Standardized cognitive test scores
(Reference=non OH group at 20 seconds; n=1173)
Global function
Executive function
Processing speed
Memory
Sustained attention

Figure 6.1 Forest plots illustrating the standardized cognitive scores for subjects with orthostatic hypotension (OH) relative to those without OH, in the whole sample and for subjects with and without supine hypertension. **= P<0.01. Analysis was adjusted for age (linear and non-linear effects), sex, education, smoking, alcohol intake, exercise, height, body mass index, cholesterol level, history of cardiovascular diseases, depression, and medications.

6.5 Discussion

The association between OH and cognitive performance appears to be dependent on supine BP in healthy middle aged and older adults. Here we report an independent association between OH and cognition in supine hypertensive subjects only, notably in the domains of global and executive function. Early OH (sustained at 20-30 seconds post-stand) is most clearly associated with lower performance. These findings are independent of potential confounders; namely demographics, clinical profile, behavioural and mental health, CVD, and medications including antihypertensives. Where results were not statistically significant, there remained a trend towards lower cognition in SH cases with OH; whereas no trend towards lower or higher cognition was observed for OH subjects without SH.

Although the literature states that BP and HR are recovered around 30 seconds [257], in this population based study of the over 50s, 15% had not recovered their supine blood pressure by 30 seconds post stand. Hence there is a significant potential burden of OH in the middle aged and older population, given its known association with clinical conditions.

Results from similar studies are inconsistent- some reporting an inverse [187] and others no relationship [189] between OH and cognition. In contrast to our findings, one study reported lower cognition in OH subjects with underlying hypotension, and higher performance in OH and hypertension [188]. Cognition was defined using MMSE alone, which has recognised limited discriminatory power and hypertension status included both self-reported and controlled BP cases. The authors suggest the positive association may be due to the therapeutic effect of anti-hypertensive treatment. Elsewhere, SH but not

orthostatic BP, was linearly associated with fronto-executive impairment [264]. Both studies had smaller sample sizes than the present study. A recent study reported hypertension to be a risk factor for global and executive function decline, without impact on attention and processing speed- similar to the domains affected here [265]. Our group recently investigated the association between cognitive performance and OH as defined using automatic digital BP measurements. The results also indicated an association between presence of OH and lower cognition – specifically in the subdomains of global performance and memory [266].

A higher prevalence of OH in the presence of SH has been established (SH-OH) [267]. Subjects with both SH and OH exhibit both markedly decreased baroreflex-cardiovagal gain and attenuated plasma Noradrenaline (NAd) responses, which implicates baroreflex failure in its pathogenesis. Cerebral autoregulation is impaired in cases of OH [130], resulting in pressure dependent perfusion. Both high and low BP alter autoregulation, raising the lower BP limit, narrowing the BP range and steepening the cerebral blood flow-BP curve [126]. Impaired vasodilatation in low BP states and higher vasoconstriction at higher BP may result from this dysautoregulatory state. In our study the SH group also demonstrated a greater orthostatic fall in both DBP and SBP, which can potentially result in greater impairment to blood flow and cerebral perfusion capacity. Sub-analysis adjusting for maximum BP drop did not attenuate results however, indicating that the association was not explained by the degree of drop.

Long-standing hypertension is known to predispose to cognitive decline [255]. As hypertension is also a risk factor for OH, it leads that its prevalence is higher

in cases of long-standing hypertension. Hence, duration of hypertension may explain a relationship between OH and lower cognitive function. Duration of preceding hypertension was not recorded in wave 1 of the TILDA study, so we were unable to control of this in analysis. However future waves of the study will allow for investigation of the role of long-standing hypertension on the subject.

The pathogenesis of cerebral damage comprises of a cascade of pathophysiological events, principally cerebral small vessel disease (mainly arteriosclerosis and cerebral amyloid angiopathy) and white matter damage, both of which are associated with cerebral hypoperfusion [248]. White matter lesions (WML) predict cognitive decline and dementia [268]. Small vessel disease is associated with more than two-times increased risk of dementia at 75 years [269]. Hypoperfusion of the prefrontal cortex has been reported in OH patients, when compared to controls [270], which may explain our association between OH and executive function- a domain controlled by this region.

As our study sample is selected from the healthy community dwelling population, the effect size of our results is relatively small. This limits the clinical interpretation of our results; however the role of our findings lies in the context of future research investigating biomarkers of cognitive ageing. The lack of a significant association between sustained OH at later times post standing and cognition is unexpected, as prolonged hypotension should equate to greater hypoperfusion and cerebral damage. However, the CI for each test and at each time is consistent with a -0.1 SD cognitive difference, indicating that cognition may actually be lower amongst subjects with OH sustained at 60-90 seconds. The lack of precision of effect estimates, possibly due to smaller numbers in these groups, does not allow us to be certain of this nonetheless. Alternatively,

an adaptive response to prolonged OH may adjust cerebral blood flow to compensate for sustained low BP, as cerebral autoregulation remains intact in a proportion of cases [130]. As the standard method for BP measurement uses the seated position, SH may be under-detected in the clinical setting. Improved vigilance and diagnosis are needed, given its potential role in clinical outcomes. Management of individuals with both OH and SH is challenging, as the beneficial effects of pharmacological treatment of one condition may worsen the other [271]. This remains however the subject of ongoing debate [272]. Symptom relief remains a priority. Additionally, assessment using major-event predictive tools, to determine which clinical sequelae pose a greater risk to the individual should be prioritised and guide management- for example major vascular events or major injuries, e.g. fractures (caused by a fall secondary to OH) [273].

Non-pharmacological management of OH includes increased salt and fluid intake, reducing/discontinuing culprit medications, performing physical counter-manoeuvres and wearing custom-fitted elastic stockings, while management of SH includes the use of reclining chairs to avoid the supine position. Pharmacological treatment for SH with anti-hypertensive therapy worsens OH, hence short-acting medications, administered at night-time, are recommended [274]. OH is often treated with midodrine and pseudoephedrine, however their use should be restricted to greater than four hours before recumbency [274].

The association between cognition and OH as measured with beat-to-beat BP monitoring at a population scale has not been assessed before. Beat-to-beat methods allow for more precise quantification of BP changes and capability of detecting more subtle fluctuations in response to orthostasis. We use

comprehensive neuropsychological measures spanning numerous domains of cognition.

Although the benefits of certain cognitive tests have been recognised over others, e.g. MoCA has greater discrimitory power over the MMSE, all tests governing each cognitive domain were weighted equally, as higher accuracies in some tests above others have not been objectively quantified in the literature to date. It also must be acknowledged that interpreting composite scores carries its own limitations. The inclusion of the chosen tests per domain was based on the representing function, considered by the originators of each test. Cognitive tests are multi-dominal, and so grouping by the predominant function such tests are considered to represent, results in a loss of a proportion of the power, using this approach.

Objective health measures were further assessed and controlled for in analysis. The protocol consisted of ten minutes supine rest in a quiet room- the optimal period to obtain stable BP readings [275]. The large nationally representative community-based design using rigorous measures of SH and OH strengthen the observations seen. Our study was designed as an epidemiological, point prevalence study and was therefore unable to draw any firm causation for the observed association. Causality will be explored in subsequent waves of the TILDA study. Subjects unwilling to undergo centre-based health assessment were offered in-home assessment; however continuous orthostatic BP response was not recorded here, due to impracticality and financial limitations. Despite subject characteristics differing between these groups, we consider that the association between SH, OH and cognitive performance would not be attenuated in the excluded group. As the sample group analysed were healthier, the

association reported in this study may have been stronger in the excluded group, given the higher levels of both physical and cognitive impairment. Measures within the same domain were weighted equally; hence the different tests accuracies for detecting reduced cognition were not adjusted for. Participants were not requested to refrain from eating, smoking, alcohol, caffeine, exercise, or medications prior to assessment, and time of day for assessment was not restricted, based on practicality of delivering health assessments to participants from all over the country. These factors may affect reproducibility of results, however time of day and food ingestion did not influence orthostatic BP behaviour in a sub-study [276].

Conclusion

In conclusion individuals with supine hypertension (SH) (defined as BP> 140/90 mmHg) coupled with OH measured using phasic BP had lower cognitive performance than those with hypertension but without OH. Sustained OH at 20 to 30 seconds post orthostasis yielded the strongest association, in the cognitive domains of global and executive function. Future studies should recognise SH when investigating the association between OH and clinical outcomes, as nocturnal hypertension is increased in SH and increases the risk for cardiovascular and cognitive disorders. Clinicians should give consideration to the measurement of SH in addition to orthostatic BP, as SH-OH management guidelines differ from those for OH in isolation. Further investigation of the mechanisms and associations between autonomic and haemodynamic dysregulation will improve understanding of the process of transition from the cognitively functional to the cognitively impaired state.

7 Higher syncope burden is associated with poor cognitive function in an older adult population study- TILDA

7.1 Abstract

Objective

To compare cognitive performance in participants with and without syncope and unexplained falls in a large population representative sample over 50 years.

Methods

Participants of the Irish longitudinal study on ageing (TILDA) were studied. Participants with a history of syncope and/or unexplained falls in the past twelve months were compared wth those with no reported events. Cognitive performance was measured using the Montreal cognitive assessment (MoCA) score. Multivariate linear regression analysis controlling for potential confounders was performed to compare cognitive function by syncope and falls status.

Results

5849 participants, median age 62 (Interquartile range=14), and 54% were female. 549 (9.4%) had a syncopal event and/or an unexplained fall in past 12 months. 238 (4.1%) subjects had two-plus events in the same period. There was a significant association between syncope history and lower MoCA score, following adjustment for all confounders (B=-0.4; 95% CI= -0.69, -0.11; P=0.006). Higher 12-month syncope burden was also associated with lower

performance (B=-1.0; 95% CI= -1.43, -0.57; p<0.0001). There was no age interaction with these findings.

Conclusion

Participants who experienced syncope and/or non accidental falls in previous year have poor global cognitive performance compared to those without. There was no effect of age on our results. Further investigation of the association between syncope burden, unexplained falls and cognitive decline is required to establish a relationship between these disorders.

7.2 Introduction

The role of vascular risk factors in the pathogenesis of cognitive disorders has gained research momentum in recent years[237]. This is partially driven by the projected increase in the burden of cognitive disorders, secondary to dramatic changes in ageing demographics worldwide[277]. Late-life hypotension and orthostatic hypotension are both reported to be associated with reduced cognitive function from cross-sectional and longitudinal studies[126, 187].

Syncope is defined as a sudden loss of consciousness due to transient global cerebral hypoperfusion characterized by rapid onset, short duration, and spontaneous complete recovery[178]. Syncope is a common symptom- up to 40% of persons report at least one episode over the course of their lifetime [278]. The prevalence peaks in youth and in older age. The majority of syncope episodes in youth (>99%) are due to vasovagal syncope [278], which is generally considered to be a benign disorder [279]. With advancing age, cardiac causes of syncope and medication-related syncope become much more common [278].

Syncope and falls are frequently unwitnessed, and often individuals are unable to recall a blackout, hence may cases of syncope may be misdiagnosed as falls. Amnesia for loss of consciousness (A-LOC) has been reproduced in experimental studies in these patients [196].

Cardiac disease, cerebral vascular pathology and neurodegeneration often coexist and share common pathophysiological substrates, such as atherosclerosis and inflammation [237]. It has been hypothesized that repeated symptomatic hypotension in older persons with poor cerebrovascular autoregulation could cause cerebral damage manifesting as cognitive impairment

?. Conversely, neurodegeneration may lead to autonomic dysfunction causing syncope due to hypotension or arrhythmias; thus, syncope and non accidental falls might parallel the progression of cognitive decline.

To the best of our knowledge no previous studies have investigated the association between syncope and cognition in healthy populations. The objective of our study was to examine the association between syncope, unexplained falls and cognitive performance, with data from a large nationally representative sample of community dwelling adults aged 50 and over.

7.3 Methods

Study population

Data from the first wave of The Irish Longitudinal Study on Ageing (TILDA) was analysed (collected June 2009- June 2011). TILDA is a large prospective cohort study on ageing, comprising healthy community dwelling adults aged 50 and over resident in the Republic of Ireland, who did not have dementia. A statistically robust nationally representative sample was selected using the regularly updated RANSAM sampling technique, from a listing of all residential addresses in the Republic of Ireland (The Irish Geodirectory). Details of the study design is published elsewhere[200]. Data collected within TILDA is comprised of (i) Computer-assisted personal interviewing (CAPI), carried out in the participant's home, (ii) Self-completion questionnaire, and (iii) Physical health assessment- carried out by trained study nurses in one of two dedicated health centres. Participants unwilling or unable to undergo centre-based assessment were offered a nurse delivered in-home health assessment (where all measures for this study were also recorded). Ethical approval was obtained and all respondents provided signed informed consent prior to participation. All experimental procedures adhered to the Declaration of Helsinki.

Classification of syncope, syncope burden and unexplained falls

Participants were asked whether they had fainted at any point during their lifetime during the CAPI interview. Those who responded positively were further asked 'have you fainted in the past 12 months? " and "how many times have you fainted in the past 12 months?". Number of syncopal events in the past 12 months was a count variable with overdispersion (standard deviation (SD) larger than the mean [mean = 0.6, SD =3.3]). This was subsequently categorized into

three groups; no events, one syncopal event, and multiple syncopal events. Participants were also asked if they had fallen in the past 12 months, the number of falls and and whether any of these falls were unexplained i.e. 'a fall with no apparent or obvious reason' or without mitigating circumstances.

Assessment of cognitive function

Cognitive function was assessed during the health assessment, using the Montreal Cognitive Assessment (MoCA)[46]. MoCA is a measure of global cognitive function (score range; 0-30), assessing the sub-domains i) memory, ii) visuospatial function, iii) executive function, iv) sustained attention, v) language, and vi) orientation.

Covariates

Other variables that were considered potential confounders and/or modifiers of the association between syncope and cognition were also collected and their effects estimated by multivariate analyses. These included age, sex, educational attainment (primary, secondary or tertiary), smoking status (never smoked, former or current), physical activity (using the International Physical Activity Questionnaire (IPAQ) short form, classified as low, medium, or high)[263], height (cm), body mass index (BMI) (kg/m^2), systolic blood pressure (BP), total blood cholesterol (mmol/L), depression (The Centre for Epidemiological Studies Depression (*CES-D*) scale was used with a cut-off score of 16 or above, to define subjects as depressed[216]), history of angina, myocardial infarction, heart failure, diabetes mellitus, stroke, transient ischaemic attack (TIA) and cardiac arrhythmias (self report).

Medication use was recorded during the home interview (CAPI) and confirmed by cross-checking with medication labels. Anatomical Therapeutic Classification

(ATC) codes were subsequently recorded for categorisation[218]. BP modifying medications were anti-adrenergic agents ('C02*'), diuretics ('C03*'), beta-blockers ('C07*'), calcium channel blockers ('C08*'), angiotensin-converting-enzyme inhibitors/ angiotensin-receptor blockers ('C09*'), benzodiazepines (N03AE, N05B, NO5C) and combinations of the above ('C02*'). Anti-psychotic medications ('N05A') were also controlled for in analysis.

Statistical analyses

Statistical analysis was performed using Stata version 12 (StataCorp, College Station, TX). Distribution of continuous variables was assessed using Q-Q plots and histograms. Normally distributed variables were described as means and standard deviations (SD), and were compared across groups using independent t-tests. Non-normally distributed variables were described as medians and percentiles and compared using Mann-Whitney tests, and categorical variables were compared using Chi-squared tests.

Linear regressions were fitted to assess the association between syncope, unexplained falls and MoCA score. Models in a 2 stage order were fitted, the first adjusting for age, sex and educational attainment, the second adjusting additionally for health behaviours, clinical profile, CVD, mental health, and medications, as described above. In order to investigate the individual associations between syncope and unexplained falls, and cognition, linear regression analysis with syncope entered as the independent variable was adjusted for falls history and vice versa. Missing data for any single covariate was ≤0.1%, hence was excluded on a case-wise basis. Statistical significance was taken as $P<0.05$.

7.4 Results

The study sample consisted of 5849 subjects, median age 62 (Interquartile range=14); 54% female (n=3163). Prevalence of syncope and/or unexplained falls in the past 12-months was 9.4% (n=549). Five percent (n=305) experienced a single syncopal event in the past 12 months, while a further 4.1% (n=238) experienced two or more events. Demographic and clinical characteristics according to syncope group are presented in table 1. Individuals with a syncope/falls history were older, had lower educational attainment, MoCA score, physical activity level, cholesterol level, and prevalence of depression. They also had higher former smoking rates, prevalence of cardiovascular disease, and anti-hypertensive and anti-psychotic medication use. There was no difference in gender, BMI, BP, and prevalence of myocardial infarction and heart failure between groups.

The overall association between syncope/falls history and MoCA score is summarized in Table 2. In model 1 (adjusted for age, sex and education) subjects reporting a syncopal event and/or an unexplained fall within the past 12 months scored significantly lower, compared to those without any events in the same period (B=-0.58; -0.87, -0.29; P<0.0001). Further adjustment was applied in model 2 for smoking status, exercise, height, body mass index, total cholesterol level, resting systolic BP, angina, myocardial infarction, heart failure, stroke, transient ischaemic attack, heart arrhythmias, depression, and anti-hypertensive and anti-psychotic medications. This association with a lower MoCA score remained significant (B=-0.4; -0.69, -0.11; P=0.006).

Next, the effect of syncope burden was assessed. In model 1, subjects reporting two-plus syncope events in the past 12 months scored significantly lower in

MoCA, than subjects with no syncope history (B=-1.23; -1.6, -0.81; P<0.0001). Further adjustment in model 2 attenuated the association, and was no longer significant (B=-1.0; -1.43, 0.57; P<0.0001). Subjects reporting a single syncope event in the same period did not score significantly better or worse to those without a syncope history, in models one or two.

Further analysis was performed to determine the effects of age. The interaction effect of age on (i) 12-month syncope/unexplained falls history (B=-0.02; -0.05, 0.01; P=0.2) and (ii) syncope burden (B=-0.01; -.07, 0.06; P=0.9) were not significant. The effect of sex was also studied. The significant association between 12-month syncope/unexplained falls history and lower MoCA was confined only to men. However, the interaction effects between sex and syncope group were also estimated, and did not reach significance (data not shown). Data was reanalysed using logistic regressions, with outcomes of scoring below various used MOCA cut-off scores (≤25, ≤23, ≤22). There was a trend in each analysis consistent with the directions of effects observed in the main analysis (data not shown). However, significant associations between syncope and lower MoCA score were limited to men and for cut-off scores of ≤22 and ≤23.

Characteristics	Any 12-month Syncope/Unexplained falls history		
	No (n=5297)	Yes (n=549)	P-value
Age, mean ± SD	63 ± 9	65 ± 10	<0.0001
Male, % (n)	91.4 (2451)	8.6 (232)	
Female, % (n)	90 (2846)	10 (317)	NS
Education, % (n)			
Primary	25.5 (1352)	41.2 (229)	0.007
Smoking status, % (n) (Ref=Never)			
Former	38.8 (2056)	43 (236)	0.03
Current	16 (845)	16.4 (90)	NS
MOCA score, median (25^{th}, 75^{th} CI)	25 (23, 27)	25 (22, 27)	<0.0001
Level of physical activity (IPAQ), % (n) (Ref=Low)			
Medium	35 (1839)	36.3 (198)	<0.0001
High	35.8 (1881)	23.6 (129)	<0.0001
Body mass index (kg/m^2), mean ± SD	28.7 ± 5	28.6 ± 5	NS
Total cholesterol (mmol/L), mean ± SD	5.1 ± 1	5 ± 1	0.001
Mental health, % (n)			
Depression (CES-D ≥16)	11.1 (389)	9.3 (218)	0.02
Disease prevalence, % (n)			
Angina	4.9 (260)	8.2 (45)	0.001
Myocardial infarction	4.5 (238)	5.5 (30)	NS
Heart failure	0.9 (48)	1.5 (8)	NS
Diabetes	7 (369)	10.4 (57)	0.003
Stroke/TIA	3.1 (164)	7.3 (40)	<0.0001
Cardiac arrhythmia	7.2 (383)	11.1 (61)	0.001
Systolic BP, mean ± SD	136 ± 20	135 ± 20	NS
Diastolic BP, mean ± SD	82 ± 11	82 ± 11	NS
Anti-hypertensive medications, % (n)	35.9 (1901)	45.2 (248)	0.001
Anti-psychotic medications, % (n)	1.1 (60)	3.1 (17)	<0.0001

[a] **Summarized as median (25^{th} percentile, 75^{th} percentile), because of skewed distribution.**

SD = standard deviation, TIA= transient ischaemic attack, BP= blood pressure.

Table 7.1 Clinical characteristics of the study cohort, comparing subjects with and without a history of syncope/unexplained falls.

(Outcome=MoCA score)	Model 1		Model 2	
Group	**B-coef. (95th Perc.)**	**P-value**	**B-coef. (95th Perc.)**	**P-value**
12-month Syncope/Non-accidental falls history				
(Reference=None)				
Event in the past 12-months	-0.58 (-0.87, -0.29)	P<0.0001	-0.4 (-0.69, -0.11)	P=0.006
12-month Syncope burden				
(Reference=None)				
1	-0.01 (-0.37, 0.37)	P=0.9	0.11 (-0.26, 0.49)	P=0.5
2+	-1.23 (-1.6, -0.81)	P<0.0001	-1.0 (-1.43, -0.57)	P<0.0001

Model 1 adjusted for age (linear and non-linear affects), sex, and education. Model 2 adjusted for Model 1 variables, smoking status, exercise, height, body mass index, total cholesterol level, resting systolic blood pressure, angina, myocardial infarction, heart failure, stroke, transient ischaemic attack, heart arrhythmias and depression, anti-hypertensive and anti-psychotic medications.

MoCA= Montreal Cognitive assessment. B-coef. = B-coefficient. 95th Perc. = 95th Percentile.

Table 7.2 Cross-sectional association between 12-month history of syncope, burden of syncope and MOCA score (B coefficient, with 95% confidence interval in parentheses).

7.5 Discussion

Syncope and unexplained falls in the past year are independently associated with poorer cognitive performance amongst individuals aged 50-plus. No age effect was observed on this association. Higher burden of syncope was also associated with poorer performance; however this was explained by confounding factors of smoking status and exercise level. The association was more evident amongst men; however there was no effect of gender on the interaction between syncope and cognitive score. Further studies are required to investigate the effect of sex on this association.

A number of pathophysiological mechanisms may explain the findings of this study. Lower cognitive performance may be caused by neurodegenerative processes triggered by hypoperfusion and hypoxia in the brain. Hypoperfusion can occur during syncope events. Cortical deoxygenation begins >3 minutes before the onset of syncope during head-up tilt[280], hence cortical ischaemia precedes haemostatic decompensation. The total number of syncopal events has been shown to correlate negatively with cerebral blood flow[281]. Impaired circulation due to cerebral hypoperfusion during syncope may result in watershed infarcts or apparent transient ischaemic attacks[1]. The magnitude of hypotensive drops in carotid sinus hypersensitivity (CSH) is correlated with the severity of cerebral white matter lesions (WML)- a biomarker of cognitive impairment[282].

Twelve-month history of syncope events has a superior predictive value for future syncope risk over the total lifetime syncope number[283]. Hence, this group we identified with recent syncope events and lower cognition, may be at risk of further assault. This further highlights the need to establish an

understanding of the relationship, as this group may be at risk of further cognitive decline, if syncope is not correctly managed to prevent future events.

Autonomic dysfunction is recognised in neurodegenerative diseases[284], including dementia[197], and has recently been recognised as a predictor of shorter survival in subjects with dementia[285]. Hence, reverse causation may explain the relationship, whereby neurodegeneration secondary to cognitive decline may lead to impairment of autonomic control centres. It may be the case that both syncope and cognitive decline may share a common neurological pathogenesis encompassing vascular, inflammatory and other neurodegenerative processes, occurring in parallel without being causally related to one another. Syncope is treatable and management includes withdrawal of culprit medications, particularly anti-hypertensives[286], physical counter-manoeuvres[287], adequate hydration and pacemaker implantation[288]. If a causal association were established, interventions to treat syncope may delay cognitive decline. Clearly this is speculative and would require a prospective study. Nonetheless, our results of an independent association between syncope and cognitive function emphasise the need for further investigation of the subject.

There are a number of consequences to the findings of this study. It is important to ascertain the directionality of this association, as intervention strategies for managing syncope may have a role in preventing cognitive decline. Older adults with syncope should undergo cognitive assessment to monitor their performance over time, which may detect subtle decline otherwise missed. The relationship between syncope and lower cognition may have implications for management of

patients with syncope i.e. driving advice. Concurrent syncope and cognitive impairment may serve to prolong the period during which driving is prohibited.

The cross-sectional design is the main limitation of this study. Future follow-up of the TILDA cohort will allow for investigation into the longitudinal relationship between syncope and cognition. We were unable to determine syncope sub-type and previous burden of syncope, as it is beyond the scope of the TILDA study; however the study sample is nationally representative of the community-dwelling population aged 50 years and older living in Ireland, hence our results are generalisable to this population. The MoCA was chosen for analysis over the Mini Mental State Examination (MMSE) due to its higher predictive value for MCI [46] and less ceiling effect in a population-representative sample. We were unable to eliminate or control for recall bias, which may play a role in ability to recall syncopal events, for subjects with lower cognitive ability.

In conclusion, this study has for the first time reported an association between syncope and lower global cognitive performance at a population level. These findings are independent and warrant further investigation using cross-validated data in relation to syncope history. Subsequent waves of the TILDA study will allow for investigation of the longitudinal association between self-reported syncope and cognition.

8 General discussion

The overarching purpose of this thesis was to investigate the relationship between autonomic dysfunction and cognitive performance in a healthy population sample. Specific objectives were: to examine associations between indices (HRV, OH) and clinical features (syncope) of autonomic dysfunction and cognitive performance. In the present chapter, the main findings of this thesis are summarised and discussed within the framework of outcomes of previous studies. Next, methodological issues relevant for this thesis are addressed and possible clinical implications of our findings are given. Finally, some topics for future research are identified.

8.1 Main findings

Heart rate variability and cognitive function

Firstly, I considered a well recognised index of general autonomic function for analysis- HRV. Our study uniquely recorded HRV over 2 protocols, the second adjusting for RSA. Reduced HRV, reflected in the indices SDNN, LF and LF:HF ratio were each associated with lower global cognitive performance- and in cases there was a dose-reponse. Retention of our findings using HRV taken during the paced breathing period provided further validation. Despite disagreement in the literature on the interpretive value of the different HRV indices, HRV markers significantly associated with lower cognition are referenced to both their traditional and more recently debated interpretative value. Previous comparable studies have reported conflicting results- one reporting a negative association between HRV and cognition [154], and the other, no association between the two [213]. Neither examined a population based study however, which places the importance of our findings at a community level. Furthermore, neither

recorded HRV during a paced breathing protocol. Hence, our findings are more robust than either of the studies in the literature.

Several different pathways may play a role in the relationship between reduced HRV and lower cognition. The cholinergic anti-inflammatory pathway implicates the expression of inflammatory markers CRP and Il-6 in cases of reduced HRV- both of which have also been linked to cognitive decline. The Noradrenaline hypothesis describes the association between depleting levels of Noradrenaline and dysfunction of elements of cognitive reserve. Both Noradrenaline and Acetylcholine are responsible for HRV. Hypertension, which often precedes both a reduction in HRV and cognition, may also control this association; however we adjusted for baseline BP in analysis so our findings are likely independent of the presence of hypertension.

Orthostatic hypotension and cognitive function

Paper 2 investigated the cross sectional association between cognitive function, measured across several domains and OH, a clinical indicator of autonomic impairment. Here we measured OH using the oscillometric method. An advantage was the inclusion of subjects unwilling or unable to undergo an in-centre health assessment, as orthostatic BP was also recorded in the home assessment. It was previously established that participants who selected a home assessment were older and had poorer cognitive performance [243]. In our study, OH had an overall prevalence of 6.1%, and was independently associated with lower global cognitive function and memory function. This was confined to subjects aged 65 years and older, and predominantly to women. Our study adds to the literature by investigating the association in a large nationally representative cohort.

Paper three again examined the relationship between OH and cognitive function, however here OH was defined using continuous BP measurement. In this way, subtle BP changes in response to orthostasis were detected at time points immediately following the active-stand. OH was defined according to definition (≥10mmHg drop in DBP or ≥20mmHg drop in SBP) as sustained at time-points 20, 30, 60, and 90 seconds post orthostasis. Results indicated a trend towards lower cognitive function for subjects with OH, however this was non-significant. We then examined subjects with supine hypertension separately, as this is a known indicator of impaired autonomic function, and equally a precursor to OH. SH subjects with a sustained BP drop following orthostasis scored lower in global and executive cognitive performance, independent of confounders. We contribute to the research on this subject by repeating the association for the first time using continuous BP recording methods. The association confined to SH-OH subjects has not been reported on in the literature.

We hypothesise that OH is associated with cognitive performance through impaired cerebral autoregulation and subsequent cerebral hypoperfusion. Cerebral small vessel disease and white matter damage are both associated with hypoperfusion. Long-standing hypertension increases the risk of OH, and leads to cognitive decline. This could explain the relationship between OH and lower cognition. We were unable to control for duration of hypertension here, which may mediate the associations reported on.

Syncope and cognitive function

In the fourth and final study we investigated the association between syncope and cognitive performance. We reported in our results that subjects with a recent burden of syncope, notably those reporting ≥2 syncopal events in the last

year, were significantly more likely to score in the lowest group of cognitive performance. Similarly, subjects reporting non-accidental falls in the last year were also significantly more likely to score lower cognitively. This study contributes to the literature by examining for the first time (to our knowledge) the association between syncope and cognition. Syncope is a clinical disorder of autonomic dysfunction, caused by transient cerebral hypoperfusion. Hence, syncope may be detrimental to structures governing cognitive function, if cerebral ischaemic damage follows hypoperfusion. Cerebral deoxygenation begins up to 3 minutes before the onset of syncope, a considerable period that may induce hypoxic and ischaemic pathological changes. These changes, in the setting of higher syncopal burden may accumulate and result in a greater degree of neurodegeneration and cognitive decline.

As a number of our findings implicate the role of cerebral hypoperfusion to explain their association with lower cognition, interventions to improve cerebral perfusion capacity may improve cognitive status. Recent trials show that the calcium channel blocker (CCB) Nilvadipine, an anti-hypertensive that crosses the blood-brain barrier, stabilises and in some cases improves the cognitive status of subjects with AD [289].

In summary, our evidence suggests that indices (reduced HRV and orthostatic BP drops) and clinical manifestations (syncope) of autonomic dysfunction are both linked to lower cognitive performance, at a population level.

Potentially, an imbalance or alteration of the output capacity of the components of the autonomic network may lead to any number of disorders characterising autonomic dysfunction. Whether expression of autonomic dysfunction a) compromises vascular integrity resulting in neural damage to networks

responsible for cognition, b) results in cognitive impairment though alternative pathways or c) is modified in tandem with networks responsible for cognitive function by an unidentified ageing process remains to be understood.

We note and distinguish the separate entities of lower cognitive performance, cognitive decline and dementia, and that they are not synonymous. Hence further research is required to investigate the role of indices of autonomic dysfunction assessed here, in other states of cognitive function, and equally their role in conversion between states.

8.2 Clinical implications

Findings from this thesis have clinical relevance in the medical specialties of cardiology, gerontology, psychiatry and general practice.

HRV biofeedback is a relatively new technique developed to train subjects to alter the variability and dominant rhythms of their heart activity. By guiding subjects to relax, reduce negative thoughts, and engage in full diaphragmatic breathing, they can learn to recognise and produce the waveform corresponding to respiratory sinus arrhythmia. Evidence indicates the role of HRV biofeedback interventions in increasing HRV [290]. Should future research clarify the causal relationship between HRV and cognition, HRV biofeedback may form an effective intervention strategy against cognitive decline. However, extrapolation from the findings of Chapter four indicate that an increase in SDNN from the lowest to the highest quintiles (mean 22 vs 81) would correspond to an direct effect estimate of +0.4 MoCA score points. The size of the effect attributable to HRV in the model applied indicates that measures taken to modify HRV may have a minor role to play in limiting cognitive decline.

OH is a treatable condition and therefore a potentially modifiable risk factor for cognitive decline. Non-pharmacologic treatments include avoidance of potentially hypotensive medications, use of physical counter manoeuvres, hydration and sodium supplementation. If these non-pharmacologic measures prove inadequate, various pharmacotherapeutic agents, including fludrocortisone, midodrine, and nonsteroidal anti-inflammatory drugs can be considered [291]. As our research highlighted the role of supine hypertension in this association, the suitable interventions for management of SH-OH differ from that of OH alone. Management of individuals with both OH and SH is challenging, as the beneficial effects of pharmacological treatment of one condition may worsen the other [271], however this remains an issue of contention [272]. Symptom relief remains a priority. Additionally, assessment using major-event predictive tools, to determine which clinical sequelae pose a greater risk to the individual should be prioritised and guide management- for example major vascular events or major injuries, e.g. fractures (caused by a fall secondary to OH) [273].

Syncope is also treatable, if its cause can be established. Management includes withdrawal of culprit medications, particularly anti-hypertensives [286], physical counter-manoeuvres [287], adequate hydration and pacemaker implantation [288].

Understanding the demographic and clinical features of subjects reporting the strongest association between markers of autonomic dysfunction and cognition may help target interventions to those at greatest risk. We reported that lower cognitive performance in older females was more associated with the presence of OH than in other groups. If older females are at preferential risk of the effects of OH, particular focus should be applied to managing this group. If sex

differences in the aetiology of autonomic or cognitive disorders were established, patient specific management practices would be required. We reported that the association between OH measured using continuous data, and cognitive performance was confined to subjects with SH. Hence, particular focus on tight BP control of these subjects may also be required. Clinicians should be aware of this and measure resting BP in the supine (as opposed to the seated) position prior to orthostasis.

Taken together, management practices aimed at improving circulation to cerebral structures may delay processes responsible for cognitive decline. Further research is first warranted to support or disprove our findings. Unless autonomic dysfunction and cognition are causally linked, therapies to manage autonomic disorders may not impact on cognitive function.

8.3 Methodological considerations

Possible limitations of the present study have been addressed in individual papers but the most important considerations with respect to the validity of our observations are (re)considered below.

This thesis is limited to cross-sectional analysis of data from the TILDA study. It is evident that follow-up analysis over time provides a broader perspective of the relationship between two systems, allowing for causal hypothesises to be tested. Hence, caution must be used when making inferences from the results of each chapter. Nonetheless, it remains that a number of the indices of autonomic dysfunction studied in this thesis have not been investigated in the past, moreover in the context of a comprehensive cognitive battery in a sample representing the over 50's population nationally. Longitudinal analysis using

TILDA data from future waves will serve to validate or discern the bidirectional relationship hypothesised between the autonomic and cognitive systems.

The source of data analysed was attained in a research setting, so the criteria required to clinical define Mild Cognitive Impairment was unavailable. Disadvantages of this include that I was unable to investigate the association between autonomic functions and clinically significant cognitive decline. In contrast, by investigating cognitive performance using linear outcomes, as opposed to the binary outcome of MCI- yes or no, I was able to analyse subtle discrepancies in cognitive performance between groups that may otherwise be missed.

A proportion of data was collected using questionnaires, such that self-reported (and hence subjective) answers were adopted for use. I acknowledge that the use of such data is subject to error. However, the use of wholly objective data is impossible in a study of this scale, as patient information in the Irish healthcare system is not computerized and hence unavailable for research use. Despite hardcopy medical records held by individual hospitals, these are not linked between hospitals, making it impossible to track the historical record of each participant within the healthcare system. For information that should otherwise be held electronically, participants were asked to self-report conditions, most often phrased *'has a doctor ever told you that you have...'*. Participants with lower cognitive status may have been at higher risk of misreporting conditions. In all analysis conducted, with the exception of Chapter 7, self-reported conditions were entered as covariates alone, hence any potential bias resulted only in modification of the adjustment effect of confounders on the principal associations tested. Furthermore, all persons were first screened for dementia by

a member of the recruitment team before being invited to participate in the study. Hence cases of severe cognitive impairment were excluded.

Our measures of HRV and OH were performed once and without standardisation for time of day, medications, meals and lifestyle factors (e.g. smoking, caffeine, alcohol), based on practicality of delivering health assessments to participants from all over the country [292]. These factors may affect reproducibility of results [140], however time of day and food ingestion did not influence orthostatic blood pressure in a previous TILDA pilot study [276]. I also examined the affect of time of day on HRV, and no significant association was established. Variability in measures of autonomic function can be considerable [293, 294] and this could have led to the misclassification of disease states in our study; but equally, there is evidence to suggest that reproducibility is not always an issue in older adults [295, 296].

Time of day was not controlled when cognitive tests were performed. A number of the tests applied (e.g. SART) are currently limited to use in the research setting, so lower performance across such tests cannot yet be directly translated into clinical meaningfulness. The high ceiling effect of certain tests, e.g. The MMSE carry additional limitations in the cohort studied here, as the sample of interest was relatively cognitively healthy, when compared to hospital patients, which such tests are designed to apply to.

In summary, despite these limitations there are several strengths of our study. Firstly it was based on a large nationally representative sample that measured a variety of factors relevant to the health of older adults. Reliable and valid objective assessment tools were used to measure autonomic function and cognitive data collection was extensive, allowing for analysis across multiple

cognitive domains. Comprehensive assessment of covariates, including demographics, clinical profile, medical history and medications allowed for extensive control of confounders in statistical analysis.

8.4 Future research

Several research questions are highlighted in consequence to the findings of this thesis. A number of these are directly applicable to existing data collected from TILDA, while others may be investigated using data collected in future waves of the study. The cross-sectional association between baroreflex sensitivity and cognition function requires investigation, as BRS is a recognised index of autonomic function. BRS can be approximated using signals acquired during the in-centre health assessment of wave 1.

Retinographic imaging was assessed in TILDA wave 1. Investigation of the association between retinal angiography and markers of both autonomic function and cognition forms the next logical course of study. Vascular integrity of the retinal vessels serves as a useful surrogate for the structure of proximal cerebral vasculature. Hence, as hypothesised in this thesis, hypoperfusion induced microvascular changes preceding neurodegeration may potentially be detected via analysis of retinal vascular tissue.

Immunological analysis of blood samples for inflammatory biomarkers would be useful for further investigation of *the cholinergic anti-inflammatory pathway's* role in the association between HRV and cognitive dysfunction.

Future waves will allow us to investigate the longitudinal association between all measures I investigated here, namely HRV, OH and syncope, with cognitive decline, as opposed to lower cognitive performance.

Another step to understanding the pathophysiology explaining the relationship between autonomics and cognitive decline is to examine whether our indices of autonomic dysfunction actually translate to a reduction in CBF in older adults with lower cognitive function. Common modalities (Computed Tomography, Positron Emission Tomography, and MRI) for monitoring cerebral blood flow (CBF) are often limited by practical and technological hurdles in large cohort and community studies. Noninvasive measures are more suited to prospective studies and include transcranial Doppler (TCD) ultrasonography and Near-infrared diffuse optical spectroscopy (NIRS). TCD is limited to observations of large vessel flow velocities, which do not necessarily reflect microvascular perfusion in patients with cerebrovascular disease, and importantly it lacks sensitivity for assessing CBF during orthostasis (signal is lost due to movement). NIRS is currently being piloted for inclusion in wave 3 of TILDA as it purports to offer a non-invasive, rapid, portable and low-cost alternative to directly monitor cerebral tissue oxygenation in microvasculature [297, 298]. Inclusion of this measure would facilitate much needed research on the magnitude of CBF reductions associated with indices of autonomic dysfunction and provide insights into the autoregulatory decline associated with ageing. These measures carry practical and financial advantages over MRI, however the quality and quantity of data acquired from cerebral autoregulation measurement is lower.

The need for neuroimaging in conjunction with analysis of autonomic function and cognition has been highlighted previously [187, 189]. Neuroimaging allows for identification and quantification of cerebral pathological markers, such as white matter hyperintensitives (WMH) and assessment of their correlation with autonomic dysfunction and cognitive decline. While a number of studies (particularly the LADIS (pan-European) series) have investigated the WMH-

Cognition association, few if any have investigated the role of autonomic dysfunction in this context- which is a fundamental cause of hypoperfusion and potentially WMH. TILDA-MRI would triangulate for the first time data relating to autonomic function, cognitive function and cerebral indicators of neurodegeneration. TILDA aims to introduce MRI assessment into wave 3 in a subgroup of participants, pending grant approval. This will afford the opportunity to compare density and location of WMHs in older adults with indices of autonomic dysfunction and lower cognitive function.

In conclusion, the studies contained within this thesis have identified an association between autonomic dysfunction indices (reduced HRV and presence of OH in those with SH and older women) and clinical manifestations (higher 1-year burden of syncope and complaints of non-accidental falls) and lower cognitive performance, specifically in the domains of global and executive function, and memory. The study sample used was a large nationally representative study of older adults, which allows for inferences relating to our results to be made at a population level. We have identified areas of future research that have potential to broaden our understanding of the relationship between autonomic and cognitive dysfunction in the ageing population.

9 Bibliography

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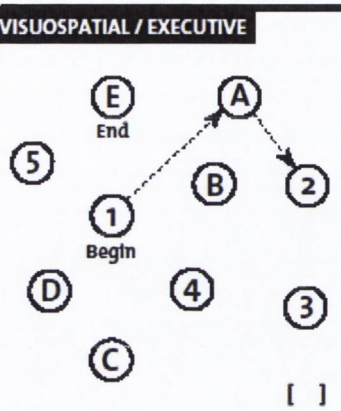
10 Appendices

Appendix 1: Montreal Cognitive Assessment Test

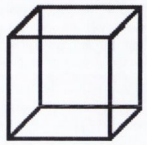
MONTREAL COGNITIVE ASSESSMENT (MOCA)

NAME :
Education :
Sex :
Date of birth :
DATE :

VISUOSPATIAL / EXECUTIVE — POINTS



Copy cube



[ ] [ ]

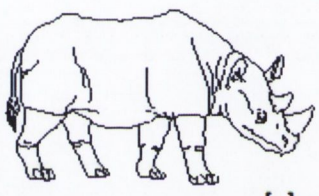
Draw CLOCK (Ten past eleven) (3 points)

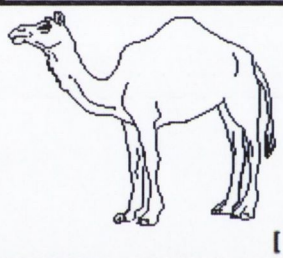
[ ] Contour [ ] Numbers [ ] Hands

__/5

NAMING







[ ] [ ] [ ]

__/3

MEMORY — Read list of words, subject must repeat them. Do 2 trials. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION — Read list of digits (1 digit/ sec.).

Subject has to repeat them in the forward order [ ] 2 1 8 5 4

Subject has to repeat them in the backward order [ ] 7 4 2

__/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B

__/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65

4 or 5 correct subtractions: 3 pts, 2 or 3 correct: 2 pts, 1 correct: 1 pt, 0 correct: 0 pt

__/3

LANGUAGE — Repeat : I only know that John is the one to help today. [ ]

The cat always hid under the couch when dogs were in the room. [ ]

__/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] ____ (N ≥ 11 words)

__/1

ABSTRACTION — Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler

__/2

DELAYED RECALL

	Has to recall words WITH NO CUE	FACE	VELVET	CHURCH	DAISY	RED	Points for UNCUED recall only
		[ ]	[ ]	[ ]	[ ]	[ ]	
Optional	Category cue						
	Multiple choice cue						

__/5

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City

__/6

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Normal ≥ 26 / 30

TOTAL __/30

Add 1 point if ≤ 12 yr edu

Appendix 2: Color Trails Two Test

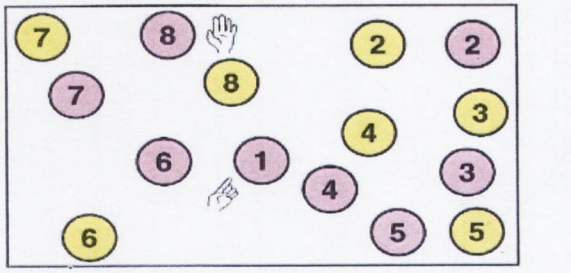
Color Trails 2

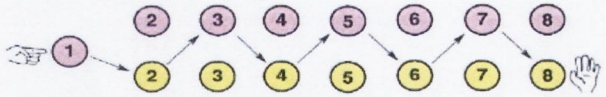
Louis F. D'Elia, PhD, and Paul Satz, PhD

Form A

Name: _____

ID#: _____ Date: _____





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